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REVIEW

Olive oil consumption and non-alcoholic fatty liver disease

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Abstract

The clinical implications of non-alcoholic fatty liver diseases (NAFLD) derive from their potential to progress to fibrosis and cirrhosis. Inappropriate dietary fat intake, excessive intake of soft drinks, insulin resistance and increased oxidative stress results in increased free fatty acid delivery to the liver and increased hepatic triglyceride (TG) accumulation. An olive oil-rich diet decreases accumulation of TGs in the liver, improves postprandial TGs, glucose and glucagon-like peptide-1 responses in insulin-resistant subjects, and upregulates glucose transporter-2 expression in the liver. The principal mechanisms include: decreased nuclear factor-kappaB activation, decreased low-density lipoprotein oxidation, and improved insulin resistance by reduced production of inflammatory cytokines (tumor necrosis factor, interleukin-6) and improvement of jun N-terminal kinase-mediated phosphorylation of insulin receptor substrate-1. The beneficial effect of the Mediterranean diet is derived from monounsaturated fatty acids, mainly from olive oil. In this review, we describe the dietary sources of the monounsaturated fatty acids, the composition of olive oil, dietary fats and their relationship to insulin resistance and postprandial lipid and glucose responses in non-alcoholic steatohepatitis, clinical and experimental studies that assess the relationship between olive oil and NAFLD, and the mechanism by which olive oil ameliorates fatty liver, and we discuss future perspectives.

Key words: Liver steatosis; Fatty liver; Olive oil; Fatty acids; Monounsaturated; Non-alcoholic steatohepatitis; Lipids; Oleic acid; Non-alcoholic fatty liver disease

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) occur in 10%-24% of the general population[1]. The potential to progress to fibrosis (20%-40%), cirrhosis (30%) and hepatocellular carcinoma[1-3] makes these conditions clinically important. Obesity, diabetes, hyperlipidemia, and the intake of soft drink beverages are risk factors frequently associated with NAFLD[4,5].

The pathogenesis of NASH includes insulin resistance, increased inflammation, tumor necrosis factor (TNF)-α, interleukin (IL)-6 and increased oxidative stress[6]. The etiologic mechanism of NAFLD includes increased influx of free fatty acids (FFAs) to the liver from dietary triglycerides (TGs) and from FFAs that are released from adipocytes during fasting, reduced FFA β-oxidation, reduced hepatic secretion of TG-rich very low density lipoprotein (VLDL), and increased lipid peroxidation[6]. An impaired postprandial TG response has been recently reported in patients with NASH and may play a pathophysiologic role by favoring TG accumulation in the liver[7].

Diet and nutrition, in particular the amount and type of fat intake, has been linked to insulin resistance, an increased risk of developing type 2 diabetes and impaired postprandial lipid metabolism[8,9]. In addition, animal models and human studies suggest that dietary factors can affect fatty infiltration and lipid peroxidation in various types of liver disease including NAFLD[10,11]. More recently, increased ingestion of soft drinks was found to be linked to NAFLD[5]. Although few studies of the effects of different diets on NAFLD have been performed in humans, a Mediterranean diet has been proposed for the prevention of metabolic syndrome, hypertension and cardiovascular disease[12]. The major

part of its beneficial effect is a high supply of energy coming from monounsaturated fatty acids (MUFAs), mainly from olive oil. The principle fatty acid esters present in normal liver are palmitate (16:0) and oleate (18:1 n-9). In patients with alcoholic fatty liver, the proportion of linoleate (C18:2 n-6) and linolenic acid (C18:3 n-3) decreases and the proportion of oleate (C18:1 n-9) increases compared with diabetics with fatty liver and control subjects who underwent liver biopsies[13].

In this review, we describe dietary habits and their relationship to insulin resistance and postprandial glucose and TG levels in NASH, the mechanism by which olive oil ameliorates fatty liver, experimental and clinical studies of olive oil and NAFLD, and future perspectives.

COMPOSITION OF OLIVE OIL

Each 100 g of olive oil contains the following fatty acids: MUFA 73.7 g (n-9 oleic acid 18:1); saturated fatty acids (SFA) 13.5 g (16:0 palmitic acid); polyunsaturated fatty acids (PUFA) 7.9 g (n-6 linoleic acid 18:2, and n-3 alpha-linoleic acid 18:3)[14].

MUFAs include palmitic (C16:1), oleic (C18:1), elaidic (C18:1) and vacentic acids (C18:1). The most abundant MUFA in the diet is oleic acid (C18:1 n-9)[15]. In Mediterranean countries, the main source of MUFA is olive oil (74 g/100 g). Other oil sources of MUFAs are canola (59 g/100 g), peanut (46 g/100 g), sunflower (32 g/100 g), corn (29 g/100 g), soybean (24 g/100 g) and safflower oils (14 g/100 g)[16]. Additionally, new oil variants, rich in oleic acid have been developed including high-oleic acid sunflower oil (84 g/100 g) and high oleic acid safflower oil (74 g/100 g)[17]. In addition to a high MUFA content, virgin (unrefined) olive oil contains a significant amount of antioxidants and α-tocopherol and phytochemicals. However, when refined or heated, olive oil loses these natural compounds[18].

