Editorial

Ad libitum Mediterranean or low fat diets as treatments for non-alcoholic fatty liver disease?

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The 2016 European Society of Cardiology guidelines recommended a total fat intake of ≤30% of which ≤10% should consist of saturated fats to reduce risk of cardiovascular disease (CVD) (1). These guidelines also suggested decreasing saturated fat intake by substitution with polyunsaturated fatty acids (1). In June 2017, the American Heart Association's presidential advisory on dietary fats stated that replacing saturated fat with polyunsaturated vegetable oil reduces the incidence of CVD by ~30% (2). Importantly, this shift from saturated to unsaturated fats occurs when a Westernised diet containing processed foods is replaced by the Mediterranean diet (MD) (2). Traditionally, the MD contains an abundance of plant foods, including legumes, vegetables, fruits, nuts, grains and fish (3). Several observational cohort studies and some randomized clinical trials (RCT) have suggested that MD reduces the incidence of CVD (3).

Currently, there are no licensed pharmacological agents for the treatment of non-alcoholic fatty liver disease (NAFLD). Lifestyle changes, including hypocaloric diet and increases in physical activity, are and should be the first line of treatment in NAFLD (4). Weight loss is beneficial in NAFLD and Vilar *et al*. reported a dose-response relationship between percentage weight loss and histological changes in non-alcoholic steatohepatitis (NASH); with the greatest reduction among individuals with the most weight loss (5). Accordingly, the 2016 EASL–EASD–EASO Clinical Practice Guidelines (6) recommended that in overweight/obese patients with NAFLD, a 7–10% weight loss is the goal of most lifestyle interventions, and results in improvements of both serum liver enzymes and liver histology.

Considering the current evidence, recommending MD for patients with NAFLD might be an appropriate therapeutic option (7), not least because patients with NAFLD are at increased risk of CVD (6). However, the evidence that the MD is beneficial in NAFLD is based on a few observational studies and small, short-term RCTs (7). Currently, MD is also recommended by the EASL–EASD–EASO Clinical Practice Guidelines for NAFLD (Grade: B1) (6). The MD is particularly attractive in NAFLD as it may benefit the liver, independently of concomitant weight loss (4,7).

Data from two small, short-term RCTs has suggested a potential beneficial effect of MD on NAFLD (8,9). In a randomized parallel-group design trial (8), 45 patients with type 2 diabetes were assigned to two 8-week isocaloric diets: either a high-carbohydrate/fiber diet or a high-monounsaturated fatty acids (MUFA) diet. Liver fat content, measured by magnetic resonance spectroscopy (MRS), decreased more in the MUFA group (−29%) than in the high

carbohydrate/fiber group (−4%), despite no weight loss in both groups. In the other randomised cross-over 6-week trial enrolling 12 nondiabetic subjects with NAFLD, who were assigned to two isocaloric diets (MD *vs*. standard low fat/high carbohydrate diet) (9), there was a significant relative reduction in hepatic steatosis after the MD compared with the low fat/high carbohydrate diet (-39% *vs*. -7% as measured by MRS), despite modest weight loss that was not different between the two diets.

The findings of Properzi *et al*. (10) add additional information to the body of evidence supporting dietary changes in NAFLD. The authors show that *ad libitum* isocaloric MD and low fat diets (LFD) are equally effective in reducing liver fat content (measured by MRS) in NAFLD. In a randomized parallel-group design trial of 51 middle-aged obese (mean BMI 31 kg/m^2) individuals with NAFLD, who were randomly assigned to a 12-week single-blinded dietary intervention (MD or LFD; with a daily energy intake of nearly 2,400-2,600 kCal for both diets during the trial), the authors showed that hepatic steatosis decreased significantly in both groups, and there was no significant difference in the mean percentage reductions in liver fat content following the MD compared with the LFD (-32.4% *vs*. -25%). Similarly, there was no difference in NAFLD resolution following adjustment for baseline hepatic fat content between the two groups. Weight loss was minimal (nearly 1.5-2 kg) and not different between the two groups, although there was a small reduction in waist circumference (~3 and ~4 cm decrease), and an increase in physical activity energy expenditure (~14 MET-h/week and ~15 MET-h/week increase) for the low fat and MD diets, respectively. Notably, diet adherence was higher with the MD than with the LFD (88% *vs*. 64%); and among the secondary outcomes, the authors found that the Framingham risk score, plasma lipids and hemoglobin A1c improved significantly from baseline in the MD group only. No differences were also observed between, or within groups, in markers of insulin resistance, and measures of both arterial stiffness and liver stiffness (as assessed by Fibroscan) (10).

