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Errazuriz I, Dube S, Slama M, et al. Randomized Controlled Trial of a MUFA or Fiber-Rich Diet on Hepatic Fat in Prediabetes. J Clin Endocrinol Metab. 2017;102(5):1765–1774.

What We Know, Think We Know, or Are Starting to Know

Although the risk of Type-2 Diabetes [T2DM] increases with greater adiposity, adiposity defined by BMI varies greatly in T2DM at diagnosis, indicating that the risk is associated with the underlying metabolic complications which accompany adiposity. One such complication is the accumulation of hepatic [liver] fat, and Non-Alcoholic Fatty Liver Disease [NAFLD] is defined as the accumulation of fat in liver cells [hepatocytes], and is diagnosed when over 5%-10% of hepatocytes have fat accumulation.

NAFLD is a bi-directional driver of cardio-metabolic issues. Why 'bi-directional'? One direction is the influence of diet on liver fat accumulation, and excess dietary sugars and saturated fat may both contribute to increased triglycerides in the liver [(1)]. The other direction is the response to diet, once liver fat is accumulated, on factors like blood lipids, elevated free fatty acids, and insulin resistance in the liver [(2)]. Collectively, these issues result in an upregulation of very-low-density-lipoprotein [VLDL] synthesis, increased small, dense low-density lipoprotein [LDL] concentrations, and low high-density lipoprotein [HDL]: all of which taken together result in increased cardiovascular disease [CVD] risk [(2)].

In addition, the elevations in circulating free-fatty acids [FFA] with fatty liver, and increase in fat stored in the liver, results in profoundly impaired glucose tolerance and insulin resistance, and both T2DM and NAFLD frequently coexist in the same individual [(3)]. Therefore, strategies to reduce liver fat accumulation, and attenuate the likelihood of progression from prediabetes to T2DM, are needed.

This study aimed to investigate the effect of diets rich in either fibre or monounsaturated fats [MUFA] on hepatic fat content, without weight loss.

The Study

The study randomised participants to two separate interventions: a high-monounsaturated [MUFA] diet, a high fibre diet [Fibre], both of which were compared to a control group. The intervention lasted 12-weeks. The two intervention diets were characterised as follows:

- MUFA-diet: 28% of total energy from MUFA, half of this coming from extra-virgin olive oil
- Fibre-diet: 20g dietary fibre per 1000kcal, up to a maximum of 72g fibre per day

The control diet continued with habitual diet.

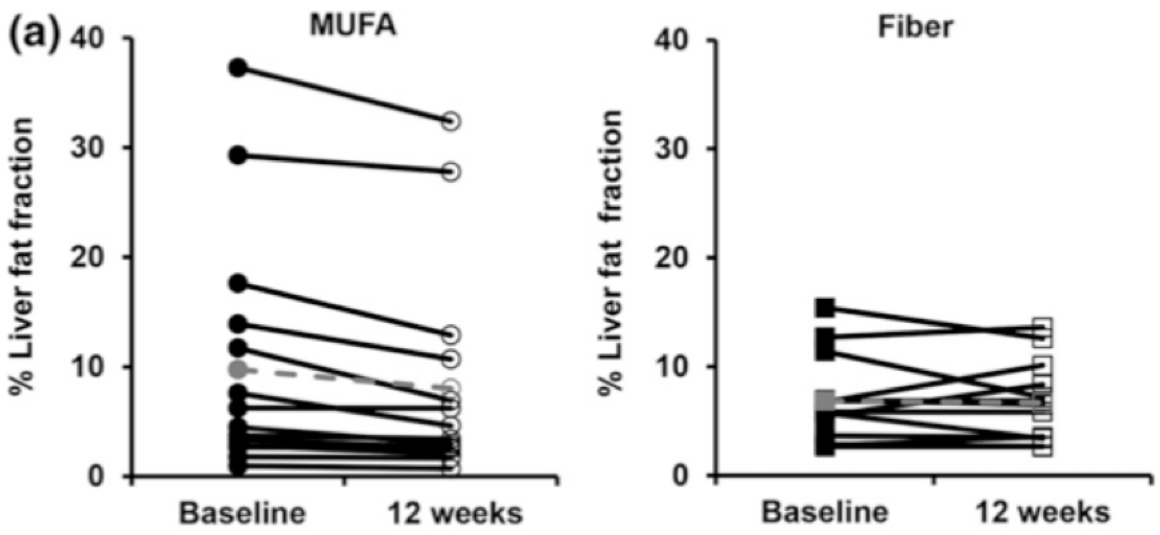
Participants visited the investigators research centre every two-weeks to collect study foods, be weighed, and to provide 3-day food diaries, which were assessed by study dietitians. Participants underwent a baseline dual-energy x-ray absorptiometry [DEXA] scan to measure body composition, and oral-glucose tolerance test [which was repeated at 8-weeks, and 12-weeks].

Results: BMI remained stable throughout the intervention in all diet groups. In the MUFA-diet, there was a statistically significant reduction in measured liver fat from 9.7% to 8%. This magnitude of difference represented an 18% reduction in liver fat compared to baseline in the MUFA-diet.

