1-1-2015

Role of diet on non-alcoholic fatty liver disease: An updated narrative review

Dimitrios Papandreou
Zayed University

Eleni Andreou
University of Nicosia

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i3.575

World J Hepatol 2015 March 27; 7(3): 575-582
ISSN 1948-5182 (online)

MINIREVIEWS

Role of diet on non-alcoholic fatty liver disease: An updated narrative review

Dimitrios Papandreou, Eleni Andreou

Dimitrios Papandreou, Department of Natural Science and Public Health, CSSH, Zayed University, Abu Dhabi 144534, United Arab Emirates
Eleni Andreou, Department of Life and Health Science, University of Nicosia, Nicosia 1700, Cyprus
Author contributions: Both authors contributed to this manuscript.
Conflict-of-interest: None of the authors have any conflict of interest.

Correspondence to: Dimitrios Papandreou, PhD, MEd, MS, RD, Associate Professor of Nutrition, Department of Natural Science and Public Health, CSSH, Zayed University, Khalifa B City, Abu Dhabi 144534,
United Arab Emirates. papandreoudimitrios@yahoo.gr
Telephone: +971-2-5993677
Received: August 28, 2014
Peer-review started: August 30, 2014
First decision: November 24, 2014
Revised: December 19, 2014
Accepted: December 29, 2014
Article in press: December 29, 2014
Published online: March 27, 2015

Abstract

The purpose of this article review is to update what is known about the role of diet on non-alcoholic fatty liver disease (NAFLD). NAFLD is the most common cause of chronic liver disease in the developed world and is considered to be a spectrum, ranging from fatty infiltration of the liver alone (steatosis), which may lead to fatty infiltration with inflammation known as non alcoholic steatohepatitis While the majority of individuals with risk factors like obesity and insulin resistance have steatosis, only few people may develop steatohepatitis. Current treatment relies on weight loss and exercise, although various insulin-sensitizing medications appear promising. Weight loss alone by dietary changes has been shown to lead to histological improvement in fatty liver making nutrition therapy to become a cornerstone of treatment for NAFLD. Supplementation of vitamin E, C and omega 3 fatty acids are under consideration with some conflicting data. Moreover, research has been showed that saturated fat, trans-fatty acid, carbohydrate, and simple sugars (fructose and sucrose) may play significant role in the intrahepatic fat accumulation. However, true associations with specific nutrients yet to be clarified.

Key words: Diet; Non-alcoholic fatty acids; Fatty acids; Obesity; Insulin resistance

Core tip: The beneficial effects of weight loss and exercise have been well documented by many authors in reducing the steatosis, inflammation and fibrosis. Vitamin E can also be used with safety in adults only with biopsy proven non alcoholic steatohepatitis. Consumption of high fructose syrup to the development of non-alcoholic fatty liver disease is still under debate. The data for vitamin C shows no clear effect while the supplementation of n-3 fatty acids and probiotics is still conflicting but shows promise.

Papandreou D, Andreou E. Role of diet on non-alcoholic fatty liver disease: An updated narrative review. *World J Hepatol* 2015; 7(3): 575-582 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i3/575.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i3.575

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the spectrum of hepatic disorders embracing uncomplicated fatty liver and nonalcoholic steatohepatitis (NASH) is associated with features of metabolic syndrome (MS) and several hepatic and extra-hepatic complications[1]. Medications such as tamoxifen, methotrexate and corticosteroids may be considered as a secondary causes of MAFLD, rarely though. Additionally, rapid weight loss, total parental nutrition and lipodystrophy may also aggravate fatty liver disease. NAFLD may also progressed to non-alcoholic steatohepatitis, a term that includes symptoms of hepatocellular damage plus inflammation and/or fibrosis[2]. The diagnosis of NAFLD remains under-recognized, as most patients are asymptomatic until late stages of disease. Liver biopsy is the gold standard in diagnosing NAFLD and the most accurate tool for grading fibrosis however is invasive and carries the risk of complications[1]. Although literature information is emerging, it is not clear what type of diet is more likely to cause fatty liver. Since it is very difficult to reduce and maintain weight loss, it looks more feasible for someone to change the dietary composition of a particular diet as a more realistic method to treat NAFLD without the need of decreasing in Kcal intake. Therefore, it is more important to look for associations between NAFLD and specific nutrients.

EPIDEMIOLOGY

Excessive fat deposition in the liver is seen in about thirty percent (30%) of the adult general population. NAFLD is very common in the general population and may effects form children to elderly[3]. This increase in the prevalence of NAFLD is possibly due to the fact that the obesity rates have been also increased the last 2 decades[3].

The prevalence of non-alcoholic fatty liver disease ranges from 9% to 36.9% of the population in different parts of the world[4-6].

Approximately 20% of the United States population suffers from non-alcoholic fatty liver, and the prevalence of this condition is increasing[7]. NAFLD is also high in elderly people. A chinese case-control study examined 4226 adults above 60 years of age from a previous cohort investigated and compared them to 3145 randomly selected younger controls (< 60 years) from the same cohort. NAFDL was higher in the elderly (26.7%) than in the non-elderly (22.8%) and similar in the elderly between men and women (26.6% *vs* 27.0%, $P > 0.05$)[8]. Similar results presented by a cross-sectional study of 6905 nonobese (BMI < 25) subjects. Risk factors for the development of NAFLD were assessed in a subsequent prospective study in NAFLD-free individuals at baseline, 494 of who had developed NAFLD during the 5-year follow-up. Prevalence of NAFL was found to be 7.27%[9].