Olive oil is graded according to its acidity. Extra virgin olive oil, the first pressed oil, having maximum free acidity, contains an abundance of squalene and phenolic antioxidants including simple phenols (hydroxytyrosol, tyrosol), aldehydic secoiridoids, flavonoids and lignans (acetoxypinoresnol, pinoresinol). Interestingly, it contains significantly higher concentrations of phenolic antioxidants and squalene than refined virgin and seed oils. In addition, seed oils, which contain very low amounts of squalene, have none of the phenolic antioxidants that are present in virgin and refined olive oils[19]. The exact composition of olive oil depends not only on the growth conditions in the year preceding the harvest, but also on the degree of ripeness of the fruit and the technical processing (cold pressing, refining)[20].

PATHOPHYSIOLOGY OF NAFLD, DIETARY FAT AND HEPATIC LIPIDS

Fat metabolism in fatty liver

Excessive inappropriate dietary fat intake combined with peripheral insulin resistance, continued TG hydrolysis *via* lipoprotein lipase and other genetic alterations in key lipid metabolic pathways results in increased blood FFA concentration[21] leading to excessive muscle fat accumulation and increased liver concentration of TG and cholesterol esters. High blood TG concentration in the form of VLDL tends to accompany this condition and induces cholesterol ester transfer protein activity, resulting in an increased transfer of TG from VLDL to high density lipoprotein (HDL) and a subsequent increase in HDL clearance and decreased HDL concentration[21].

Insulin resistance in fatty liver

Peripheral insulin resistance affects carbohydrate and fat metabolism causing TG accumulation in the liver. Resistance to insulin stimulation of glucose uptake *via* glucose transporter-4 by skeletal muscle and adipose tissue, in conjunction with the inhibition of lipolysis in adipose tissue by insulin, diverts glucose to the liver where the insulin continues to stimulate de novo lipogenesis and increase the flux of fatty acids from adipose tissue to the liver[6,22]. As a result, the liver TG concentration increases. It is unclear how impairment in lipid export *via* VLDL secretion, β-oxidation of FFAs, or other metabolic pathways result in an inability to maintain fat balance, which leads to the development of fatty liver[22].

Fat induces hepatic insulin resistance

The mechanism underlying fat-induced hepatic insulin resistance is not understood. Recent evidence points to an accumulation of fat metabolites (IL-6, TNF-α) that activate various signal transduction pathways, such as serine/threonine kinases, i.e. protein kinase-C (PKC), c-JUN NH2-terminal kinase-1, (JNK) and inhibitor of kappa B kinase, as a key event in the pathway of fat-induced hepatic insulin resistance. Downstream effects include: nuclear factor-kappaB (NF-κB) and activator protein-1 translocation to the nucleus resulting in increased production of inflammatory cytokines which inhibit insulin action[6,23] (Figure 1). Under conditions of insulin resistance, excess lipid metabolites such as diacylglycerol can cause insulin resistance by activating PKC which binds to the insulin receptor and inhibits its tyrosine kinase activity. The activation of PKC may also interfere with the ability of insulin to phosphorylate insulin receptor substrate-2[24].

Relationships among dietary habits, insulin resistance, postprandial lipemia and fatty liver

In the setting of excessive dietary fat intake, high levels of FFAs are delivered to the liver. Hepatocyte stimulation by FFAs leads to the intracellular translocation of Bax to the lysosome. Lysosomal permeability is increased, leading to release of cathepsin B. The presence of capthepsin B in the cytosol causes NF-κB translocation into the nucleus with increased production and release of TNF-α which inhibits insulin action. Cathepsin B also induces mitochondrial dysfunction leading to hepatocyte apoptosis and progression from fatty liver to

