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Parry SA, Rosqvist F, Mozes FE, Cornfield T, Hutchinson M, Piche ME, et al. Intrahepatic fat and postprandial glycemia increase after consumption of a diet enriched in saturated fat compared with free sugars. Diabetes Care. 2020;43(5):1134–41.

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

What we know is that non-alcoholic fatty liver disease [NAFLD] affects nearly a quarter of the global population, with estimates of >25% prevalence [(1)]. The distribution and type of adipose tissue - the accumulation of fat in the liver and subsequent spillover of fat from the liver to other important metabolic organs and tissue, in particular the pancreas - is recognised as a critical factor influencing metabolic health* [(2)].

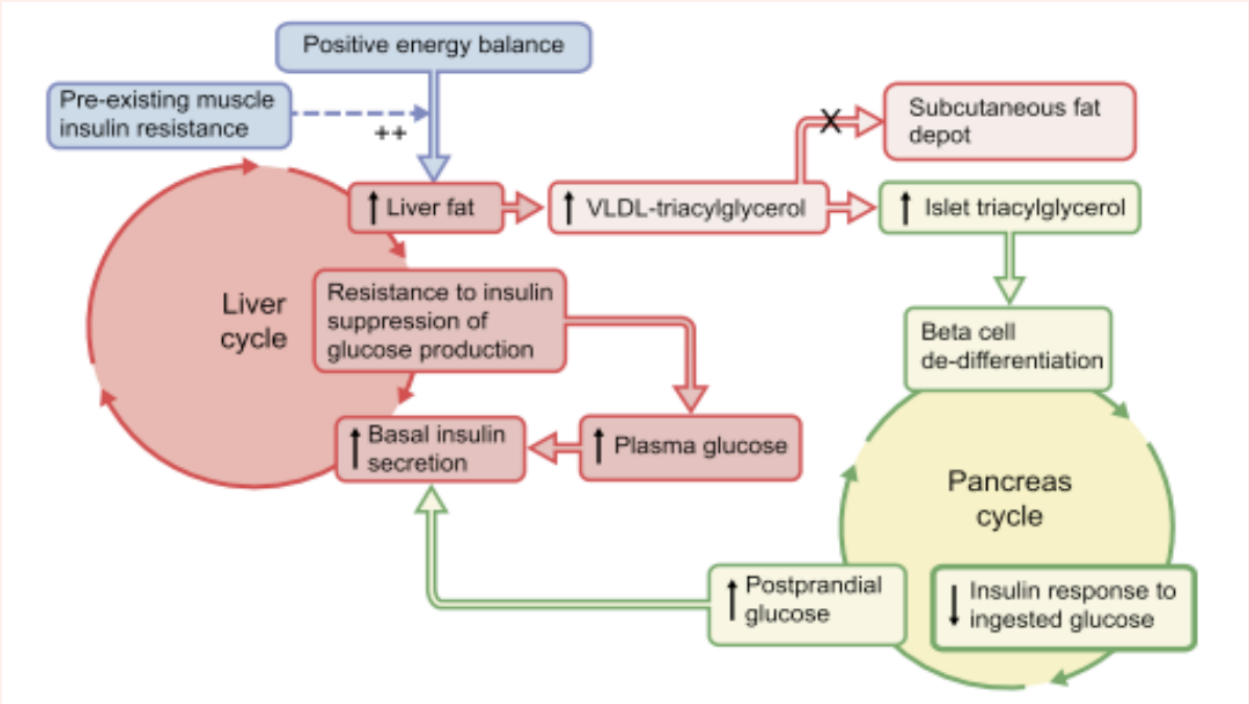
NALFD in fact covers a spectrum of liver diseases that are not caused by alcohol, from hepatic steatosis to hepatocellular carcinoma. In nutrition, we are primarily concerned with the former: hepatic steatosis, characterised by the the net retention of triglycerides in liver cells, and defined by intracellular TGs in >5% of liver cells [(1)].

