Olive oil consumption and 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[2-3] 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[7]. 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[8].

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[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[12]. 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 benefits of the Mediterranean diet is derived from monounsaturated fatty acids, mainly from olive oil.
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. 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: MUFAs 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-linolenic acid 18:3). MUFAs include palmitic (C16:1), oleic (C18:1), elaidic (C18:1) and vaccenic acids (C18:1). The most abundant MUFA in the diet is oleic acid (C18:1 n-9). 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).[13] 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).[13] 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.[13]

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 (acetoxypinoresinol, pinoresinol). Interestingly, it contains significantly higher concentrations of phenolic antioxidants and squalene than refined virgin and refined olive oils.[13] Olive oils lose these natural compounds during the technical processing (cold pressing, refining) in the production of oils.

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 cathepsin 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 NASH, the mechanism by which olive oil ameliorates fatty liver, experimental and clinical studies of olive oil and NAFLD, and future perspectives.

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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 triglycerides. 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)\[^{39}\] or by reducing the activation of sterol regulatory element binding protein (SREBP) and inhibiting lipogenesis. Dietary MUFAs activate PPAR\[^{\alpha}\] and PPAR\[^{\gamma}\], increasing lipid oxidation, and decreasing insulin resistance leading to a reduction in hepatic steatosis\[^{40}\].

NAFLD, hypertension and hypertriglyceridemia are major components of metabolic syndrome. Four clinical studies have documented the beneficial effect of MUFAs in decreasing blood pressure\[^{41-43}\]. 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, MUFAs 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...
Experimental NAFLD\cite{43}. 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\cite{43}. 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\cite{39}. This was achieved by decreasing activation of hepatic stellate cells by MUFAs, which are less susceptible to lipid peroxidation compared to PUFA. Moreover, previous studies carried out in fibrotic rats showed that olive oil, in contrast to polysaturated oils, could protect against the development of fibrosis\cite{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 polysaturated acids ranged somewhere between the two\cite{48}. In humans, shifting from a diet rich in SFA to one rich in MUFAs improved insulin sensitivity in healthy people\cite{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\cite{50}. Furthermore, fasting plasma leptin fell during a MUFA-rich diet and has been associated with improved insulin action\cite{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\cite{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 \textit{V}, tissue factor and plasminogen activator inhibitor type 1 plasma levels. The postprandial increase in activated factor \textit{V} is reduced by the intake of virgin olive oil in comparison with saturated fat\cite{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\cite{50,54}. Mechanistic studies show a direct beneficial role for olive oil in improving plasma lipids in the treatment of metabolic syndrome\cite{54}. Unrefined or virgin olive oil has bioactive compounds with beneficial antioxidants action (Table 2)\cite{56}. 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\cite{55}. The exact mechanism through which MUFA 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\cite{56}. An olive oil–enriched diet contributes to redistribution of body fat and modifies the lipolytic efficiency of fat cells\cite{57}. Furthermore, n-9 fatty acids may regulate gene expression related to peripheral insulin sensitivity\cite{58}.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Effect of olive oil on percentage of fatty acids in rat liver</th>
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<tbody>
<tr>
<td>Fatty acid components</td>
<td>Control</td>
</tr>
<tr>
<td>C14:0 myristic</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>C16:0 palmitic</td>
<td>19 ± 1</td>
</tr>
<tr>
<td>C16:1 palmitoleic</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>C18:0 Stearic</td>
<td>21.8 ± 1.6</td>
</tr>
<tr>
<td>C18:1n9 elaidic</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>C18:2n6 oleic</td>
<td>4.9 ± 0.8</td>
</tr>
<tr>
<td>C18:2n6 linolealaidic</td>
<td>18.6 ± 1.8</td>
</tr>
<tr>
<td>C18:3n3 linolenic</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>C22:0 tricosanoic</td>
<td>22.0 ± 2.4</td>
</tr>
<tr>
<td>C22:6n3 arachidonic</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>C22:6n3 docosahexaenoic</td>
<td>4.5 ± 0.9</td>
</tr>
<tr>
<td>C20:5n3 eicosapentaenoic</td>
<td>0</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Table 2</th>
<th>Mechanisms of action of olive oil on fatty liver</th>
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<tbody>
<tr>
<td>Mechanism</td>
<td>Component involved</td>
</tr>
<tr>
<td>Anti-inflammatory and immunomodulatory effects</td>
<td>Oleic acid</td>
</tr>
<tr>
<td>Anti-oxidants</td>
<td>Oleic acid</td>
</tr>
<tr>
<td>Decrease lipid peroxidation</td>
<td>Phenolic compounds</td>
</tr>
<tr>
<td>Decrease oxidative DNA damage</td>
<td>Hydroxytyrosol, oleuropein, caffeic acid, o-coumaric acid, vanillic acid, and 3,4-dihydroxyphenylethanol (3,4-DHPEA).</td>
</tr>
<tr>
<td>Modulation of transduction pathways:</td>
<td>Oleic acid</td>
</tr>
<tr>
<td>Decreases arachidonic acid</td>
<td>Phenolic compounds: protocateucic acid</td>
</tr>
<tr>
<td>Inhibits lipoxygenase</td>
<td>Hydroxytyrosol</td>
</tr>
<tr>
<td>Inhibits HMG-CoA reductase</td>
<td>Squalene</td>
</tr>
<tr>
<td>Decreases RAS activation</td>
<td>Squalene</td>
</tr>
<tr>
<td>Regulation of gene expression in liver regeneration:</td>
<td>Oleic acid</td>
</tr>
<tr>
<td>Minor compounds</td>
<td>(Oleic acid inhibits 66-desaturase which decreases PGE2 and inhibits liver regeneration)</td>
</tr>
<tr>
<td>Change in membrane fluidity and membrane peroxidation (estrogen modulator, regulates G protein)</td>
<td>Oleic acid</td>
</tr>
</tbody>
</table>

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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 oleuropein, 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-\(\alpha\) 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-\(\kappa B\) 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 MUFA's found in olive oil (20\%-40\% of total energy) or n-3 PUFA's 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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