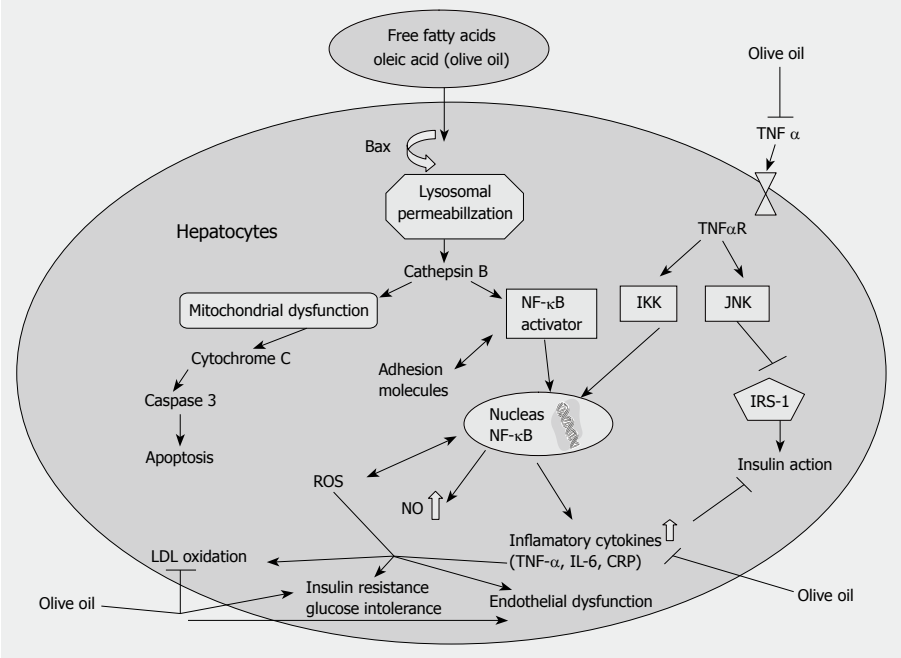

Figure 1 Molecular mechanism of the benefit of oleic acid in NAFLD. Increased levels of TNF-α leads to activation of stress-related protein kinases (IKKβ, JNK) which induce NF-κB translocation to the nucleus, resulting in increased production of inflammatory cytokines and reduced insulin sensitivity. Insulin sensitivity is further impaired by JNK-mediated phosphorylation of IRS-1. In the postprandial setting or after excessive inappropriate dietary intake, free fatty acids are delivered to the liver, taken up and accumulated in hepatocytes. This leads to the intracellular translocation of Bax to the lysosomes which leads to increased cathepsin B. This causes NF-κB translocation to the nucleus with increased production and release of TNF-α and increased insulin resistance. Cathepsin B also causes mitochondrial dysfunction leading to hepatocyte apoptosis and progression to NASH. The role of olive oil in decreasing NF-κB activation, decreasing LDL oxidation and in improving insulin resistance is illustrated.

steatohepatitis (Figure 1)[25].

An impaired postprandial TG response has been reported in patients with NASH. This may promote the infiltration of fat into the liver by increasing TG uptake in the postprandial period[26]. Enhanced lipogenesis appears as a prominent abnormality of hepatic fatty metabolism in subjects with NASH; the contribution of hepatic lipogenesis to TG secretion was 3 × higher in patients with NAFLD as compared to healthy controls[27]. NASH patients had significantly higher overnight fasting glucose or FFAs than controls, as well as higher saturated and monounsaturated levels in both studied lipid fractions, mainly due to an increase in palmitate, palmitoleate and oleic acids[28]. NASH patients showed depletion of PUFAs (n-3 and n-6) in liver triglycerols. This results from defective PUFA desaturation or from a higher lipid peroxidation[28]. The diet of NAFLD patients who were free of hyperlipidemia, diabetes and obesity was richer in saturated fat and poorer in PUFAs[29]. Finally, a MUFA-rich diet improves postprandial glucose, lipid and glyp-1 responses in insulin-resistant subjects. Ingestion of an olive oil-based breakfast decreased postprandial glucose and insulin levels[30].

DIETARY MUFAs AND NAFLD: HUMAN STUDIES

The beneficial effect of MUFAs such as those found in olive oil, nuts and avocados, on risk of cardiovascular disease and on lipid profile has been studied[31]. Dietary MUFA (oleic acid) decreased oxidized LDL[32,33], LDL cholesterol and TG concentration without the concomitant decrease in HDL[34,35]. Additionally, replacement of carbohydrate and saturated fat with MUFAs led to a reduction in glucose and blood pressure and to an increase in HDL in patients with diabetes[36]. A MUFA-rich diet (40% of energy as fat), also decreased VLDL cholesterol and VLDL triglycerol and was more acceptable to patients with non insulin-dependent diabetes mellitus (NIDDM) than was a higher carbohydrate diet (28% of energy as fat)[37]. A meta-analysis of studies in individuals with diabetes showed that a high fat diet with 22%-33% of the energy from MUFAs resulted in lower plasma total cholesterol, VLDL, and TG levels than did a low fat, high carbohydrate (49%-60% energy) diet[38]. Therefore, an increase in intake of MUFAs, particularly as a replacement for SFA and as a higher proportion in the diet, instead of carbohydrate, may be beneficial for NAFLD patients. It has been demonstrated that consumption of MUFAs decreases blood TGs by increasing fatty acid oxidation through activation of peroxisome proliferator-activated receptor (PPAR)α or by reducing the activation of sterol regulatory element binding protein (SREBP) and inhibiting lipogenesis. Dietary MUFAs activate PPARα and PPARγ, increasing lipid oxidation, and decreasing insulin resistance leading to a reduction in hepatic steatosis[39].