PATHOGENESIS

Even though the pathogenesis of nonalcoholic fatty liver disease is not clear yet, the most important factor of the development of NAFLD is insulin resistance. Insulin résistance increase fat breakdown from adipose tissue, which in turn, increases circulating free fatty acids having as a final result the retention of lipids within the liver, called steatosis[10]. De novo synthesis of fatty acids is also regulated by hyperinsulinemia and hyperglycemia. This is a result of transcription factors such as sterol regulatory binding protein-1c and carbohydrate response element binding protein[11]. Then, the mitochondrial-oxidation system is overloaded by the extra amount of fatty acids leading to the accumulation of free fatty acid within the hepatocytes. Finally, production of free oxygen radicals is generated by the cytochrome P450 4A and 2E1 isoenzymes-lypoxygenases[12].

Age- related data even though still undefined might reveal some connection of alterations in cholesterol synthesis in patients with NAFLD[13]. Finally this lipid peroxidation leads to the release of malondial-dehyde and 4-hydroxynonenal, which causes cell death and protein cross-linkage, resulting in the formation of Mallory's hyaline in the hepatocyte[14]. They also activate stellate cells, which lead to collagen synthesis and fibrosis[15]. Altered distribution of inflammatory cytokines in the different body compartments may further contribute to worsening NAFLD course in the elderly[16].

HISTOLOGY

Recently, information from consensus conference defined NASH as steatosis that includes hepatocellular ballooning plus lobular inflammation. However, in the absence of inflammation, subjects with steatosis in conjunction with peri-cellular fibrosis may also considered to present NASH[2]. This histological distinction between NASH and simple steatosis, yet to be clarified. Histologically, a minimum of 5% steatosis is required to confirm NAFLD. The histologic features of steatohepatitis, which include steatosis, inflammation, ballooning hepatocyte necrosis, are similar to those of alcoholic liver disease. A new development system for grading and staging was recently developed by Alkhouri *et al*[17]. The diagnosis of NASH was based on Brunt's criteria. Histological features were scored: steatosis (0-3), lobular inflammation (0-3), ballooning (0-2), and PI (0-2). The new score was called the Pediatric NAFLD Histological Score or PNHS and was found to have excellent correlation with NASH.

DIAGNOSIS

Even though significant liver disease can exist with normal levels of transaminases, increased levels of

the hepatic enzymes aspartate aminotransferase and alanine aminotransferase (ALT) are usually very good predictors of the presence of NAFLD and NASH. Serum ALT levels can be found up to 10 times higher than normal in general population with fatty liver disease[18-21]. The last few years, different non-invasive tests have been developed to estimate liver fibrosis (FibroTest)[22] and simple steatosis (SteatoTest)[23]. However, both of them have not been widely adopted[24].

Histological examination of biopsy samples can assess the presence of necro-inflammation and fibrosis[25,26], and can differentiate between macro- and micro-vesicular steatosis, thus it remains the reference standard for the grading and staging of NAFLD[27]. However, it is subject to sampling error due to histological heterogeneity[28,29] scoring is semi-quantitative, limiting its ability to detect modest changes, and scoring systems vary between reports precluding direct comparisons. Ultrasound provides semi-quantitative estimates of hepatic steatosis based on diffuse increases in echogenicity[30]. Reported sensitivity and specificity vary between 60%-94% and 66%-95%, respectively[30]. Even though it is important to diagnose NAFLD, special attention must be give when it comes for the diagnosis of NASH. Symptoms and physical examination may not be enough while presence of MS most of the times will reveal the presence of NASH. Increased liver enzymes have been found to highly related with NASH, however, may not be reliable[31]. Lately, it has come to the literature a new model namely the fragment of keratin 18 (CK18), which is for now, the best marker for detecting NASH, however showed lower accuracy with sensitivity (60%)[32].

TREATMENT

Drug management

Improvement of insulin sensitivity remains the main strategic treatment for NAFLD as well as the modification of all others underlying metabolic risk factors. One of the most common drugs, metformin, it has been used to reduce hyperinsulinemia and to improve insulin resistance. Data for mice studies has been shown to reverse fatty liver in obese, leptin deficient mice[33]. Moreover, a trial using adults who underwent a therapy of 4 mo with metformin demonstrated significant reduction in serum ALT[34]. Nobili *et al*[35] found that metformin was no more effective than lifestyle interventions improving liver enzymes or histology. Additionally, other studies have also failed to prove benefits of using metformin to improve liver histology[36]. Another agent, pioglitazone was found in a metanalysis[37] of reducing liver enzymes and inflammation and benefit of metabolism of glucose, however, the review failed to reveal an improvement of liver fibrosis. Statins are also a promising drug agent; two large studies examine the effect of statins in cardiovascular disease. The authors showed that NAFLD patients with high liver enzymes had lower cardiovascular events compared to patients with normal liver enzymes[38,39]. These results are very encouraging of using statins as a treatment for NAFLD patients with high liver enzymes. Losartan, which is also used in NAFLD patients as a anti-hypertensive drug, has been found to decrease liver fibrosis[40]. Finally, Telmisartan *et al*[41] has been found to reduce insulin resistance and fat deposition in the liver and seems to be looks even more promising in the near future.

