Available online at www.sciencedirect.com

Integrative Medicine Research

journal homepage: www.imr-journal.com

Review Article

Practical approaches to the nutritional management of nonalcoholic fatty liver disease

Leila Freidoony[a], *In Deok Kong*[b,*]

[a] *Department of Preventive Medicine, Wonju College of Medicine, Yonsei University, Wonju, Gangwon-Do, Korea*
[b] *Department of Physiology, Wonju College of Medicine, Yonsei University, Wonju, Gangwon-Do, Korea*

ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form
5 September 2014
Accepted 11 September 2014
Available online 19 September 2014

Keywords:
carbohydrates
fatty acids
nonalcoholic fatty liver disease
nutrition
protein

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and a serious health burden worldwide which increases risk of cirrhosis, type 2 diabetes mellitus (T2DM), and cardiovascular complications. Current epidemics of obesity, unhealthy dietary patterns, and sedentary lifestyles, all contribute to the high prevalence of NAFLD. Dietary patterns and nutrients are important contributors to the development, progression, and treatment of NAFLD. A healthy diet is beneficial for all NAFLD patients beyond weight reduction. Generally, hypercaloric diets, especially rich in trans/saturated fat and cholesterol, high consumption of red and processed meat, and fructose-sweetened beverages seem to increase the risk of progression toward nonalcoholic steatohepatitis (NASH), whereas reducing caloric intake and high-glycemic index (GI) foods, increasing consumption of monounsaturated fatty acids, omega-3 fatty acids, fibers, and specific protein sources such as fish and poultry have preventive and therapeutic effects. Therefore, nutrition serves as a major route of prevention and treatment of NAFLD, and patients with NAFLD should have an individualized diet recommendation. In this review, the evidence linking macronutrients to NAFLD are discussed.

© 2014 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic stress-related liver disease defined as the hepatic accumulation of lipids, mainly triglyceride, in the absence of substantial alcohol consumption (< 20 g/day) or other secondary causes. It encompasses a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which increases the risk of cirrhosis and hepatocellular carcinoma. Currently, NAFLD is the main cause of chronic liver disease worldwide. Its prevalence is much higher in diabetic or obese individuals. Patients with NAFLD should be treated for steatohepatitis and the associated metabolic comorbidities, whereas patients with simple steatosis only need to treat the associated conditions to prevent hepatic and metabolic complications.[1,2]

As pharmacotherapy is not effective and safe enough, and obesity is intimately associated with hepatic steatosis, lifestyle modification is the first line of treatment. The usual steps for the management of NAFLD are gradual weight loss,

* *Corresponding author at*: Department of Physiology, Wonju College of Medicine, Yonsei University, 20 Ilsan-ro, Wonju, Gangwondo 220-701, South Korea.
E-mail address: Kong@yonsei.ac.kr (I.D. Kong).
http://dx.doi.org/10.1016/j.imr.2014.09.003
2213-4220/© 2014 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

adopting a healthy diet which has benefits beyond weight reduction, and increased physical activity. Several studies have demonstrated the beneficial impacts of dietary interventions in treating obesity, insulin resistance, and NAFLD and that specific macronutrients might benefit NAFLD independent of weight loss.[3–8] This review summarizes the evidence for the macronutrient effects including carbohydrates, lipids, and proteins in the management of patients with NAFLD.

2. Macronutrient effects on NAFLD carbohydrates

Carbohydrates (CHO) are the main source of body energy for both children and adults. Based on the level of polymerization, they are categorized as sugars (monosaccharides and disaccharides), oligosaccharides, and polysaccharides. Although studies have shown that several carbohydrates may be linked to NAFLD, the main focus has been on glycemic index, fructose, and fiber.[9]