NAFLD, hypertension and hypertriglyceridemia are major components of metabolic syndrome. Four clinical studies have documented the beneficial effect of MUFAs in decreasing blood pressure[40-43]. Moreover, another 6 dietary trials assessing the effect of MUFA intake on blood pressure showed beneficial effects[44]. Although there are some inconsistencies in these studies, MUFA from olive oil in the context of the Mediterranean diet, plays a role in the primary prevention of NAFLD.

DIETARY MUFAs AND NAFLD: ANIMAL STUDIES

Recently, the authors evaluated the effect of different types of dietary fats on the hepatic lipid content and oxidative stress parameters in the livers of rats with

Table 1 Effect of olive oil on percentage of fatty acids in rat liver

Fatty acid components	Control	MCDD	MCDD + olive oil
C14:0 myristic	0.2 ± 0.2	0.5 ± 0.1	0.3 ± 0.2
C16:0 palmitic	19 ± 1	17 ± 1.1	15.3 ± 1.4
C16:1 palmitoleic	0.1 ± 0.2	0.7 ± 0.1	0.4 ± 0.2
C18:0 Stearic	21.8 ± 1.6	5.8 ± 0.6	5.7 ± 0.7
C18:1n9t elaidic	2.1 ± 0.1	1.5 ± 1.3	22.8 ± 1.3
C18:1n9c oleic	4.9 ± 0.8	20.7 ± 0.7	25.9 ± 3.3
C18:2n6c linolelaidic	18.6 ± 1.8	32.4 ± 0.7	30.5 ± 1.7
C18:3n3 linolenic	0.5 ± 0.3	0.3 ± 0.1	0.2 ± 0.2
C23:0 tricosanoic	22.0 ± 2.4	10.0 ± 1.1	7.8 ± 2.1
C20:4n6 arachidonic	0.1 ± 0.2	0	9.2 ± 0.6
C22:6n3 docosahexaenoic	4.5 ± 0.9	1.3 ± 0.5	1.2 ± 0.4
C20:5n3 eicosapentaenoic	0	0.1 ± 0.1	0

Enrichment of a MCDD by olive oil increases the oleic acid, long chain PUFA n6:n3 ratio, and arachidonic acid percentages in the rat livers. Data from reference 39.

Table 2 Mechanisms of action of olive oil on fatty liver

Mechanism	Component involved
Anti-inflammatory and immunomodulatory effects	Oleic acid Phenolic compounds
Anti-oxidants:	Oleic acid
Decrease lipid peroxidation Decrease oxidative DNA damage	Phenolic compounds: hydroxytyrosol, oleuropein, caffeic acid, o-coumaric acid, vanillic acid, and 3,4-dihydroxyphenylethanol (3,4-DHPEA).
Modulation of transduction pathways:	Oleic acid
Decreases arachidonic acid	Phenolic compounds: protocatecuic acid
Inhibits lipooxygenase	Hydroxytyrosol
Inhibits HMG-CoA reductase	Squalene
Decreases RAS activation	Squalene
Regulation of gene expression in liver regeneration: (Oleic acid inhibits δ6-desaturase which decreases PGE2 and inhibits liver regeneration)	Oleic acid Minor compounds
Change in membrane fluidity and membrane peroxidation (estrogen modulator, regulates G protein)	Oleic acid Lignans

experimental NAFLD[45]. The study demonstrated that olive oil decreases the accumulation of TGs in the liver of rats. Severe fatty liver was seen in methionine-choline deficient diet (MCDD), MCDD + fish oil and in MCDD + butter fat groups, but not in the MCDD + olive oil group. The hepatic TG increase in the MCDD + olive oil group was blunted by 30% compared with the MCDD group. The serum TG increase was 10% lower in the MCDD + olive oil group compared with the MCDD group. In comparison with the control group, the long chain PUFA n6:n3 ratio increased in the MCDD + olive oil group by 345-fold (Table 1). Olive oil improved insulin resistance, increased the release of TG from the liver and decreased the flux of FFAs from peripheral adipose tissue back to the liver[45]. A study from Spain showed that treatment with a balanced diet rich in olive oil contributed to the recovery of the liver from hepatic steatosis[46]. This was achieved by decreasing activation of hepatic stellate cells by MUFAs, which are less susceptible to lipid peroxidation compared to PUFAs. Moreover, previous studies carried out in fibrotic rats showed that olive oil, in contrast to polyunsaturated oils, could protect against the development of fibrosis[47]. In animal studies, saturated fat significantly increased insulin resistance, long and short chain omega-3 fatty acids improved it, and the effect of MUFAs and omega-6 polyunsaturated acids ranged somewhere between the two[48]. In humans, shifting from a diet rich in SFA to one rich in MUFAs improved insulin sensitivity in healthy people[49]. A MUFA-rich diet prevented central body fat distribution, improved insulin sensitivity and increased postprandial adiponectin expression compared to a carbohydrate-rich diet (with similar caloric intake) in insulin-resistant subjects[50]. Furthermore, fasting plasma leptin fell during a MUFA-rich diet and has been associated with improved insulin action[51]. Weight maintenance with a MUFA-rich diet improved homeostasis model assessment (HOMA) and fasting pro-insulin levels in insulin-resistant subjects. Ingestion of a virgin olive oil-based breakfast decreased postprandial glucose, triacylglycerol, and insulin concentrations, and increased HDL cholesterol and glucagon-like peptide-1 (GLP-1) concentrations as compared with a carbohydrate-rich diet[50,52]. The Mediterranean diet elicits a less prothrombotic environment by modifying different hemostatic components, such as platelet aggregation, fibrinogen, Von Willebrand factor, plasma factor Ⅶ, tissue factor and plasminogen activator inhibitor type 1 plasma levels. The postprandial increase in activated factor Ⅶ is reduced by the intake of virgin olive oil in comparison with saturated fat[53].