Dietary modifications and exercise

One of the most effective method of treating NAFLD is weight loss and exercise together. In a recent review by Schwenger *et al*[42], the authors summarized the effects of weight loss and exercise intervention studies in obese patients with NAFLD. A randomized controlled trial conducted by Promrat *et al*[43] used a combination of diet, physical activity and behavior modification to trigger 7%-10% weight loss in obese NASH patients. Those who achieved a minimum of 7% weight loss had improvements in their liver histology. A similar study used NAFLD patients with elevated liver enzymes and central obesity to assess the effectiveness of lifestyle interventions. Patients were randomly assigned to either low (3 sessions/4 wk) or moderate (6 sessions/10 wk) physical activity intensity groups and were compared to a control group. The lifestyle interventions included physical activity and dietary guidance as well as behavior modification. The authors found that there was a decrease in aminotransferases, which was greater in the group with the moderate-intensity lifestyle compared to the control one[44].

Exercise alone has been also found to have positive results. Hallsworth *et al*[45] found that after 8 wk (3 times per week lasting 45-60 min) of resistance based exercise resulted in a reduction of liver lipids, and improvements of lipid oxidation, glucose control and insulin resistance.

Additionally a recent review conducted by Thoma *et al*[46] analyzed 23 studies using diet modification, physical activity, or a combination of both. He concluded that lifestyle modifications that led to weight reduction and/or increased physical activity greatly reduced liver fat and improved insulin sensitivity. More recently a study led by Montesi *et al*[47] found that intensive psychological counseling for physical activity improves physical fitness and liver fat independent of weight loss. Similar effects have been also verified by a recent meta-analysis study[48].

Dietary changes for 1-3 mo have shown to reduce liver enzymes and even normalize them (Table 1)[49-55].

Many study in adults[50,55,56] and children[56] have shown improvement in the histological profile that underwent a weight loss program. The type of weight loss with a traditional low fat diet or calorie restriction is still debatable. All of these studies though, have

Table 1 Nutritional recommendations for non-alcoholic fatty liver disease

Diet trials in NAFLD
Decrease of about 600-800 kcal per day[49]
Based on IBW, a reduction of caloric intake to < 25 kcals/kg per day[50]
Reduction of total fat intake of < 30% of energy intake with no more of 10% of saturated fatty acids[51-53]
Reduction of total Kcal per day of < 30 kcal/kg[54]
A diet low in calories and carbohydrates of 40%-45%[55]

NAFLD: Non-alcoholic fatty liver disease.

failed to examine any decrease of NAFLD as the final result[57-59]. However, the main outcome from these studies was that a reduction of total body weight between 5%-10% would have the most benefits to these patients. This probably verify the theory where the amount of fat that is delivered to the liver may play very important role in the lipid metabolism as well to the total real weight loss itself[55]. Therefore, it is important for dietitians and other health professionals to direct the patients with NAFLD to lose weight, as this interventions therapy seems to offer the most advantages. Rapid weight loss of more than 1.6 kg/wk has been also found in studies[60] to cause deterioration of the inflammation in people with NAFLD and may increase the progression pace of the disease by promoting increase of fatty breakdown from fatty tissue and increasing transport to the liver. Patel *et al*[61] observed that a reduction in BMI of at least 5% is associated with a significant decrease in liver fat and volume in patients with biopsy-proven NASH. Even for the normal weight people, losing weight has an effect on the improvement of non-alcoholic fatty liver disease. A Korean study of 180 subjects, compared with the stable group, the loss group showed an almost 19-fold increase in the odds of disappearance of non-alcoholic fatty liver disease[62].

Even though factors that determine the severity of NAFLD are still unclear in some studies[63], the exercise component is a recommended treatment. Physical activity intensity and histological severity of NAFLD were evaluated in 813 adults (males = 302, females = 511). Moderate-intensity exercise and total exercise per week was associated with decreased levels of NASH or stage of fibrosis. In the same study vigorous exercise was relate with beneficial results in subjects with NAFLD. The authors concluded that intensity of exercise may be more important than duration or total volume. Resistance training (RT) has been also found to be beneficial recently. Three months of RT improves hepatic fat content accompanied by favorable changes in body composition and ferritin and may serve as a complement to treatment of NAFLD[64]. In addition, intensive psychological counseling for PA produces hepatic effects the same as standard cognitive behavior counseling, improving physical fitness and liver fat independent of weight loss. Strategies promoting exercise are effective in motivated patients, particularly in lean NAFLD patients where large weight loss cannot be systematically pursued[47,65].