Much of the early work on the accumulation of intracellular TGs in the liver focused on the dietary sugar, fructose. Fructose overfeeding was shown to induce de novo lipogenesis [the term for synthesis of new fat from non-fat dietary sources, in particular carbohydrate] of liver TGs, and impair clearance of TGs [(3)]. However, in 2018, the esteemed Finnish NAFLD researcher, Hanelle Yki-Järvinen, and her group demonstrated in an elegant feeding study that overfeeding with saturated fat increased liver TGs by 55%, compared to 33% by free sugars [(4)].

Nonetheless, both of these lines of evidence have been in the context of overfeeding total energy intake, and it is known that hyper-caloric diets increase liver fat, whilst hypo-caloric diets decrease liver fat [(5)]. Thus, the effects of either sugars or saturated fat on liver fat in the context of energy balance remains to be fully elucidated. The present study investigated this research question.

*Geek Box: The 'Twin Cycle' Hypothesis

The earliest detectable characteristic of deteriorating glucose tolerance is insulin resistance in skeletal muscle tissue, which is followed by a progressive decline in pancreatic beta-cell function as the pancreas attempts to secrete more insulin to keep blood glucose levels in range. This view of diabetes has been considered, however, to be glucose-centric, particularly as evidence for the substantial accumulation of excess intracellular triglycerides in both skeletal muscle, and the liver. In view of this evidence, in 2008 Professor Roy Taylor at Newcastle University developed the 'twin cycle hypothesis', which focused more on chronic energy excess and the effects on visceral fat accumulation, than simply glucose alone. The hypothesis stated that during conditions of energy excess, surplus carbohydrate is converted into fat [triglycerides] in the liver [de novo lipogenesis], while excess dietary fat also accumulates in the liver. This increase in liver fat inhibits the ability of insulin to suppress glucose production in the liver, resulting in liver insulin resistance and elevated blood glucose levels. The liver attempts to clear fat by upregulating very-low-density lipoprotein [VLDL] production, which transports TGs from the liver and results in elevated circulating TGs. However, these VLDL-TGs need to go somewhere, and if subcutaneous fat storage is at capacity, VLDL deposits its TGs into other visceral areas, in particular the pancreatic cells that secrete insulin. This build up of fat in the pancreas impairs the capacity of beta-cells, which ultimately results in complete loss of function of beta-cells. Type-2 diabetes is characterised by this twin cycle of excess fat accumulation in the liver spilling over the pancreas, and this is central to the progressive loss of beta-cell function that characterises diabetes progression. To date, the only dietary intervention which appears to reverse this is the diet Taylor and his colleagues implemented in a number of interventions, using liquid-based extreme energy deficit diets consisting of ~800kcal/d, which reduce these hepatic and pancreatic fat depots, restoring beta-cell function in individuals who still retain a degree of functionality [i.e., patients who long ago lost beta-cell function may not reverse the condition].



The Study

16 healthy males defined as overweight by BMI [27.7] underwent a randomised, crossover design study investigating the effects of two eucaloric [meaning energy balance calorie] diets:

- Saturated fat-enriched diet [SFA]: 45% total fat [20% saturated fat], 40% carbohydrate, 15% protein
- Sugar-enriched diet [SUGAR]: 20% total fat, 65% total carbohydrate [20% free sugars], 15% protein

Participants were randomised to either the SFA diet or SUGAR diet first, diets were followed for 4-weeks, followed by a 7-week washout period where participants returned to their habitual diet, before crossing over to the comparison diet [i.e., either SFA>SUGAR or SUGAR>SFA]. For 1-week before beginning each intervention, participants followed a diet based on the UK Eatwell plate. Diets were consumed free-living and participants were provided with certain study foods to meet the goals of each diet.

At the start and end of each 4-week diet phase, participants underwent two laboratory study days:

1. Fasting study day in which liver fat content was measured by MRI, blood lipid and glucose measures taken, and body composition assessments conducted, and;
2. Post-prandial study day where stable isotopes, which allow for the precise measure of the metabolic fate of nutrients in and out of tissues, were used to trace the metabolism of dietary fat and sugar. Energy expenditure and post-prandial blood measures of lipids and glucose was also conducted.