There was no significant difference in the Fibre-diet group, which increased insignificantly by 2% from baseline*. Liver fat non-significantly increased by 13% in the control group. There was no significant difference in any of the glucose tolerance or insulin parameters in any diet group.

*Geek Box: Average Treatment Effects

*One very misunderstood aspect of interpreting studies, in particular intervention studies, is that a lack of effect means that the intervention worked for no one. This is an easy trap to fall into, because what RCTs compare between the intervention and control group is the mean, or average, treatment effect. This is the average of the effect from all the participants in the intervention group vs. the average effect from all participants in the control. This is often referred to as the 'ATE' [average treatment effect]. The difficulty, particularly for nutrition interventions, is that the results and conclusions are based off the ATE, which often results in an over-simplistic extrapolation of "there is no effect of X intervention on Y outcome". But look closer at the data, what can you see? You may often see that in some participants [**figure below**], there was an effect. For example, in the present study, look at Figure 1(a), and look at the paired line graph for fibre; clearly a number of participants had quite a substantial decrease in liver fat. Many didn't, and some increased; so overall the mean, the average, is 'no effect'. But it is important to bear in mind that it worked for someone. Now, to figure out 'why' it worked for some, not others, generally requires further, post-hoc analysis by the investigators. This is something that should be done, but in practice often isn't. The take home point, particularly for you reading nutrition studies, is to always bear in mind that it is the ATE being reported, and compared, but sometimes it can pay to dig a little further and see if the ATE is masking an effect in a subgroup of participants.*



The Critical Breakdown

Pros: Participants were excluded if they habitually consumed a high MUFA or fibre-rich diet. For a 1-week run-in period before the intervention, participants excluded the intervention foods. The weight-stable protocol allowed an examination of the true effects of the nutrients, independent by weight loss reductions in liver fat. Nutrients that may have an impact, in particular saturated fat [SFA] and polyunsaturated fats [PUFA], were matched across diets. Key study foods [extra-virgin olive oil, beans] were provided to the participants.

Cons: The Fibre-diet was arguably not 'high' enough [more under Interesting Finding, below] to see an effect. The Fibre-diet overall, with the exception of 10g/d extra dietary fibre, did not in fact differ significantly from the control diet. The study free living, and arguably it is easier to significantly increase MUFA from an oil, than fibre from whole foods. A lack of compliance with the Fibre-diet cannot be ruled out, which is a caveat of all free-living interventions. The Methods section states: "Subjects were allowed to be off the diet, if necessary, for up to a maximum of 2d/wk." The rationale for this may be pragmatism, however, the instruction is ambiguous. Carbohydrate intake was not matched across interventions, and was significantly lower in the MUFA-diet, which could have influenced the results.

Key Characteristic

Keeping PUFA and SFA constant across the dietary interventions - 13% for SFA and 4-5% for PUFA - was an important factor to determine a true effect of increased MUFA.

Both SFA and PUFA have been shown in other interventions to have differential effects on liver fat accumulation under isocaloric conditions, with SFA significantly increasing and PUFA significantly decreasing liver fat, respectively [(4)]. Interventions comparing high-SFA/low-PUFA diets vs. low-SFA/high-PUFA diets have shown that low-SFA/high-PUFA diets decrease liver fat significantly, and therefore the ratio of these two fat subtypes appears to be an important determinant of changes in liver fat [(4)].

By maintaining constant SFA and, in particular, quite a low PUFA level throughout the intervention period, the study was able to more fully examine the effects of MUFA on liver fat*. However, it is also worth mentioning here again that carbohydrate content was not matched across diets, and average intake during the study was 188g/d in the MUFA-diet, compared to 256g/d on the Fibre-diet, and 241g/d on the control, and this may have modified the effect of the MUFA-diet.

*Geek Box: Comparison Levels in Nutrition Research

One issue for nutrition interventions that differ from drug interventions, is that nutrient intake tends to have a narrow range of variability. Think about it; it would be uncommon to go from eating 5% carbohydrate one day to 55% the next. If we look at dietary fat, for example, individuals tend to have relatively consistent levels of intake that may fluctuate over time only by a few percentage points. In contrast, in a drug trial, an intervention is able to compare the effects of an exposure [the drug] to zero exposure, i.e., a true placebo; when you compare something to nothing, there will generally always be some degree of effect size. However, in nutrition, even the 'control' group will have at least adequate levels of a nutrient, because it is considered unethical to expose people in a trial to a deficiency. This often means that there isn't that much a difference in levels of intake between two comparison groups, and it can result in 'null' findings, or 'weak' effect sizes. This can be complicated if, for example, the trial will examine a nutrient or food as the exposure, but participants habitually consume that food or nutrient before the trial. One way to try and address this is to get participants to exclude certain foods or macronutrients [as opposed to micronutrients, which may result in nutrient deficiencies], in the run-in to the trial. The second, and more important, way to address this is to create a sufficient contrast in the exposure. For example, in this study, the MUFA-diet had 22% from MUFA, while the control had 8%. This may then create a big enough difference to detect an effect of the intervention, compared to the control.