Several studies suggest that CHO restriction can improve insulin resistance through reducing glycemic load and beta-cell insulin secretion.[10] Low-CHO diets could also reduce serum triglycerides, insulin, and glucose and increase high-density lipoprotein (HDL).[11] Concerning NAFLD, a recent cross-sectional study showed a positive correlation between aminotransferase levels (a surrogate measure of NAFLD at population level) and CHO intake after adjusting for age, body mass index (BMI), and energy intake.[12] In another report, a *post hoc* analysis showed that of 52 obese insulin-resistant patients subjected to a hypocaloric diet based on a low-CHO/high-fat diet (40% and 45% total calories per day, respectively) or a high-CHO/low-fat diet (60% and 25%, respectively), reduction of alanine transaminase (ALT) and serum insulin was significantly greater in the patients allocated to the low CHO diet.[13] Similarly, a randomized study of 22 obese patients comparing a low-CHO (< 50 g/day) versus a high-CHO (> 180 g/day) hypocaloric diet, showed a greater reduction of liver glucose production and hepatic steatosis at 48 hours in patients on the low-CHO diet. Nonetheless, the differences in liver steatosis were insignificant after achieving > 7% weight loss, irrespective of the CHO composition of the diet.[14] This data propose that in spite of an early weight-independent effect of low-CHO diets on liver steatosis and insulin resistance, this effect is surpassed by significant weight loss. Congruent with this, another randomized study of 170 obese or overweight patients comparing a hypocaloric low-CHO diet (> 1200 calories restriction per day, < 90 g CHO per day, and > 30% calories per day from fat) versus a hypocaloric low-fat diet (< 20% of total calorie intake), showed a similar reduction in weight (7.4%), fat mass, visceral adipose mass, insulin resistance, and liver fat after a 6-month follow-up.[15] Histology assessments were not provided by any of these studies. Therefore, although moderate CHO restriction seems to have no further effect on liver steatosis in patients with significant weight loss (≥ 7%), its impact on liver inflammation and fibrosis and its utility in patients without significant weight loss have not yet been elucidated.

Glycemic load is defined as the absolute amount of glucose in grams that is provided by the food group concerned. High-glycemic-load foods (including those rich in simple and complex carbohydrates, such as chocolates, candies, cookies, or potato, pasta, bread, and rice) increase postprandial glycemia and insulinemia, especially in patients with insulin resistance.[16] Glycemic index (GI) is defined as the proportion of food converted and absorbed as glucose, and it is expressed as a percentage. A recent meta-analysis of studies on dietary regimens based on GI, concluded that higher glucose and insulin exposure is associated with long-term complications, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[17,18] Likewise, a Cochrane meta-analysis of six trials with a follow-up time between 1 month and 6 months concluded that a diet based on low-GI products induces a significantly higher weight loss (−1.1 kg) and fat mass reduction.[19] In a cross-sectional analysis of 257 healthy individuals, Valtueña et al[20] demonstrated that there is an association between high-GI food intake and the presence of liver steatosis (assessed by ultrasound). However, longitudinal prospective studies are needed to explore the effects of such diets on NAFLD and hepatic inflammation.

During the past decades, fructose intake has considerably increased. It is mainly derived from sucrose (table sugar) and corn syrup which is abundantly used in sugar-sweetened beverages.[21] Fructose metabolism increases lipogenesis, free radical oxygen species production, gut permeability, bacterial overgrowth, and serum lipopolysaccharide levels. Furthermore, it reduces lipid oxidation.[9,22] In animal studies, some of these mechanisms have been suggested to play a role in NASH and insulin resistance pathogenesis.