Primary outcome measures were intrahepatic triglyceride [IHTAG, i.e., fat in liver cells] content, hepatic de novo lipogenesis [DNL, i.e., the synthesis of new triglycerides], and hepatic and whole-body postprandial metabolism [i.e., carbohydrate and fat oxidation, and energy expenditure].

Results: Bodyweight increased by ~1.5kg during the SFA diet and 0.2kg on the SUGAR diet, which may be explained by the ~300kcal/d extra energy in self-reported intake during the SFA diet. There were no significant differences in fasting glucose or insulin levels in response to either intervention.

- ***Intrahepatic triglycerides:*** During the SFA diet IHTAG increased by 39%, compared to no changed in response to the SUGAR diet. In linear regression analysis*, the increase in body weight of ~1.5kg on the SFA diet explained only 17.2% of the increase, indicating that the increase in IHTAG occurred independent of the increase in body weight.

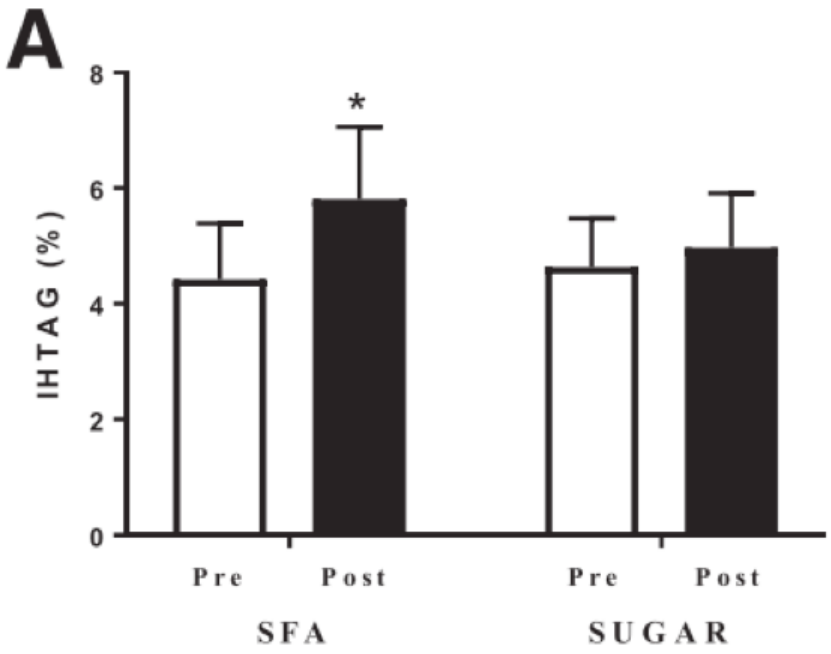


Figure *from paper illustrating difference in intrahepatic triglycerides between baseline and after 4-weeks consuming a diet enriched with ~20% saturated fat vs. ~20% free sugars.*

- ***Post-prandial metabolism:*** Post-prandial glucose and insulin over both the early [0-180mins] and whole [360min] post-prandial period measured, were significantly greater and more prolonged in response to the SFA diet, compared to the SUGAR diet. Post-prandial non-esterified fatty acids [NEFA, aka 'free fatty acids'] were significantly higher in response to the SUGAR diet, compared to the SFA diet. There were no significant differences in fatty acid oxidation from diet or adipose tissue breakdown, or dietary carbohydrate oxidation.