THE SPECIAL MECHANISM OF OLIVE OIL

Olive oil has traditionally been the principal oil of the Mediterranean diet. The MUFA diet prevents central body fat accumulation and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects[50,54]. Mechanistic studies show a direct beneficial role for olive oil in improving plasma lipids in the treatment of metabolic syndrome[44]. Unrefined or virgin olive oil has bioactive compounds with beneficial antioxidants action (Table 2)[48]. Oleocanthal, a component found in extra virgin olive oil, is a natural anti-inflammatory compound that has a potency and profile strikingly similar to that of ibuprofen[55]. The exact mechanism through which MUFAs and olive oil could modify hepatic TG content is not clear. Oleic acid from cooking oil was associated with lower insulin resistance in the general population[56]. An olive oil-enriched diet contributes to redistribution of body fat and modifies the lipolytic efficiency of fat cells[57]. Furthermore, n-9 fatty acids may regulate gene expression related to peripheral insulin sensitivity[58],

increased endothelial vasoreactivity[59], up-regulation of uncoupling protein mRNA in adipose tissue and muscle[60], and expression of upregulates glucose transporter-2 in the liver[61]. Oleic acid decreases the expression of genes involved in hepatic gluconeogenesis and lipogenesis and SREBP in Zucker fatty rats[62]. Additional effects of olive oil beyond its MUFA composition relate to its polyphenols. Polyphenols present in olive oil, such as oleuropin, hydroxytyrosol, tyrosol and caffeic acid, have an important antioxidant and anti-inflammatory effect[63,64]. In rat leukocytes, these molecules have been shown to inhibit leukotriene B4 generation at the 5-lipoxygenase level and to reduce the generation of reactive oxygen species[65]. Moreover, a diet rich in olive oil improves endothelial function compared with a high carbohydrate diet or a high linoleic acid diet[66,67]. Finally, the consumption of olive oil as a single item or within a Mediterranean diet showed a significant inverse association with TNF-α and vascular cell adhesion molecule-1 serum levels[68], and improved glycemic tolerance through increased secretion of GLP-1[69]. Moreover, an oleic acid-rich Mediterranean type diet may reduce the risk of atherosclerosis by decreasing the number of chylomicron remnant particles as compared to a linoleic acid-enriched diet[70]. The principal mechanisms of action of olive oil are a decrease in NF-κB activation, a decrease in LDL oxidation and an improvement in insulin resistance (Figure 1).

CONCLUSION

Dietary fat content modifies liver fat in overweight non diabetic subjects[71]. NAFLD patients have a higher postprandial TG response and an increased production of large VLDL after an oral fat load compared with controls, despite normal fasting blood lipid concentration, which suggests that the metabolism of dietary fat is impaired in these individuals[72]. Decreasing total fat consumption and shifting to MUFAs found in olive oil (20%-40% of total energy) or n-3 PUFAs found in fish oil (2 g/d) could lead to a decrease in postprandial lipidemia and steatosis[73]. Further studies in humans are needed to ascertain whether the consumption of olive oil may be helpful in NAFLD patients.