OTHER NUTRIENTS

Vitamin C

Vitamin C and E together with weight loss or without has been also examined in children with fatty liver disease. The authors concluded that significant histologic improvements (degree of steatosis, inflammation and ballooning degeneration) were produced by a weight loss of around 5 kg. However, the study failed to prove and beneficial effects of Vitamin C and E on weight loss[56]. Data for Vitamin C and its effects on NAFLD shows no clear beneficial effects. The statement of the most recent consensus was that vitamin C is not recommended for patients with NAFLD outside the context of research protocols[66].

Vitamin E

Oxidative stress and depletion of endogenous antioxidants are important in the pathogenesis of disease progression in NASH. Many drugs with antioxidant features were tried in studies for the treatment of NASH with variable conclusions. Vitamin E (a-tocopherol) is a well-known antioxidant and this feature is the best studied of its many other biological functions. The largest randomized controlled study on vitamin E, the PIVENS trial, demonstrated a greater histological improvement in inflammation in non-diabetic patients with biopsy-proven NASH compared with the placebo and pioglitazone groups. However, only 42% of patients receiving high dose vitamin E (800 IU/d) for 96 wk achieved an improvement in histological parameters compared with 19% in placebo-treated patients[67]. Recently, the Nonalcoholic Steatohepatitis Clinical Research Network conducted a multicenter study comparing metformin and vitamin E in 173 pediatric patients with NAFLD, who were followed up for 96 wk and underwent a post-treatment biopsy (the TONIC study). This study did not show significant benefits of vitamin E for aminotransferase levels; however, it did show differences in the histological characteristics (ballooning and NAFLD activity score) of the liver biopsy performed at 96 wk[68]. Several concerns have been raised regarding an increase in all-cause mortality with the long-term use of vitamin E[69]. Thus, the statement of the consensus was that the use of vitamin E is well supported for nondiabetic adults with biopsy-proven NASH[66].

n-3 fatty acids

A decrease rate in the development of NASH has been demonstrated by a diet high in n-3 PUFA in animal studies[70]. This is possibly due to the fact that n-3 PUFAs have the ability to regulate lipid processing to the liver by reducing oxidative stress and liver inflammation[70].

Capanni *et al*[71] examined the effects of n-3 PUFA

in non-alcoholic fatty liver disease in 42 patients who received 1 gm n-3 PUFA per day for 1 year. Both liver enzymes as well as ultrasound results were improved. A 53% reduction in NAFLD was also observed in 134 patients who received 2 gm of n-3 PUFA three times per day compared with a 35% reduction of NAFLD group who follow a diet low in kcal, respectively[72]. Other similar studies using n-3 PUFA to treat NAFLD have shown pararell results when used aminotransferases and ultrasound to asses fatty liver[73,74]. A recent systematic review and meta-analysis[75] found significant heterogeneity between these studies and concluded that although omega-3 PUFA supplementation may decrease liver fat (with no effects on aminotransferase levels), the optimal dose has not been established. Additional trials are needed to support the routine use of omega-3 PUFA in patients with NAFLD. To date, there is insufficient evidence to support the routine use of omega-3 PUFA supplementation in patients with NAFLD[66].

Fructose

The most common sugar found in fruit and soft drinks is high fructose corn syrup (HFCS). Sucrose is 50% fructose and 50% glucose. In a recent study that included health people the authors demonstrated an increase of liver enzymes of those subjects consuming ¼ of total calories per day in the form of sucrose[76]. In another similar study patients with fatty liver found to have twice the consumption of high fructose syrup compare with those without fatty liver disease (365 kcal *vs* 170 kcal)[77].

In another study, patients that consumed a diet high in calories and fructose were found to have an increase in hepatic fat deposition compared to the normal group[78]. Most recently, Sullivan *et al*[79] showed that children with NAFLD absorbed and metabolized fructose more effectively than lean subjects. Fructose ingestion was associated with an exacerbated metabolic profile[79]. In a 4-wk randomized, controlled, double-blinded beverage intervention study, Jin *et al*[80] demonstrated that reduction of dietary fructose in Hispanic-American adolescents with NAFLD improved several important factors related to cardiovascular disease risk, including adipose insulin sensitivity, high sensitivity C-reactive protein and low-density lipoprotein oxidation. On the other side a recent study by Kanerva *et al*[81] found that high fructose intake was inversely associated with risk of NAFLD in older Finnish adult. A latest meta-analysis of 21 intervention studies concluded that there was insufficient evidence to draw a conclusion for effects of HFCS or sucrose on NAFLD[82].

Prebiotics and probiotics

Dietary prebiotic consumption, which modulates gut microbiota[83] although associated with subjective satiety, reduced postprandial glucose and insulin concentrations and exhibits inconsistent results regarding total energy intake, body weight, gut peptides, insulin sensitivity, serum lipids, inflammatory markers and immune function[84]. Despite the positive results in animals[85], data of probiotics on metabolic effect in humans is still conflicting. Further studies are needed to identify strategies to target gut microbiota composition as an innovative NAFLD treatment in humans.