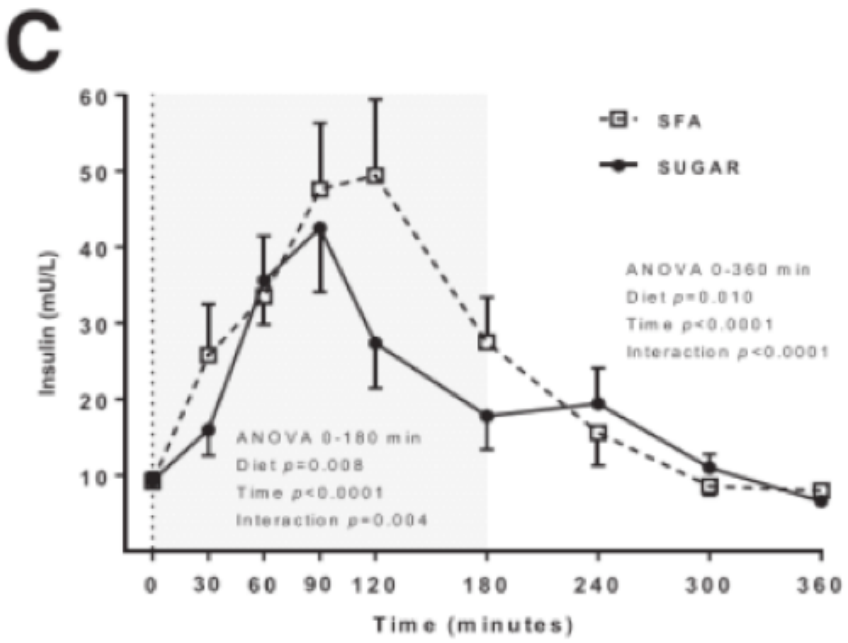


Figure *from paper illustrating difference in insulin responses to a test meal after 4-weeks consuming a diet enriched with ~20% saturated fat vs. ~20% free sugars.*

- ***De novolipogenesis:*** There was no significant difference between either diet in post-prandial hepatic DNL.

*Geek Box: Linear Regression

You'll likely come across the statistical method known as 'linear regression' very regularly when reading research. So what is it? Linear regression is a way to model the relationship between a dependent variable and one or more independent variables. A dependent variable may also be known as an outcome variable or response variable: this is the factor whose variation we want to understand. An independent variable(s) may also be known as exposure variables or risk factors: these are the factors that may influence the occurrence of the outcome, or the size of the effect of the outcome. In a simple linear regression, only one independent [exposure] variable is modelled for its association with the dependent [outcome] variable, while in a multiple [also known as multivariate] linear regression, more than one independent variable is modelled for their associations with the dependent [outcome] variable. A linear regression analysis predicts how the outcome either increases or decreases with an increase in the exposure. For example, you could want to model how blood glucose levels are affected by increasing carbohydrate content, or how likely heart disease is to occur with increasing levels of LDL-cholesterol, i.e., you can predict the value of the outcome from the value of the exposure variable. So lets take the present study to bring this concept to life; we know that intrahepatic triglycerides increased by 39% on the SFA diet, but we also know that participants gained ~1.5kg over the course of the intervention, when the goal was weight maintenance. So, to see whether the increase in IHTAG was more related to weight gain rather than diet, the authors conducted a linear regression to determine the relationship between IHTAG [the outcome, dependent variable], and the change in bodyweight [the exposure, independent variable]. Because the analysis predicts the value of one variable from another, it indicated that the change in bodyweight [the exposure variable] only predicted 17% of the increase in IHTAG [the outcome variable]. This indicates that it was the dietary intervention that was responsible for the majority of the increase in IHTAG.

The Critical Breakdown

Pros: The laboratory measures were extensive, and the use of stable isotopes provides robust analysis of the metabolic effects of saturated fat vs. sugars. Participants were otherwise healthy, compared to previous research where participants had >4% liver fat [4]. The dietary targets appear to have been met for macronutrients, and for saturated fat and sugar, however this is self-reported [see ***Cons,*** below].

Cons: The main limitation is dietary assessment; 3-day diet diaries were completed during the 1-week lead-in and interventions, but it doesn't state which 3-days - presumable 2 weekday and 1 weekend, which would be desirable. Participants could have followed the Eatwell guide for the full washout period, to minimise any effect of significant differences in their habitual diets. According to the self-reported dietary intake in the Supplementary Data, total energy intake in the SFA diet was ~300kcal/d greater than the SUGAR diet, which could have influenced the results.