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REFERENCES

1 **Willner IR**, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *Am J Gastroenterol* 2001; **96**: 2957-2961
2 **Bugianesi E**, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; **123**: 134-140
3 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231
4 **Assy N**, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. *Dig Dis Sci* 2000; **45**: 1929-1934
5 **Assy N**, Nasser G, Kamayse I, Nseir W, Beniashvili Z, Djibre A, Grosovski M. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. *Can J Gastroenterol* 2008; **22**: 811-816
6 **Postic C**, Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. *J Clin Invest* 2008; **118**: 829-838
7 **Cassader M**, Gambino R, Musso G, Depetris N, Mecca F, Cavallo-Perin P, Pacini G, Rizzetto M, Pagano G. Postprandial triglyceride-rich lipoprotein metabolism and insulin sensitivity in nonalcoholic steatohepatitis patients. *Lipids* 2001; **36**: 1117-1124
8 **Hu FB**, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 2001; **44**: 805-817
9 **Thomsen C**, Rasmussen O, Lousen T, Holst JJ, Fenselau S, Schrezenmeir J, Hermansen K. Differential effects of saturated and monounsaturated fatty acids on postprandial lipemia and incretin responses in healthy subjects. *Am J Clin Nutr* 1999; **69**: 1135-1143
10 **Mezey E**. Dietary fat and alcoholic liver disease. *Hepatology* 1998; **28**: 901-905
11 **Fernández MI**, Torres MI, Gil A, Ríos A. Steatosis and collagen content in experimental liver cirrhosis are affected by dietary monounsaturated and polyunsaturated fatty acids. *Scand J Gastroenterol* 1997; **32**: 350-356
12 **Martínez-González MA**, Sánchez-Villegas A. The emerging role of Mediterranean diets in cardiovascular epidemiology: monounsaturated fats, olive oil, red wine or the whole pattern? *Eur J Epidemiol* 2004; **19**: 9-13
13 **Cairns SR**, Peters TJ. Biochemical analysis of hepatic lipid in alcoholic and diabetic and control subjects. *Clin Sci* (Lond) 1983; **65**: 645-652
14 **Ramirez-Tortosa MC**, Grandaos S, Quiles JL. Olive Oil and Health. In: Quiles JL, Ramírez-Tortosa C, Yaqoob P, eds. Wallingford: CABI International; 2006: 45-62
15 **Aghdassi E**, Wendland BE, Stapleton M, Raman M, Allard JP. Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. *J Am Diet Assoc* 2007; **107**: 1575-1580
16 **Nicklas TA**, Hampl JS, Taylor CA, Thompson VJ, Heird WC. Monounsaturated fatty acid intake by children and adults: temporal trends and demographic differences. *Nutr Rev* 2004; **62**: 132-141
17 **Cantisán S**, Martínez-Force E, Alvarez-Ortega R, Garcés R. Lipid characterization in vegetative tissues of high saturated fatty acid sunflower mutants. *J Agric Food Chem* 1999; **47**: 78-82
18 **Ros E**. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am J Clin Nutr* 2003; **78**: 617S-625S
19 **Owen RW**, Giacosa A, Hull WE, Haubner R, Würtele G, Spiegelhalder B, Bartsch H. Olive-oil consumption and health: the possible role of antioxidants. *Lancet Oncol* 2000; **1**: 107-112
20 **Hanf V**, Gonder U. Nutrition and primary prevention of breast cancer: foods, nutrients and breast cancer risk. *Eur J Obstet Gynecol Reprod Biol* 2005; **123**: 139-149
21 **Sanyal AJ**, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001; **120**: 1183-1192
22 **Salmenniemi U**, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen K, Vanninen E, Laakso M. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines,