Collectively, although some of the benefits on liver fat may have been due to a small decrease in abdominal adiposity (visceral fat mass) and an increase in physical activity energy expenditure, we consider that these findings are clinically relevant for patients with NAFLD and provide support for the view that both MD and LFD have the potential to improve hepatic steatosis (by approximately -25% to -30%), even in the absence of significant weight reduction (10). There are some differences in the benefits conferred by the MD versus the LFD on cardiometabolic risk factors, as

illustrated in the linked paper (10). Furthermore, the dietary components (or the absence of some dietary factors) that contribute to the benefit of either diet in NAFLD remain unclear. Nevertheless, in **Fig. 1**, we have suggested some of the dietary factors (or the absence of factors) that could mediate the beneficial effects of MD and LFD on NAFLD and associated cardiometabolic risk factors. We have also speculated how these two diets might favourably influence certain pathways involving the intestine, adipose tissue and liver, to mediate benefits in NAFLD.

Despite these promising results, we believe that longer-term RCTs are needed, preferably with histological liver outcomes to test whether there is any benefit on NASH and/or hepatic fibrosis. It has to be stressed that in most cases any form of healthy diet (e.g. LFD or MD), which leads to caloric reduction and is acceptable to the patient, should be encouraged for patients with NAFLD. For the patient who finds caloric restriction difficult, changing dietary composition without necessarily reducing caloric intake could offer a more feasible alternative, although the benefit on liver health is not as marked as weight reduction alone (4,6). The importance of weight loss has been highlighted in patients with NASH, where weight loss *per se* is able to induce NASH resolution, without any worsening of fibrosis (5). If the MD is also effective in causing resolution of NASH, a weight-reduction-centered approach ("weight-normative") could be replaced in some patients with a healthy-behaviors-centered approach ("weight-inclusive").

That said, the evidence from this and other RCTs strongly supports the role of dietary changes as a primary therapy in NAFLD treatment. The question is no longer, is dietary change an effective therapy; rather, how can we ensure patient adherence to beneficial changes in their diet in NAFLD.

