Editorial

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Hepatic fat: Pathogenic trigger or passenger?

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See Article, pages 379–388

The study by Gepner *at al.* is a secondary analysis of a large randomised clinical trial (RCT) (CENTRAL RCT), testing long-term dietary interventions with or without physical activity.[1] The current analysis focused on the possible role of liver fat in mediating the improvement in cardiovascular disease (CVD) risk factors induced by the Mediterranean diet (MD). Indeed, it has been well established that the MD improves insulin sensitivity and features of the metabolic syndrome[2,6] and reduces the incidence of CVD outcomes in both observational studies and RCTs.[2–6] However, previous studies did not measure liver fat and therefore could not test whether liver fat reduction mediates the beneficial effects of MD.

The MD pattern improves steatosis even without weight reduction and caloric restriction as supported by two short-term tightly-controlled RCTs in patients with non-alcoholic fatty liver disease (NAFLD), with or without type-2 diabetes (T2DM),[7,8] as well as larger population level dietary assessments indicating an inverse association between adherence to the MD and degree of liver fat.[9,10] Support for these findings is needed from longer-term trials, such as the 18-month CENTRAL RCT.[1]

Gepner *et al.* have made an excellent attempt to clarify the mechanisms by which the MD achieves the observed CVD risk reduction. They have demonstrated that the MD combined with a low carbohydrate (LC) diet conferred a reduction in hepatic fat, which was associated with improvements in surrogate measures of CVD risk, beyond those seen with visceral fat loss. However, many questions remain regarding the relationship between hepatic fat and CVD risk. In addition, there is a complex interplay between impaired insulin sensitivity, visceral fat, systemic inflammation, endothelial dysfunction, platelet biology and lipid and glucose metabolism that leads to the development of both CVD and NAFLD, and the mechanisms by which the MD achieves all of these benefits remain unclear.

What are the components of the MD that improve liver and heart health?

Suggested mechanisms for the observed benefit of the MD are many.[11] In terms of individual dietary components, olive oil is associated with a reduced overall and CVD mortality in large population studies.[12] It's key constituents are oleic acid, a monounsaturated fatty acid (MUFA), as well as over 30 types of phenolic compounds all of which exhibit antioxidant properties. In RCTs, extra-virgin olive oil (EVOO) added to an MD significantly improved glycaemic control, with increased serum levels of glucagon-like peptide-1 and gastric inhibitory polypeptide, as well as increased insulin secretion, compared with MD without EVOO.[13]

Fruit, vegetables, legumes and olive oil were found to be the most protective elements of the MD in a meta-analysis.[4] Wholegrains induce satiety and reduce overall food intake, therefore reducing the free fatty acid burden that contributes to impaired insulin sensitivity. The high intake of prebiotic fibre in the MD is also associated with beneficial microbiome-related metabolomic profiles which could reduce lipopolysaccharide production, alter systemic inflammation and alter bile acid activity,[14] all mechanisms postulated to play a role in the development of NAFLD and insulin resistance. Many other possible mechanisms are at play. For example, the MD has been associated with lower levels of depression and stress, and improved cognitive function, all of which could impact on eating behaviours, cortisol levels and other potential mechanisms to affect risk of adiposity, insulin resistance and NAFLD/CVD. In addition, a switch to an MD style-eating pattern may have benefits by reducing the intake of fructose and saturated fat, which are known risk factors in NAFLD.[15]

Does improvement in hepatic fat alter T2DM risk?

Gepner *et al.* have shown that liver fat reduction is independently associated with improvements in glycated haemoglobin (HbA1c), even after adjustment for total weight loss or visceral adipose tissue (VAT) change.

Previous evidence has shown that the development of liver fat is closely associated with the development of insulin resistance and T2DM.[16] Conversely, improvement or resolution of liver fat has been shown to be associated with improved insulin sensitivity and glucose control, whether it is achieved via weight loss or not, and regardless of method: calorie restriction,

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exercise, surgery or insulin sensitising medications.[17] However, no causality between loss of hepatic fat and improvements in insulin sensitivity and glucose control has been established.

Gepner *et al.* showed that liver fat reduction is independently associated with improvements in HbA1c, even after adjustment for change in VAT, which highlights the central role of hepatic steatosis in this complex dysmetabolism.

Does improvement in hepatic fat alter CVD risk?