Longitudinal epidemiologic data from an analysis of the Framingham study database ($n = 6039$) demonstrated that the consumption of one or more soft drinks per day increases risk of obesity and metabolic syndrome, including all of its components (impaired fasting glucose, high blood pressure, hypertriglyceridemia, and low HDL).[23] Additionally, a cross-sectional analysis of 427 patients with biopsy-proven NAFLD demonstrated that intake of seven or more sugar-sweetened drinks per week is associated with significantly higher fibrosis, inflammation, and hepatocyte ballooning after adjustment for age, sex, BMI, and total calorie intake.[24] Recently, a study of 47 overweight patients allocated to a daily intake of 1 L of sugar-sweetened soft drinks per day for 6 months showed a significant increase in liver fat (150%), muscle fat (200%), visceral adipose tissue fat (25%), serum triglycerides (32.7%), and cholesterol (11.4%).[25] It is important to note that whether this effect is specific for an excess intake of fructose or is only a consequence of calorie excess, is still under debate. Meta-analyses have not demonstrated significant effects of high fructose intake on weight,[26] and increased fasting triglycerides are only observed in normal individuals with a high intake of fructose.[27] A recent study of 55 healthy individuals who were allocated either to a high-fructose (1.5 g/kg/day, 3.0 g/kg/day, or 4.0 g/kg/day, $n = 7$, $n = 17$, and $n = 11$, respectively), high-glucose (3 g/kg/day, $n = 10$), or high-saturated fat diet (30% of total calorie intake, $n = 10$) showed a significant increase in liver steatosis [assessed by magnetic resonance spectroscopy (MRS))] only in patients exposed to 3 g/kg/day or more of fructose, and this was higher compared with the glucose group (60%, $p < 0.05$) and similar to the saturated-fat exposed groups (90%, $p =$ insignificant).[28] Although a direct role of fructose in human NAFLD pathogenesis remains to be

elucidated, patients should be advised to restrict fructose-rich food and beverages.

Fibers are mainly plant-derived carbohydrates which are generally resistant to human digestion.[29] Several beneficial metabolic effects have been attributed to fiber, including increased satiety, increased incretin secretion, reduced absorption rate of CHO and proteins, systemic antiinflammatory effect, improved glycemic control, and modulation of gut microbiota.[29–31] A meta-analysis proposed that whole-grain intake could significantly reduce the CVD and T2DM risk.[32] In spite of several studies providing evidence of the association between fiber consumption and decreased risk of metabolic syndrome and type 2 diabetes, limited research has been done regarding dietary fiber and NAFLD. In a cross-sectional study of 247 healthy adults, higher degrees of steatosis (assessed by ultrasound) correlated with high GI diets, but there was no association between fiber intake and hepatic steatosis.[33] In another study, NAFLD patients were supplemented with 10 g/day of soluble fiber for 3 months and a beneficial effect on body weight, insulin sensitivity, and transaminase levels was found. No histology assessment was available in this study.[34] There are no other human studies focusing on the potential link between fiber consumption and NAFLD.

3. Fat

Increased fat intake and Western diets have been linked to insulin resistance, impaired postprandial lipid metabolism, and the development or progression of NAFLD.[35] In contrast to cardiovascular and metabolic diseases, there is little epidemiological evidence that the type of dietary fat is associated with fatty liver.[36]

Impacts of polyunsaturated fatty acids (PUFAs) on NAFLD have been extensively studied. Omega 3 fatty acids (ω-3 FAs), particularly docosahexaenoic acid and eicosapentaenoic acid, reduce liver steatosis by upregulation of peroxisome proliferator-activated receptor α, resulting in higher FA oxidation and lower lipogenesis.[37] Furthermore, ω-3 FAs have potent antiinflammatory and insulin sensitizing effects.[38] In line with this, a cross-sectional analysis has reported that patients with NAFLD have lower ω-3 FAs and ω-3/ω-6 FAs ratio than the controls.[39] In addition, epidemiologic studies suggest that increased fish intake (major source of ω-3 FAs) may reduce the risk of hepatocellular carcinoma and CVD.[40,41] A recent meta-analysis of nine intervention studies clearly showed that patients who were supplemented with an average of 4 g/day of ω-3 in the form of capsules or oil, had a significant reduction in liver steatosis (assessed by MRS or liver ultrasound). However, liver function tests were not significantly affected.[42]

Meta-analyses suggest that higher consumption of monounsaturated FA (MUFA) is associated with higher HDL and lower triglycerides and that it improves glycemic control in diabetic patients. Oleic acid is the most prevalent MUFA in the diet, and olive oil is one of its major sources (other sources are nuts and avocado).[43] In animal models, MUFAs have shown a positive effect on fat distribution, favoring the deposition of fat in adipose tissues rather than in the liver.[44] Concerning this, a recent randomized study of 45 diabetic patients comparing a high-CHO/low-GI/high-fiber diet (CHO 52% of total calorie intake and 28 g of fiber) with a high MUFA diet (28% of total calorie intake) for 8 weeks, demonstrated a significantly greater reduction of steatosis in the high-MUFA-diet group (27% vs. 5%, $p<0.05$).[45] Notwithstanding the promising data on PUFA and MUFA, further randomized controlled trials assessing histology outcomes are needed to confirm the beneficial effects of these interventions in NAFLD.