CONCLUSION

NAFLD is one of the major causes of liver diseases in the world. As the disease progresses from simple steatosis to steatohepatitis, and finally, cirrhosis should alarm health professionals to look over in order to avoid high mortality rates that have been found to related with the disease. The treatment should lie on the management of the "insulin resistance-metabolic syndrome" and not in fatty liver disease itself. The significant recognition of the disease will involve a challenge in educating people as well in the initiation of the appropriate interventions. Weight loss and exercise has been proven in reducing the steatosis inflammation and reversion of fibrosis in some cases. Vitamin E can also be used with safety in adults only with biopsy proven NASH. Consumption of high fructose syrup to the development of NAFLD is still under debate. The data for vitamin C shows no clear effect while the supplementation of n-3 FA and probiotics is still conflicting but shows promise.

REFERENCES

1 **Loria P**, Lonardo A, Carulli L, Verrone AM, Ricchi M, Lombardini S, Rudilosso A, Ballestri S, Carulli N. Review article: the metabolic syndrome and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2005; **22** Suppl 2: 31-36 [PMID: 16225469 DOI: 10.1111/j.1365-2036.2005.02592.x]

2 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219 [PMID: 12717402 DOI: 10.1053/jhep.2003.50193]

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

4 **Omagari K**, Kadokawa Y, Masuda J, Egawa I, Sawa T, Hazama H, Ohba K, Isomoto H, Mizuta Y, Hayashida K, Murase K, Kadota T, Murata I, Kohno S. Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J Gastroenterol Hepatol* 2002; **17**: 1098-1105 [PMID: 12201871 DOI: 10.1046/j.1440-1746.2002.02846.x]

5 **Hilden M**, Christoffersen P, Juhl E, Dalgaard JB. Liver histology in a 'normal' population--examinations of 503 consecutive fatal traffic casualties. *Scand J Gastroenterol* 1977; **12**: 593-597 [PMID: 918553 DOI: 10.3109/00365527709181339]

6 **Shen L**, Fan JG, Shao Y, Zeng MD, Wang JR, Luo GH, Li JQ, Chen SY. Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey. *World J Gastroenterol* 2003; **9**: 1106-1110 [PMID: 12717867]

7 **Lazo M**, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. *BMJ* 2011; **343**: d6891 [PMID: 22102439 DOI: 10.1136/bmj.d6891]

8 **Wang Z**, Xu M, Peng J, Jiang L, Hu Z, Wang H, Zhou S, Zhou R, Hultström M, Lai EY. Prevalence and associated metabolic factors of fatty liver disease in the elderly. *Exp Gerontol* 2013; **48**: 705-709 [PMID: 23721951 DOI: 10.1016/j.exger.2013.05.059]

9 **Xu C**, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. *Am J Gastroenterol* 2013; **108**: 1299-1304 [PMID: 23567356 DOI: 10.1038/ajg.2013.104]

10 **Marchesini G**, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999; **107**: 450-455 [PMID: 10569299 DOI: 10.1016/S0002-9343(99)00271-5]

11 **Lambert JE**, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology* 2014; **146**: 726-735 [PMID: 24316260 DOI: 10.1053/j.gastro]

12 **Weltman MD**, Farrell GC, Hall P, Ingelman-Sundberg M, Liddle C. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. *Hepatology* 1998; **27**: 128-133 [PMID: 9425928 DOI: 10.1002/hep.510270121]

13 **Bertolotti M**, Mussi C, Pellegrini E, Magni A, Del Puppo M, Ognibene S, Carulli L, Anzivino C, Baldelli E, Loria P, Carulli N. Age-associated alterations in cholesterol homeostasis: evidence from a cross-sectional study in a Northern Italy population. *Clin Interv Aging* 2014; **9**: 425-432 [PMID: 24669190 DOI: 10.2147/CIA.S57714]

14 **Zatloukal K**, Böck G, Rainer I, Denk H, Weber K. High molecular weight components are main constituents of Mallory bodies isolated with a fluorescence activated cell sorter. *Lab Invest* 1991; **64**: 200-206 [PMID: 1705301]

15 **Leonarduzzi G**, Scavazza A, Biasi F, Chiarpotto E, Camandola S, Vogel S, Dargel R, Poli G. The lipid peroxidation end product 4-hydroxy-2,3-nonenal up-regulates transforming growth factor beta1 expression in the macrophage lineage: a link between oxidative injury and fibrosclerosis. *FASEB J* 1997; **11**: 851-857 [PMID: 9285483]

16 **Nakamura Y**, Sekikawa A, Kadowaki T, Kadota A, Kadowaki S, Maegawa H, Kita Y, Evans RW, Edmundowicz D, Curb JD, Ueshima H. Visceral and subcutaneous adiposity and adiponectin in middle-aged Japanese men: the ERA JUMP study. *Obesity* (Silver Spring) 2009; **17**: 1269-1273 [PMID: 19584883 DOI: 10.1038/oby.2009.3]

17 **Alkhouri N**, De Vito R, Alisi A, Yerian L, Lopez R, Feldstein AE, Nobili V. Development and validation of a new histological score for pediatric non-alcoholic fatty liver disease. *J Hepatol* 2012; **57**: 1312-1318 [PMID: 22871498 DOI: 10.1016/j.jhep.2012.07.027]