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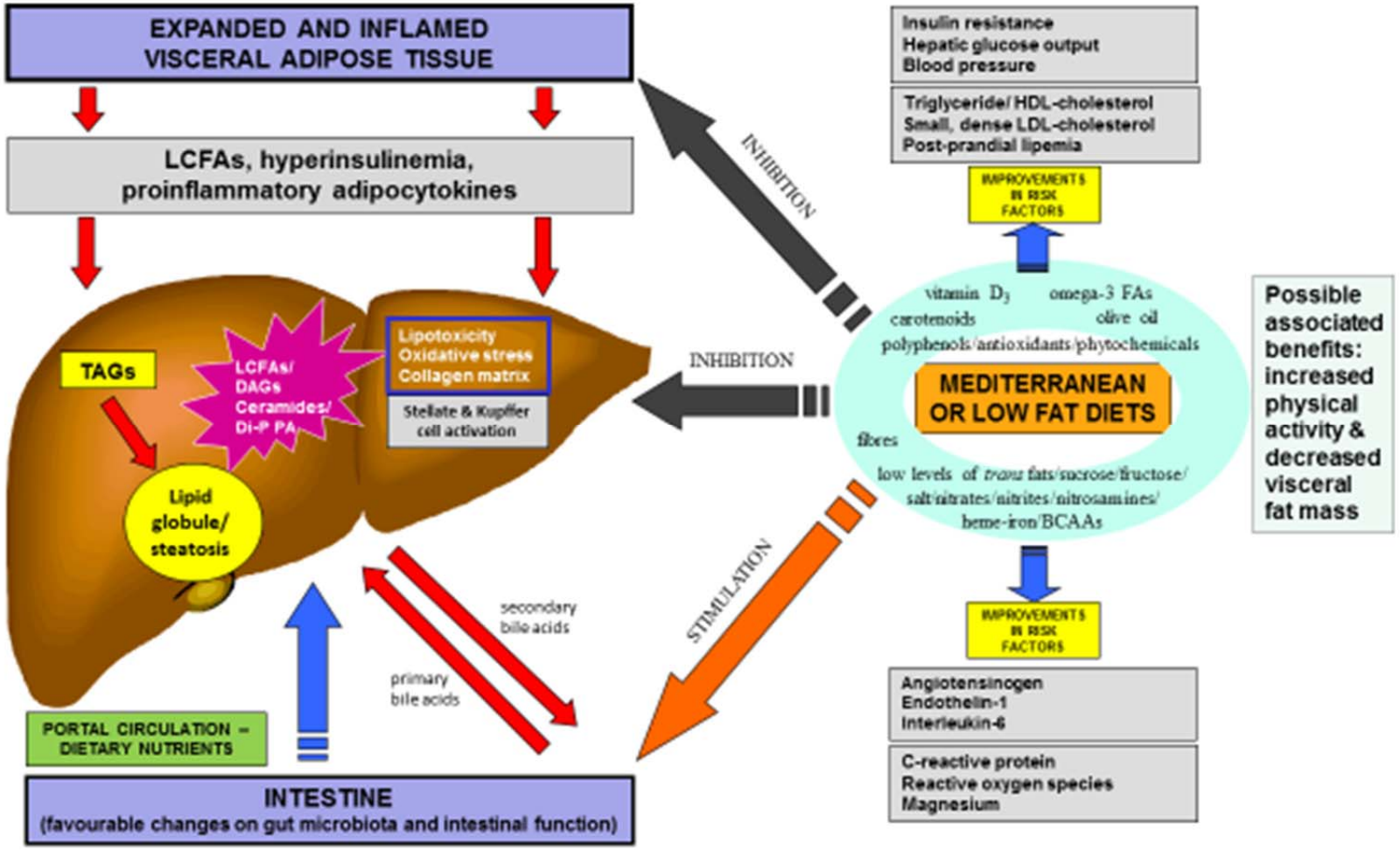
FIGURE LEGEND

Figure 1. Putative mechanisms by which *ad libitum* Mediterranean or low fat diets (and their individual dietary components) might contribute to the improvement of liver fat content and associated cardiometabolic risk factors in NAFLD.

Abbreviations. BCAA, branched chain amino acids. DAGs, di-acyl glycerol; di-P-PA, di-palmitoyl phosphatidic acid; HDL-cholesterol, high density lipoprotein-cholesterol; LCFA, long chain fatty acids, LDL-cholesterol, low density lipoprotein-cholesterol; TAGs, tri-acyl glycerols.

Figure 1.


EXPANDED AND INFLAMED VISCERAL ADIPOSE TISSUE
LCFAs, hyperinsulinemia, proinflammatory adipocytokines
TAGs
LCFAs/ DAGs Ceramides/ Di-P PA
Lipotoxicity Oxidative stress Collagen matrix
Stellate & Kupffer cell activation
Lipid globule/ steatosis
INHIBITION
INHIBITION
STIMULATION
secondary bile acids
primary bile acids
PORTAL CIRCULATION – DIETARY NUTRIENTS
INTESTINE
(favourable changes on gut microbiota and intestinal function)
Insulin resistance
Hepatic glucose output
Blood pressure
Triglyceride/ HDL-cholesterol
Small, dense LDL-cholesterol
Post-prandial lipemia
IMPROVEMENTS IN RISK FACTORS
vitamin D3
omega-3 FAs
carotenoids
olive oil
polyphenols/antioxidants/phytochemicals
MEDITERRANEAN OR LOW FAT DIETS
fibres
low levels of trans fats/sucrose/fructose/ salt/nitrates/nitrites/nitrosamines/ heme-iron/BCAAs
IMPROVEMENTS IN RISK FACTORS
Angiotensinogen
Endothelin-1
Interleukin-6
C-reactive protein
Reactive oxygen species
Magnesium
Possible associated benefits: increased physical activity & decreased visceral fat mass