Trans FAs and saturated FAs have been associated with insulin resistance, elevated low-density lipoprotein (LDL), decreased HDL, and higher cardiovascular risk[46,47] which suggest that they may be involved in NAFLD pathogenesis. However, little evidence is available for their impacts on NAFLD. In a cross-sectional case control trial, Musso et al[48] compared 7-day nutritional records of 25 patients with NASH with those of the controls. Patients with NAFLD had a higher consumption of saturated fat and cholesterol and a lower intake of PUFA, fiber, and vitamins C and E. Animal models have shown that receiving high fat (63.33% of total calories per day), high-trans FA diet (28.5% of total calorie intake) increases body weight, aminotransferase levels, serum FA, liver steatosis, lipogenesis, and inflammatory mediators.[49]

Analysis of lipid profile has demonstrated that free cholesterol is significantly elevated in the livers of patients with NASH. In line with this, a large epidemiologic study reported an adverse role of dietary cholesterol on liver disease outcomes, significantly increasing the risk of cirrhosis and liver cancer.[50] In animal models, high-cholesterol diets (1–2% w/w) have increased hepatocyte-free cholesterol accumulation in mitochondria, resulting in glutathione depletion, increased susceptibility to tumor necrosis factor (TNF)-mediated apoptosis, macrophages recruitment, and liver fibrosis.[51] Thus, considering their association with increased cardiovascular risk, excessive consumption of saturated fats, trans FAs, and cholesterol should be reduced in patients with NAFLD, especially in those with hypercholesterolemia.

4. Protein

A multicenter randomized study ($n=773$ overweight adults) demonstrated that a fair increase in protein intake (15.4% of total calorie intake) combined with a low-GI diet, is associated with improved weight-loss maintenance.[52] This finding may be associated with the satiating effect and increased energy expenditure relating to protein metabolism. However, long-term effects of this type of diet should be considered. In two long-term follow-up cohorts ($n=129,716$ and 10–16 years of follow-up[53]; $n=38,094$ with 10 years of follow-up[54]), higher consumption of animal-derived protein significantly increased the incidence of diabetes and cardiovascular mortality, although this association was only significant for processed meat.[55] Moreover, a further analysis of one of these cohorts showed that nuts, low-fat dairy, fish, and poultry actually reduce cardiovascular risk.[56] Concisely, high-protein diets can be an alternative for weight maintenance but one should be cautious regarding the protein source, prioritizing fish, poultry, nuts, and legume-derived protein.

Table 1 – Recommended nutritional intervention for patients with NAFLD* [60,61]

Dietary Recommendation	Do	Do not
1. Calories restriction (500–1000 kcal/d deficit): low fat (<30%) or low CHO (<40%) 2. If low-CHO diet is decided, use more PUFA, MUFA, and proteins derived from fish, poultry, nuts, and legumes 3. If low-fat diet is decided, use more low–GI foods and proteins derived from fish, poultry, nuts, and legumes 4. Reduce consumption of trans FA (<1%), saturated fats (<7%), and cholesterol (<200 mg/d) 5. Increase intake of cereal-derived non-soluble fiber (wholegrain) (25 g/d)	• Vegetables (3–5 servings/d) • Legumes (4 servings/wk) • Fruits (2–4 servings/d) • Whole grains (daily) • Nuts (4 servings/wk) • Olive oil • Oily fish (tuna, salmon, and sardines) (≈100-gr serving at least 2/wk) • Low-fat dairy products	• Fast food (least possible) • Empty calories (cakes, cookies, ice cream, candies) • Unprocessed red meats (>300 g/wk) • Processed meats (>2/wk) • Potato chips (least possible) • Potatoes • Sugar-sweetened beverages (least possible) • Salt

CHO: Carbohydrate; GI: Glycemic Index

* Adapted from US Department of Agriculture. Available at: www.choosemyplate.gov; and American Heart Association. Available at: www.heart.org.