18 **Baldridge AD**, Perez-Atayde AR, Graeme-Cook F, Higgins L, Lavine JE. Idiopathic steatohepatitis in childhood: a multicenter retrospective study. *J Pediatr* 1995; **127**: 700-704 [PMID: 7472819 DOI: 10.1016/S0022-3476(95)70156-7]

19 **Rashid M**, Roberts EA. Nonalcoholic steatohepatitis in children. *J Pediatr Gastroenterol Nutr* 2000; **30**: 48-53 [PMID: 10630439 DOI: 10.1097/00005176-200001000-00017]

20 **Schwimmer JB**, Deutsch R, Rauch JB, Behling C, Newbury R, Lavine JE. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. *J Pediatr* 2003; **143**: 500-505 [PMID: 14571229 DOI: 10.1067/S0022-3476(03)00325-1]

21 **Manton ND**, Lipsett J, Moore DJ, Davidson GP, Bourne AJ, Couper RT. Non-alcoholic steatohepatitis in children and adolescents. *Med J Aust* 2000; **173**: 476-479 [PMID: 11149304]

22 **Halfon P**, Munteanu M, Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. *Gastroenterol Clin Biol* 2008; **32**: 22-39 [PMID: 18973844 DOI: 10.1016/S0399-8320(08)73991-5]

23 **Ratziu V**, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L, Tahiri M, Munteanu M, Thabut D, Cadranel JF, Le Bail B, de Ledinghen V, Poynard T. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol* 2006; **6**: 6 [PMID: 16503961 DOI: 10.1186/1471-230X-6-6]

24 **Vuppalanchi R**, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306-317 [PMID: 19065650 DOI: 10.1002/hep.22603]

25 **Feldstein AE**, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. *Hepatology* 2009; **50**: 1072-1078 [PMID: 19585618 DOI: 10.1002/hep.23050]

26 **Musso G**, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med* 2011; **43**: 617-649 [PMID: 21039302 DOI: 10.3109/07853890.2010.518623]

27 **Loria P**, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, Gasbarrini A, Loguercio C, Lonardo A, Marchesini G, Marra F, Persico M, Prati D, Baroni GS. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis* 2010; **42**: 272-282 [PMID: 20171943 DOI: 10.1016/j.dld.2010.01.021]

28 **Merriman RB**, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology* 2006; **44**: 874-880 [PMID: 17006934 DOI: 10.1002/hep.21346]

29 **Larson SP**, Bowers SP, Palekar NA, Ward JA, Pulcini JP, Harrison SA. Histopathologic variability between the right and left lobes of the liver in morbidly obese patients undergoing Roux-en-Y bypass. *Clin Gastroenterol Hepatol* 2007; **5**: 1329-1332 [PMID: 17702661 DOI: 10.1016/j.cgh.2007.06.005]

30 **Schwenzer NF**, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol* 2009; **51**: 433-445 [PMID: 19604596 DOI: 10.1016/j.jhep.2009.05.023]

31 **Verma S**, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver Int* 2013; **33**: 1398-1405 [PMID: 23763360 DOI: 10.1111/liv.12226]

32 **Cusi K**, Chang Z, Harrison S, Lomonaco R, Bril F, Orsak B, Ortiz-Lopez C, Hecht J, Feldstein AE, Webb A, Louden C, Goros M, Tio F. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. *J Hepatol* 2014; **60**: 167-174 [PMID: 23973932]

33 **Lin HZ**, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin-deficient mice. *Nat Med* 2000; **6**: 998-1003 [PMID: 10973319 DOI: 10.1038/79697]

34 **Marchesini G**, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet* 2001; **358**: 893-894 [PMID: 11567710 DOI: 10.1016/S0140-6736(01)06042-1]

35 **Nobili V**, Manco M, Ciampalini P, Alisi A, Devito R, Bugianesi E, Marcellini M, Marchesini G. Metformin use in children with nonalcoholic fatty liver disease: an open-label, 24-month, observational pilot study. *Clin Ther* 2008; **30**: 1168-1176 [PMID: 18640473 DOI: 10.1016/j.clinthera.2008.06.012]

36 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852]

37 **Musso G**, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012; **55**: 885-904 [PMID: 22278337 DOI: 10.1007/s00125-011-2446-4]

38 **Athyros VG**, Tziomalos K, Gossios TD, Griva T, Anagnostis P,

Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet* 2010; **376**: 1916-1922 [PMID: 21109302 DOI: 10.1016/S0140-6736(10)61272-X]

39 **Athyros VG**, Katsiki N, Karagiannis A, Mikhailidis DP. Are statins 'IDEAL' for non-alcoholic fatty liver disease? *Curr Med Res Opin* 2014; **30**: 229-231 [PMID: 24127654]

40 **Yokohama S**, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, Hasegawa T, Tokusashi Y, Miyokawa N, Nakamura K. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology* 2004; **40**: 1222-1225 [PMID: 15382153 DOI: 10.1002/hep.20420]

41 **Hirata T**, Tomita K, Kawai T, Yokoyama H, Shimada A, Kikuchi M, Hirose H, Ebinuma H, Irie J, Ojiro K, Oikawa Y, Saito H, Itoh H, Hibi T. Effect of Telmisartan or Losartan for Treatment of Nonalcoholic Fatty Liver Disease: Fatty Liver Protection Trial by Telmisartan or Losartan Study (FANTASY). *Int J Endocrinol* 2013; **2013**: 587140 [PMID: 23997767 DOI: 10.1155/2013/587140]