Gepner *et al.* have shown that the MED/LC diet was superior to the low-fat (LF) diet in decreasing several cardiometabolic risk factors, a difference that was attenuated when adjusting for the decrease in liver fat, but not following adjustment for weight or VAT. Therefore, this paper raises interesting questions regarding the mechanisms by which the MD achieves its benefit in CVD prevention.

It has long been recognised that the presence of NAFLD is related to subclinical and clinical CVD, although some evidence questions the robustness and causality of this association.[18,19] Amongst 7,196 individuals free of CVD, NAFLD presence and severity was associated with aortic stiffness beyond abdominal obesity[20] and with subclinical atherosclerosis; increased carotid artery intima-media thickness/plaques, arterial stiffness, coronary artery calcification, and endothelial dysfunction.[21] The presence and amount of steatosis was also recently related with impaired cardiac and autonomic function when compared with controls.[22] However, it is difficult to separate the effect of reduced insulin sensitivity from the direct effect of NAFLD on CVD risk.[23] For example, elevated levels of markers of endothelial dysfunction in individuals with NAFLD were attenuated once corrected for insulin resistance,[24] and in the Framingham Heart Study, amongst multiple measures of vascular function, the relationship with NAFLD was determined by the shared risk factors for CVD.[25] Moreover, NAFLD patients with genetic variation in *PNPLA3* (1148 M genotype – rs738409 G allele), which confers susceptibility to hepatic steatosis that is unrelated to impairments in insulin sensitivity, did not have increased risk for CVD.[19] Therefore, it seems that hepatic fat is more likely to be a very sensitive marker of reduced peripheral and hepatic insulin sensitivity, which is a potent risk factor for both CVD and NAFLD.

In addition, a key cause of chronic inflammation in patients at risk of CVD is adipocyte-induced inflammation through the production of adipokines.[26] Therefore, the specific contribution of hepatic fat to CVD risk is difficult to discern beyond the contribution of whole-body fat, particularly visceral fat. NAFLD may contribute to a vicious cycle of systemic inflammation and altered lipid and glucose metabolism, with a complex interplay between the liver, muscle tissue, VAT and the gut microbiome that contributes to the further development of CVD.[27]

Gepner *et al.* have demonstrated that MD/LC leads to improvement in CVD risk factors including serum lipids and all-together CVD risk scores, associated with the reduction of liver fat. However, it does not necessarily follow simply that a reduction in hepatic steatosis itself will reduce CVD risk. In fact, a large study examining the effects of the PPARα agonist fenofibrate on serum levels of triglyceride and high-density lipoprotein-cholesterol demonstrated improved lipid profiles but no reduction in macrovascular CVD risk.[28] In that manner, the results of Gepner *et al.* are limited by using only cardiovascular risk scores rather than direct subclinical or clinical cardiovascular outcomes.

What are the practical implications for the lifestyle treatment of NAFLD?

Gepner *et al.* observed that the MED/LC induced a significantly greater decrease in liver fat than the LF diet. Going back to the CENTRAL trial,[1] intrahepatic fat was reduced similarly following the MD/LC and the LF diet in the arms without a physical activity intervention. The superiority of the MD was evident only in the arms with the added physical activity intervention. Exercise itself even without weight loss has been demonstrated to reduce liver fat,[17] and therefore these data may imply that the MD interacts with physical activity to improve insulin sensitivity and reduce liver fat, pointing to a need for comprehensive lifestyle advice to optimise liver fat reduction.

The compliance to the MD is relatively good in a trial setting; for example in a 12-week blinded *ad libitum* trial, adherence was higher to the MD than the LF diet (88% *vs.* 64%).[29] However, today, the increasing exposure to industrialised ultra-processed food has led to adoption of a less healthy diet even in countries that were traditionally characterised by a Mediterranean dietary pattern.[31–33] However, it seems that even with partial adherence to an MD, health benefits can be achieved due to the vast array of beneficial components of the diet. This is an encouraging message for patients. Notably, in the study of Gepner *et al.*, a LC diet version the MD was implemented, accompanied by supportive measures (*e.g.* nutritionist sessions, lunch provided by the workplace). However, long-term restricted carbohydrate intake is challenging and may be unnecessary since it has no proven superiority in reductions in liver fat and aminotransferases.[29]

Gepner *et al.* have provided an interesting contribution to the literature in this area, but more studies are needed to clarify a potential causal role for liver steatosis in the pathophysiology of CVD and the preventive potential of lifestyle interventions.

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Authors' contributions

The two authors contributed equally to this manuscript.

Supplementary data

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