Interesting Finding

There was no effect of the Fibre-diet intervention overall, which may be surprising. The investigators stated that participants on the Fibre-diet were instructed to have 'a maximum of 72g of dietary fibre per day'. One has to question why, if we know from the literature examining very high fibre diets, this wasn't the threshold that the intervention diets aimed to reach. Instead, the prescription was for 20g/1000kcal.

Average energy intake is reported as 1,926kcal in the Fibre-diet group, and reported fibre intake as 21g/1000kcal, suggesting that a maximum of 40-42g was consumed during the intervention. While not addressing liver fat as an outcome, James Anderson's research on very high-fibre diets - often 60-70g/d - for T2DM management has demonstrated significantly positive benefits in terms of insulin sensitivity and reductions in mediation. In epidemiology, dietary fibre is associated with a significant 16% reduced risk of NAFLD [5].

The lack of effect in the present study may reflect a genuine lack of direct effect of dietary fibre, or may reflect that fibre intake was not sufficiently high to demonstrate an effect. Further interventions should address this, and why the investigators in the present study did not have dietary fibre, if they were willing to allow up to 72g/d, around such a threshold, is a head-scratch.

Relevance

This study adds to a wider body of interventions examining the effects of dietary fat on fatty liver, which consistently demonstrate a benefit to unsaturated over saturated fats.

However, a word of caution before this study is interpreted as "high-fat diets reduce liver fat": this is not necessarily the case, and isocaloric diets comparing low-carb/high-fat diets vs. low-fat/high-carb diets consistently show greater reductions in liver fat on the low-fat/high-carb diets [6].

However, it is important to distinguish effects; lowering carbohydrate intake is very effective at reducing liver fat, and thus, the increase in liver fat on these LCHF diets is attributable to the high fat content, not the low-carb content [6,7].

It is important to bear in mind that the magnitude of effect may have been influenced by the lower carbohydrate content, as well as the additional MUFA, in the present study. It also important to bear in mind that the magnitude of effect is relevant, but small compared to the effects of weight loss.

Reductions in adiposity result in decreases in liver fat, with interventions finding decreases in liver fat content of 30-45% after energy-restricted diets, and a threshold of 7% weight loss from baseline [8,9].

Thus, while weight-neutral interventions are important, and this study does demonstrate an effect of MUFA independent of weight loss, the potential additive effect of reducing adiposity and dietary modifications could have significantly greater clinical impact on a condition with substantial comorbidity.

Application to Practice

This first aspect of extrapolating this study to bear in mind is the elderly population in which it was conducted; mean age 62. It may not necessarily be generalisable to younger populations, but this is still a clinically relevant age-group so the findings are certainly relevant to risk management in that demographic. The main application is that dietary fat composition appears to be quite important for management, and treatment, of fatty liver. A combination of reductions in carbohydrate, coupled with dietary fat modification, may be effective dietary strategies to target reductions in liver fat.

References

1. Luukkonen P, Sadevirta S, Zhou Y, Ali A, Ahonen L, Lallukka S et al. Saturated fat is more metabolically harmful for the human liver than polyunsaturated fat or simple sugars. Journal of Hepatology. 2018;68:S836.
2. Kotronen A, Yki-Järvinen H. Fatty Liver: A Novel Component of the Metabolic Syndrome. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28(1):27-38.
3. Anstee Q, McPherson S, Day C. How big a problem is non-alcoholic fatty liver disease?. BMJ. 2011;343(jul18 1):d3897-d3897.
4. Bjermo H, Iggman D, Kullberg J, Dahlman I, Johansson L, Persson L et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. The American Journal of Clinical Nutrition. 2012;95(5):1003-1012.
5. Noureddin M, Zelber‐Sagi S, Wilkens L, Porcel J, Boushey C, Le Marchand L et al. Diet Associations With Nonalcoholic Fatty Liver Disease in an Ethnically Diverse Population: The Multiethnic Cohort. Hepatology. 2020;.
6. van Herpen N, Schrauwen-Hinderling V, Schaart G, Mensink R, Schrauwen P. Three Weeks on a High-Fat Diet Increases Intrahepatic Lipid Accumulation and Decreases Metabolic Flexibility in Healthy Overweight Men. The Journal of Clinical Endocrinology & Metabolism. 2011;96(4):E691-E695.
7. Green C, Hodson L. The Influence of Dietary Fat on Liver Fat Accumulation. Nutrients. 2014;6(11):5018-5033.
8. Kirk E, Reeds D, Finck B, Mayurranjan M, Patterson B, Klein S. Dietary Fat and Carbohydrates Differentially Alter Insulin Sensitivity During Caloric Restriction. Gastroenterology. 2009;136(5):1552-1560.
9. Sevastianova K, Kotronen A, Gastaldelli A, Perttila J, Hakkarainen A, Lundbom J et al. Genetic variation in PNPLA3 (adiponutrin) confers sensitivity to weight loss-induced decrease in liver fat in humans. American Journal of Clinical Nutrition. 2011;94(1):104-111.