42 **Schwenger KJ**, Allard JP. Clinical approaches to non-alcoholic fatty liver disease. *World J Gastroenterol* 2014; **20**: 1712-1723 [PMID: 24587650 DOI: 10.3748/wjg.v20.i7.1712]

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

44 **Zelber-Sagi S**, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. *World J Gastroenterol* 2011; **17**: 3377-3389 [PMID: 21876630]

45 **Hallsworth K**, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, Day CP, Trenell MI. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut* 2011; **60**: 1278-1283 [PMID: 21708823 DOI: 10.1136/gut.2011.242073]

46 **Thoma C**, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *J Hepatol* 2012; **56**: 255-266 [PMID: 21723839 DOI: 10.1016/j.jhep.2011.06.010]

47 **Montesi L**, Caselli C, Centis E, Nuccitelli C, Moscatiello S, Suppini A, Marchesini G. Physical activity support or weight loss counseling for nonalcoholic fatty liver disease? *World J Gastroenterol* 2014; **20**: 10128-10136 [PMID: 25110440 DOI: 10.3748/wjg.v20.i29.10128]

48 **Keating SE**, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **57**: 157-166 [PMID: 22414768 DOI: 10.1016/j.jhep.2012.02.023]

49 **Palmer M**, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology* 1990; **99**: 1408-1413 [PMID: 2210247]

50 **Ueno T**, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, Torimura T, Inuzuka S, Sata M, Tanikawa K. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997; **27**: 103-107 [PMID: 9252081 DOI: 10.1016/S0168-8278(97)80287-5]

51 **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 [PMID: 12883485 DOI: 10.1053/jhep.2003.50316]

52 **Schäfer S**, Kantartzis K, Machann J, Venter C, Niess A, Schick F, Machicao F, Häring HU, Fritsche A, Stefan N. Lifestyle intervention in individuals with normal versus impaired glucose tolerance. *Eur J Clin Invest* 2007; **37**: 535-543 [PMID: 17576204 DOI: 10.1111/j.1365-2362.2007.01820.x]

53 **Hickman IJ**, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, Powell EE. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 2004; **53**: 413-419 [PMID: 14960526 DOI: 10.1136/gut.2003.027581]

54 **Vajro P**, Mandato C, Franzese A, Ciccimarra E, Lucariello S, Savoia M, Capuano G, Migliaro F. Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *J Pediatr Gastroenterol Nutr* 2004; **38**: 48-55 [PMID: 14676594 DOI: 10.1097/00005176-200401000-00012]

55 **Huang MA**, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, Emick D, Lok AS, Conjeevaram HS. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. *Am J Gastroenterol* 2005; **100**: 1072-1081 [PMID: 15842581 DOI: 10.1111/j.1572-0241.2005.41334.x]

56 **Nobili V**, Manco M, Devito R, Di Ciommo V, Comparcola D, Sartorelli MR, Piemonte F, Marcellini M, Angulo P. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology* 2008; **48**: 119-128 [PMID: 18537181 DOI: 10.1002/hep.22336]

57 **Samaha FF**, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T, Williams M, Gracely EJ, Stern L. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074-2081 [PMID: 12761364 DOI: 10.1056/NEJMoa022637]

58 **Stern L**, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004; **140**: 778-785 [PMID: 15148064 DOI: 10.7326/0003-4819-140-10-200405180-00007]

59 **Dansinger ML**, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005; **293**: 43-53 [PMID: 15632335 DOI: 10.1001/jama.293.1.43]

60 **Andersen T**, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol* 1991; **12**: 224-229 [PMID: 2051001 DOI: 10.1016/0168-8278(91)90942-5]

61 **Patel NS**, Doycheva I, Peterson MR, Hooker J, Kisselva T, Schnabl B, Seki E, Sirlin CB, Loomba R. Effect of weight loss on magnetic resonance imaging estimation of liver fat and volume in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2015; **13**: 561-568.e1 [PMID: 25218667 DOI: 10.1016/j.cgh.2014]

62 **Cho JY**, Chung TH, Lim KM, Park HJ, Jang JM. The impact of weight changes on nonalcoholic Fatty liver disease in adult men with normal weight. *Korean J Fam Med* 2014; **35**: 243-250 [PMID: 25309705 DOI: 10.4082/kjfm.2014.35.5.243]

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

64 **Zelber-Sagi S**, Buch A, Yeshua H, Vaisman N, Webb M, Harari G, Kis O, Fliss-Isakov N, Izkhakov E, Halpern Z, Santo E, Oren R, Shibolet O. Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial. *World J Gastroenterol* 2014; **20**: 4382-4392 [PMID: 24764677 DOI: 10.3748/wjg.v20.i15.4382]

65 **Montesi L**, Moscatiello S, Malavolti M, Marzocchi R, Marchesini G. Physical activity for the prevention and treatment of metabolic disorders. *Intern Emerg Med* 2013; **8**: 655-666 [PMID: 23657989 DOI: 10.1007/s11739-013-0953-7]