5. Practical approaches

The typical Western diet pattern which is abundant in red meat, trans FAs, fructose-sweetened beverages, and high-GI CHO and is low in PUFA, MUFA, vegetable-derived proteins, and fiber provides a threatening mixture of nutrients for the liver and for metabolic processes. Kechagias et al[57] properly illustrated this point. They submitted 16 healthy young patients to a high calorie, fast food-based diet (> 2 fast food-based meals per day) for 4 weeks which led to a significant increase in weight and ALT, and a doubling of the liver fat content. Therefore, from the standpoint of effective management of NAFLD, the elements of this markedly unbalanced diet should be corrected and in line with this, leisure time physical activity should be increased. However, to address subtle dietary abnormalities in patients' diets, every patient should get an individualized diet recommendation with adequate support.

Food-oriented nutritional recommendations are highly profitable because they provide a more practical approach toward synergistic beneficial effects of nutrient combinations, reduced portion sizes and caloric content, more satiety, and displacement of other foods or beverages.[58] The Mediterranean diet which is rich in olive oil, nuts, fruits, vegetables, fish, legumes, dairy products, and wine, is an example of food-oriented nutritional recommendation. In a recent randomized crossover trial, the Mediterranean diet was compared with a low-fat/high-CHO diet for 6 weeks in 12 biopsy-proven patients with NAFLD. The results clearly showed a significant reduction in hepatic steatosis (39% vs. 7% assessed by MRS) and insulin resistance.[59] The Mediterranean diet has also been demonstrated to reduce T2DM risk, CVD, cancer, and all-cause mortality.[60] A summary of recommendations and specific food groups that should be promoted in patients with NAFLD, is provided in Table 1.

6. Summary

NAFLD is the most prevalent chronic liver disease in many countries. Pharmacologic interventions are few, with low efficacy and high potential adverse effects, and obesity has an intimate association with hepatic steatosis; therefore, lifestyle intervention should be considered as a centerpiece of therapy. The usual steps for the management of NAFLD are gradual weight reduction and increased physical activity which ameliorate the disease in different aspects.

Recent studies have presented clear evidence for weight-independent effects of diets, rich in MUFA and PUFA and low in CHO, particularly fructose, on steatosis, liver tests, and insulin resistance. Given that NAFLD is the hepatic manifestation of a systemic metabolic disturbance, interventions should address four major associated complications: liver disease progression, diabetes mellitus and its complications, CVD, and cancer; interventions such as the Mediterranean diet, reduction of high-GI foods, trans Fas, and saturated fat consumption which could reduce development of T2DM and CVD. On the whole, it is recommended to consider these specific recommendations in NAFLD therapy even in the absence of definitive histology-based supportive evidence (see Table 1). To conclude, whether specific nutrient interventions are effective on liver histology or nutritional supplements could be beneficial, needs further research.

Conflicts of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Barrera F, George J. Nonalcoholic fatty liver disease: more than just ectopic fat accumulation. *Drug Discov Today Dis Mech* 2013;10:e47–54.
2. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet* 2011;378:804–14.
3. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: arandomized, prospective trial. *Hepatology* 2009;49:80–6.
4. Huang MA, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, et al. One-year intense nutritional counseling results in histological improvement in patients with