and adhesion molecules in subjects with metabolic syndrome. *Circulation* 2004; **110**: 3842-3848
23 **Park E**, Giacca A. Mechanisms underlying fat-induced hepatic insulin resistance. *Future Lipidol* 2007; **2**: 503-512
24 **Samuel VT**, Liu ZX, Wang A, Beddow SA, Geisler JG, Kahn M, Zhang XM, Monia BP, Bhanot S, Shulman GI. Inhibition of protein kinase Cepsilon prevents hepatic insulin resistance in nonalcoholic fatty liver disease. *J Clin Invest* 2007; **117**: 739-745
25 **Carter-Kent C**, Zein NN, Feldstein AE. Cytokines in the pathogenesis of fatty liver and disease progression to steatohepatitis: implications for treatment. *Am J Gastroenterol* 2008; **103**: 1036-1042
26 **Cooper AD**. Hepatic uptake of chylomicron remnants. *J Lipid Res* 1997; **38**: 2173-2192
27 **Diraison F**, Moulin P, Beylot M. Contribution of hepatic de novo lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease. *Diabetes Metab* 2003; **29**: 478-485
28 **Araya J**, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, Poniachik J. Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clin Sci* (Lond) 2004; **106**: 635-643
29 **Musso G**, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, Fagà E, Silli B, Pagano G. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. *Hepatology* 2003; **37**: 909-916
30 **Paniagua JA**, de la Sacristana AG, Sánchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Perés-Martinez P, López-Miranda J, Pérez-Jiménez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. *J Am Coll Nutr* 2007; **26**: 434-444
31 **Erkkilä AT**, Matthan NR, Herrington DM, Lichtenstein AH. Higher plasma docosahexaenoic acid is associated with reduced progression of coronary atherosclerosis in women with CAD. *J Lipid Res* 2006; **47**: 2814-2819
32 **Lapointe A**, Couillard C, Lemieux S. Effects of dietary factors on oxidation of low-density lipoprotein particles. *J Nutr Biochem* 2006; **17**: 645-658
33 **Fitó M**, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F, Cabezas C, del Carmen López-Sabater M, Marrugat J, García-Arellano A, Arós F, Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI. Effect of a traditional mediterranean diet on lipoprotein oxidation. *Arch Intern Med* 2007; **167**: 1195-1203
34 **Sacks FM**. Dietary fat, the Mediterranean diet, and health: reports from scientific exchanges, 1998 and 2000. Introduction. *Am J Med* 2002; **113** Suppl 9B: 1S-4S
35 **Williams CM**. Beneficial nutritional properties of olive oil: implications for postprandial lipoproteins and factor VII. *Nutr Metab Cardiovasc Dis* 2001; **11**: 51-56
36 **Julius U**. Influence of plasma free fatty acids on lipoprotein synthesis and diabetic dyslipidemia. *Exp Clin Endocrinol Diabetes* 2003; **111**: 246-250
37 **Rodríguez-Villar C**, Pérez-Heras A, Mercadé I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. *Diabet Med* 2004; **21**: 142-149
38 **Garg A**. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* 1998; **67**: 577S-582S
39 **Soriguer F**, Morcillo S, Cardona F, Rojo-Martínez G, de la Cruz Almaráz M, Ruiz de Adana Mde L, Olveira G, Tinahones F, Esteva I. Pro12Ala polymorphism of the PPARG2 gene is associated with type 2 diabetes mellitus and peripheral insulin sensitivity in a population with a high intake of oleic acid. *J Nutr* 2006; **136**: 2325-2330
40 **Williams PT**, Fortmann SP, Terry RB, Garay SC, Vranizan KM, Ellsworth N, Wood PD. Associations of dietary fat, regional adiposity, and blood pressure in men. *JAMA* 1987; **257**: 3251-3256
41 **Trevisan M**, Krogh V, Freudenheim J, Blake A, Muti P, Panico S, Farinaro E, Mancini M, Menotti A, Ricci G. Consumption of olive oil, butter, and vegetable oils and coronary heart disease risk factors. The Research Group ATS-RF2 of the Italian National Research Council. *JAMA* 1990; **263**: 688-692
42 **Alonso A**, Martínez-González MA. Olive oil consumption and reduced incidence of hypertension: the SUN study. *Lipids* 2004; **39**: 1233-1238
43 **Psaltopoulou T**, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2004; **80**: 1012-1018
44 **Alonso A**, Ruiz-Gutierrez V, Martínez-González MA. Monounsaturated fatty acids, olive oil and blood pressure: epidemiological, clinical and experimental evidence. *Public Health Nutr* 2006; **9**: 251-257
45 **Hussein O**, Grosovski M, Lasri E, Svalb S, Ravid U, Assy N. Monounsaturated fat decreases hepatic lipid content in non-alcoholic fatty liver disease in rats. *World J Gastroenterol* 2007; **13**: 361-368
46 **Hernández R**, Martínez-Lara E, Cañuelo A, del Moral ML, Blanco S, Siles E, Jiménez A, Pedrosa JA, Peinado MA. Steatosis recovery after treatment with a balanced sunflower or olive oil-based diet: involvement of perisinusoidal stellate cells. *World J Gastroenterol* 2005; **11**: 7480-7485
47 **Szende B**, Timár F, Hargitai B. Olive oil decreases liver damage in rats caused by carbon tetrachloride (CCl4). *Exp Toxicol Pathol* 1994; **46**: 355-359
48 **Kris-Etherton PM**, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, Griel AE, Etherton TD. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. *Am J Med* 2002; **113** Suppl 9B: 71S-88S
49 **Rivellese AA**, De Natale C, Lilli S. Type of dietary fat and insulin resistance. *Ann N Y Acad Sci* 2002; **967**: 329-335
50 **Paniagua JA**, Gallego de la Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Monounsaturated fat-rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. *Diabetes Care* 2007; **30**: 1717-1723
51 **Ruige JB**, Dekker JM, Blum WF, Stehouwer CD, Nijpels G, Mooy J, Kostense PJ, Bouter LM, Heine RJ. Leptin and variables of body adiposity, energy balance, and insulin resistance in a population-based study. The Hoorn Study. *Diabetes Care* 1999; **22**: 1097-1104
52 **Thomsen C**, Storm H, Holst JJ, Hermansen K. Differential effects of saturated and monounsaturated fats on postprandial lipemia and glucagon-like peptide 1 responses in patients with type 2 diabetes. *Am J Clin Nutr* 2003; **77**: 605-611
53 **Pérez-Jiménez F**, López-Miranda J, Mata P. Protective effect of dietary monounsaturated fat on arteriosclerosis: beyond cholesterol. *Atherosclerosis* 2002; **163**: 385-398
54 **Rodríguez-Villar C**, Manzanares JM, Casals E, Pérez-Heras A, Zambón D, Gomis R, Ros E. High-monounsaturated fat, olive oil-rich diet has effects similar to a high-carbohydrate diet on fasting and postprandial state and metabolic profiles of patients with type 2 diabetes. *Metabolism* 2000; **49**: 1511-1517
55 **Beauchamp GK**, Keast RS, Morel D, Lin J, Pika J, Han Q, Lee CH, Smith AB, Breslin PA. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. *Nature* 2005; **437**: 45-46
56 **Soriguer F**, Esteva I, Rojo-Martinez G, Ruiz de Adana MS, Dobarganes MC, García-Almeida JM, Tinahones F, Beltrán M, González-Romero S, Olveira G, Gómez-Zumaquero JM.