66 **Arab JP**, Candia R, Zapata R, Muñoz C, Arancibia JP, Poniachik J, Soza A, Fuster F, Brahm J, Sanhueza E, Contreras J, Cuellar MC, Arrese M, Riquelme A. Management of nonalcoholic fatty liver disease: an evidence-based clinical practice review. *World J Gastroenterol* 2014; **20**: 12182-12201 [PMID: 25232252 DOI: 10.3748/wjg.v20.i34.12182]

67 **Chalasani NP**, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, Unalp A, Tonascia J. Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design. *Contemp Clin Trials*

2009; **30**: 88-96 [PMID: 18804555 DOI: 10.1016/j.cct.2008.09.00]
68 **Lavine JE**, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, Abrams SH, Scheimann AO, Sanyal AJ, Chalasani N, Tonascia J, Ünalp A, Clark JM, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA* 2011; **305**: 1659-1668 [PMID: 21521847 DOI: 10.1001/jama.2011.520]
69 **Bjelakovic G**, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007; **297**: 842-857 [PMID: 17327526 DOI: 10.1001/jama.297.8.842]
70 **Mummadi RR**, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2008; **6**: 1396-1402 [PMID: 18986848]
71 **Capanni M**, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther* 2006; **23**: 1143-1151 [PMID: 16611275 DOI: 10.1111/j.1365-2036.2006.02885.x]
72 **Reddy JK**. Nonalcoholic steatosis and steatohepatitis. III. Peroxisomal beta-oxidation, PPAR alpha, and steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G1333-G1339 [PMID: 11705737]
73 **Zhu FS**, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World J Gastroenterol* 2008; **14**: 6395-6400 [PMID: 19009658 DOI: 10.3748/wjg.14.6395]
74 **Spadaro L**, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, Papa G, Rabuazzo AM, Purrello F. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 194-199 [PMID: 18054848 DOI: 10.1016/j.dld.2007.10.003]
75 **Parker HM**, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **56**: 944-951 [PMID: 22023985 DOI: 10.1016/j.jhep.2011.08.018]
76 **Porikos KP**, Van Itallie TB. Diet-induced changes in serum transaminase and triglyceride levels in healthy adult men. Role of sucrose and excess calories. *Am J Med* 1983; **75**: 624-630 [PMID: 6624769 DOI: 10.1016/0002-9343(83)90444-8]
77 **Ouyang X**, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, Johnson RJ, Abdelmalek MF. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol* 2008; **48**: 993-999 [PMID: 18395287 DOI: 10.1016/j.jhep.2008.02.011]
78 **Lê KA**, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, Boesch C, Tappy L. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. *Am J Clin Nutr* 2009; **89**: 1760-1765 [PMID: 19403641 DOI: 10.3945/ajcn.2008.27336]
79 **Sullivan JS**, Le MT, Pan Z, Rivard C, Love-Osborne K, Robbins K, Johnson RJ, Sokol RJ, Sundaram SS. Oral fructose absorption in obese children with non-alcoholic fatty liver disease. *Pediatr Obes* 2014 Jun 24; Epub ahead of print [PMID: 24961681 DOI: 10.1111/ijpo.238]
80 **Jin R**, Welsh JA, Le NA, Holzberg J, Sharma P, Martin DR, Vos MB. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. *Nutrients* 2014; **6**: 3187-3201 [PMID: 25111123 DOI: 10.3390/nu6083187]
81 **Kanerva N**, Sandboge S, Kaartinen NE, Männistö S, Eriksson JG. Higher fructose intake is inversely associated with risk of nonalcoholic fatty liver disease in older Finnish adults. *Am J Clin Nutr* 2014; **100**: 1133-1138 [PMID: 25099548 DOI: 10.3945/ajcn.114.086074]
82 **Chung M**, Ma J, Patel K, Berger S, Lau J, Lichtenstein AH. Fructose, high-fructose corn syrup, sucrose, and nonalcoholic fatty liver disease or indexes of liver health: a systematic review and meta-analysis. *Am J Clin Nutr* 2014; **100**: 833-849 [PMID: 25099546 DOI: 10.3945/ajcn.114.086314]
83 **D'Aversa F**, Tortora A, Ianiro G, Ponziani FR, Annicchiarico BE, Gasbarrini A. Gut microbiota and metabolic syndrome. *Intern Emerg Med* 2013; **8** Suppl 1: S11-S15 [PMID: 23468402 DOI: 10.1007/s11739-013-0916-z]
84 **Kellow NJ**, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr* 2014; **111**: 1147-1161 [PMID: 24230488 DOI: 10.1017/S0007114513003607]
85 **Ritze Y**, Bárdos G, Claus A, Ehrmann V, Bergheim I, Schwiertz A, Bischoff SC. Lactobacillus rhamnosus GG protects against non-alcoholic fatty liver disease in mice. *PLoS One* 2014; **9**: e80169 [PMID: 24475018 DOI: 10.1371/journal.pone.0080169]

P- Reviewer: Dehghani SM, Liang J, Malnick S, Swierczynski JT
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

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