nonalcoholic steatohepatitis: a pilot study. *Am J Gastroenterol* 2005;100:1072–81.
5. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010;51:121–9.
6. Tendler D, Lin S, Yancy Jr WS, Mavropoulos J, Sylvestre P, Rockey DC, et al. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007;52:589–93.
7. Tilg H, Moschen A. Weight loss: cornerstone in the treatment of nonalcoholic fatty liver disease. *Minerva Gastroenterol Dietol* 2010;56:159–67.
8. Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997;27:103–7.
9. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol* 2010;7:251–64.
10. Ebbeling CB, Swain JF, Feldman HA, Wong WW, Hachey DL, Garcia-Lago E, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* 2012;307:2627–34.
11. Santos FL, Esteves SS, da Costa Pereira A, Yancy Jr WS, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. *Obes Rev* 2012;13:1048–66.
12. Kwon OW, Jun DW, Lee SM, Lee KN, Lee HL, Lee OY, et al. Carbohydrate but not fat is associated with elevated aminotransferases. *Aliment Pharmacol Ther* 2012;35:1064–72.
13. Ryan MC, Abbasi F, Lamendola C, Carter S, McLaughlin TL. Serum alanine aminotransferase levels decrease further with carbohydrate than fat restriction in insulin-resistant adults. *Diabetes Care* 2007;30:1075–80.
14. Kirk E, Reeds DN, Finck BN, Mayurranjan MS, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology* 2009;136:1552–60.
15. Haufe S, Engeli S, Kast P, Böhnke J, Utz W, Haas V, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology* 2011;53:1504–14.
16. Thomas T, Pfeiffer AF. Foods for the prevention of diabetes: how do they work? *Diabetes Metab Res Rev* 2012;28:25–49.
17. Livesey G, Taylor R, Livesey H, Liu S. Is there a dose-response relation of dietary glycemic load to risk of type 2 diabetes? Meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2013;97:584–96.
18. Ma XY, Liu JP, Song ZY. Glycemic load, glycemic index, and risk of cardiovascular diseases: meta-analyses of prospective studies. *Atherosclerosis* 2012;223:491–6.
19. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database of Syst Rev* 2007.
20. Valtueña S, Pellegrini N, Ardigo D, Del Rio D, Numeroso F, Scazzina F, et al. Dietary glycemic index and liver steatosis. *Am J Clin Nutr* 2006;84:136–42, quiz 268–9.
21. Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* 2010;90:23–46.
22. Vos MB, Lavine JE. Dietary fructose in nonalcoholic fatty liver disease. *Hepatology* 2013;57:2525–31.
23. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 2007;116:480–8.
24. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology* 2010;51:1961–71.
25. Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-month randomized intervention study. *Am J Clin Nutr* 2012;95:283–9.
26. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. *Ann Intern Med* 2012;156:291–304.
27. Tappy L. Q&A: 'toxic' effects of sugar: should we be afraid of fructose? *BMC Biol* 2012;10:42.
28. Lecoultre V, Egli L, Carrel G, Theytaz F, Kreis R, Schneiter P, et al. Effects of fructose and glucose overfeeding on hepatic insulin sensitivity and intrahepatic lipids in healthy humans. *Obesity (Silver Spring)* 2013;21:782–5.
29. Klosterbuer A, Roughead ZF, Slavin J. Benefits of dietary fiber in clinical nutrition. *Nutr Clin Pract* 2011;26:625–35.
30. Bouhnik Y, Achour L, Paineau D, Riottot M, Attar A, Bornet F. Four-week short chain fructo-oligosaccharides ingestion leads to increasing fecal bifidobacteria and cholesterol excretion in healthy elderly volunteers. *Nutr J* 2007;6:42.
31. Papathanasopoulos A, Camilleri M. Dietary fiber supplements: effects in obesity and metabolic syndrome and relationship to gastrointestinal functions. *Gastroenterology* 2010;138:65–72, e1-2.
32. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr* 2012;142:1304–13.
33. Carvalhana S, Machado MV, Cortez-Pinto H. Improving dietary patterns in patients with nonalcoholic fatty liver disease. *Curr Opin Clin Nutr Metab Care* 2012;15:468–73.
34. Rocha R, Cotrim HP, Siqueira AC, Floriano S. Non alcoholic fatty liver disease: treatment with soluble fibres. *Arq Gastroenterol* 2007;44:350–2.
35. Bedogni G, Bellentani S. Fatty liver: how frequent is it and why? *Ann Hepatol* 2004;3:63–5.
36. Mouzaki M, Allard JP. The role of nutrients in the development, progression, and treatment of nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2012;46:457–67.
37. Pettinelli P, Del Pozo T, Araya J, Rodrigo R, Araya AV, Smok G, et al. Enhancement in liver SREBP-1c/PPAR-alpha ratio and steatosis in obese patients: correlations with insulin resistance and n-3 long-chain polyunsaturated fatty acid depletion. *Biochim Biophys Acta* 2009;1792:1080–6.
38. Yan Y, Jiang W, Spinetti T, Tardivel A, Castillo R, Bourquin C, et al. Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. *Immunity* 2013;38:1154–63.
39. Elizondo A, Araya J, Rodrigo R, Signorini C, Sgherri C, Comporti M, et al. Effects of weight loss on liver and erythrocyte polyunsaturated fatty acid pattern and oxidative stress status in obese patients with nonalcoholic fatty liver disease. *Biol Res* 2008;41:59–68.
40. Joensen AM, Overvad K, Dethlefsen C, Johnsen SP, Tjonneland A, Rasmussen LH, et al. Marine n-3 polyunsaturated fatty acids in adipose tissue and the risk of acute coronary syndrome. *Circulation* 2011;124:1232–8.
41. Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012;56:944–51.
42. Sawada N, Inoue M, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, et al. Consumption of n-3 fatty acids and fish