Oleic acid from cooking oils is associated with lower insulin resistance in the general population (Pizarra study). *Eur J Endocrinol* 2004; **150**: 33-39
57 **Soriguer F**, Moreno F, Rojo-Martínez G, García-Fuentes E, Tinahones F, Gómez-Zumaquero JM, Cuesta-Muñoz AL, Cardona F, Morcillo S. Monounsaturated n-9 fatty acids and adipocyte lipolysis in rats. *Br J Nutr* 2003; **90**: 1015-1022
58 **Clark SJ**, Shojaee-Moradie F, Croos P, Seed PT, Umpleby AM, Wendon JA, Miell J. Temporal changes in insulin sensitivity following the development of acute liver failure secondary to acetaminophen. *Hepatology* 2001; **34**: 109-115
59 **Ryan M**, McInerney D, Owens D, Collins P, Johnson A, Tomkin GH. Diabetes and the Mediterranean diet: a beneficial effect of oleic acid on insulin sensitivity, adipocyte glucose transport and endothelium-dependent vasoreactivity. *QJM* 2000; **93**: 85-91
60 **Rodríguez VM**, Portillo MP, Picó C, Macarulla MT, Palou A. Olive oil feeding up-regulates uncoupling protein genes in rat brown adipose tissue and skeletal muscle. *Am J Clin Nutr* 2002; **75**: 213-220
61 **Berry EM**. Dietary fatty acids in the management of diabetes mellitus. *Am J Clin Nutr* 1997; **66**: 991S-997S
62 **Sato K**, Arai H, Mizuno A, Fukaya M, Sato T, Koganei M, Sasaki H, Yamamoto H, Taketani Y, Doi T, Takeda E. Dietary palatinose and oleic acid ameliorate disorders of glucose and lipid metabolism in Zucker fatty rats. *J Nutr* 2007; **137**: 1908-1915
63 **Lampe JW**. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. *Am J Clin Nutr* 1999; **70**: 475S-490S
64 **Covas MI**, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, Gaddi A, de la Torre R, Mursu J, Bäumler H, Nascetti S, Salonen JT, Fitó M, Virtanen J, Marrugat J, EUROLIVE Study Group. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med* 2006; **145**: 333-341
65 **de la Puerta R**, Ruiz Gutierrez V, Hoult JR. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol* 1999; **57**: 445-449
66 **Fuentes F**, López-Miranda J, Sánchez E, Sánchez F, Paez J, Paz-Rojas E, Marín C, Gómez P, Jimenez-Perepérez J, Ordovás JM, Pérez-Jiménez F. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. *Ann Intern Med* 2001; **134**: 1115-1119
67 **Esposito K**, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004; **292**: 1440-1446
68 **Serrano-Martinez M**, Palacios M, Martinez-Losa E, Lezaun R, Maravi C, Prado M, Martínez JA, Martinez-Gonzalez MA. A Mediterranean dietary style influences TNF-alpha and VCAM-1 coronary blood levels in unstable angina patients. *Eur J Nutr* 2005; **44**: 348-354
69 **Rocca AS**, LaGreca J, Kalitsky J, Brubaker PL. Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. *Endocrinology* 2001; **142**: 1148-1155
70 **Madigan C**, Ryan M, Owens D, Collins P, Tomkin GH. Dietary unsaturated fatty acids in type 2 diabetes: higher levels of postprandial lipoprotein on a linoleic acid-rich sunflower oil diet compared with an oleic acid-rich olive oil diet. *Diabetes Care* 2000; **23**: 1472-1477
71 **Yki-Järvinen H**. Fat in the liver and insulin resistance. *Ann Med* 2005; **37**: 347-356
72 **Bergman RN**, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* 2000; **11**: 351-356
73 **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

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