reduces risk of hepatocellular carcinoma. *Gastroenterology* 2012;142:1468–75.
43. Schwingshackl L, Hoffmann G. Monounsaturated fatty acids and risk of cardiovascular disease: synopsis of the evidence available from systematic reviews and meta-analyses. *Nutrients* 2012;4:1989–2007.
44. Bessesen DH, Vensor SH, Jackman MR. Trafficking of dietary oleic, linolenic, and stearic acids in fasted or fed lean rats. *Am J Physiol Endocrinol Metab* 2000;278:E1124–32.
45. Bozzetto L, Prinster A, Annuzzi G, Costagliola L, Mangione A, Vitelli A, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. *Diabetes Care* 2012;35:1429–35.
46. Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, et al. A prospective study of trans fatty acids in erythrocytes and risk of coronary heart disease. *Circulation* 2007;115:1858–65.
47. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010;7:e1000252.
48. Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. *Hepatology* 2003;37:909–16.
49. Obara N, Fukushima K, Ueno Y, Wakui Y, Kimura O, Tamai K, et al. Possible involvement and the mechanisms of excess transfatty acid consumption in severe NAFLD in mice. *J Hepatol* 2010;53:326–34.
50. Ioannou GN, Morrow OB, Connole ML, Lee SP. Association between dietary nutrient composition and the incidence of cirrhosis or liver cancer in the United States population. *Hepatology* 2009;50:175–84.
51. Van Rooyen DM, Larter CZ, Haigh WG, Yeh MM, Ioannou G, Kuver R, et al. Hepatic free cholesterol accumulates in obese, diabetic mice and causes nonalcoholic steatohepatitis. *Gastroenterology* 2011;141:1393–403, 403 e1–5.
52. Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med* 2010;363:2102–13.
53. Fung TT, van Dam RM, Hankinson SE, Stampfer M, Willett WC, Hu FB. Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. *Ann Intern Med* 2010;153:289–98.
54. Sluijs I, Beulens JW, van der AD, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care* 2010;33:43–8.
55. Bryan NS. Letter by Bryan regarding article, "Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis". *Circulation* 2011;123:e16, author reply e7.
56. Bernstein AM, Sun Q, Hu FB, Stampfer MJ, Manson JE, Willett WC. Major dietary protein sources and risk of coronary heart disease in women. *Circulation* 2010;122:876–83.
57. Kechagias S, Ernersson A, Dahlqvist O, Lundberg P, Lindstrom T, Nystrom FH. Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. *Gut* 2008;57:649–54.
58. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med* 2011;364(25):2392–404.
59. Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with nonalcoholic fatty liver disease. *J Hepatol* 2013;59: 138–43.
60. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
61. US Department of Agriculture. Website. http://www.choosemyplate.gov. Accessed June 20, 2014.