Key Characteristic

Although the diets were consumed under free-living conditions, targeting calorie balance was an important design characteristic given that much of the previous literature looking at the effects of fat and/or sugar on hepatic fat were in the context of overfeeding, or energy deficit weight loss diets [3-6].

For example, a review of fructose-overfeeding trials indicated that the average doses of fructose was 187.3 g/day [6]. However, studies in which fructose is substituted isocalorically for other sugars show no adverse effect on cardiometabolic risk, where calories are controlled [7]. Conversely, while increased IHTAG has been previously demonstrated from overfeeding saturated fat by 1,000kcal/d, weight maintenance studies have also demonstrated that the increase in IHTAG from SFA intake occurs independent of changes in body weight [8]. There has been little evidence for the effects of dietary factors in the context of relative energy balance, and the present study adds an important additional data point for the role of fat and sugar in the development of fatty liver.

Interesting Finding

Despite the 23% free sugar intake, and 62% total carbohydrate intake, post-prandial glucose and insulin excursions were greater and more prolonged over the entire post-prandial period, after the SFA diet.

Isn' t sugar supposed to cause insulin resistance? The reality is that insulin resistance and glucose intolerance may be influenced by a number of dietary fat factors, including elevated circulating levels of NEFA, increased IHTAG, and impaired TG clearance [2]. Studies have demonstrate diametrically opposed effects of SFA and unsaturated fat [UFA] in these contexts: UFA reduce post-prandial TGs, reduce IHTAG and overall visceral fat, and reduce DNL [8,9]. These factors may induce insulin resistance, and experimental human studies have demonstrated that SFA-enriched diets and ketogenic diets induce insulin resistance [10,11], with one study finding that following an acute 1-day SFA-rich, residual effects on insulin resistance were observed up to 36hrs after the last meal [11]. Guess et al. [12] found that overall percentage of energy from SFA was associated with impaired fasting and post-prandial glucose tolerance. Cumulatively, the hypothesis that dietary fat has little effect on glucose tolerance and insulin action finds little to no support in well conducted human studies.

Relevance

The asinine 'fat vs. carbs' debate rages on, and the singling out of free sugars is often used to argue that we "wrongly demonised" saturated fat. But let's look closer at the sugar issue. The profound adverse effects of free sugars are generally observed around 20% of total energy intake, but this appears to be in the context of energy excess [13]. The lack of effect of sugar on IHTG in the present study is consistent with wider research indicating that in the absence of energy excess, dietary sugars do not appear to exert the deleterious effects evident in overfeeding studies [6,7]. The primary negative effect of free sugars, therefore, is their addition to the diet without compensatory adjustments in total energy intake, i.e., caloric intake from sugar under ad libitum conditions [i.e., no control on diet] drives increased adiposity [14].

However, the historic emphasis on the role of saturated fat has focused on cardiovascular disease [CVD], rather than metabolic disease, i.e., type-2 diabetes and NAFLD. The link with CVD is mediated primarily by effects of SFA on LDL-cholesterol, and most evidence when dietary SFA is >18% total energy [15]. But recent evidence indicates that the balance of fat subtypes we typically associated with CVD, i.e., PUFA>SFA, is equally important for metabolic disease risk, given the oppositional effects of these fat types on liver fat and insulin resistance.

The fact that the ~20% energy from SFA in this study may be substantially higher than the 12.5% in the general population should not overshadow the enormous current popularity of animal-fat based diets, where levels of SFA intake may be >30% total energy. What the present suggests is that once total energy intake is accounted for, SFA may have a more deleterious effects than free sugars on liver fat, which runs contrary to much of the popular current narratives about diet and health.

Application to Practice

Hopefully it goes without saying that this study doesn't mean we should recommend pouring on the sugar, however, the practitioners amongst you will no doubt regularly encounter ingrained beliefs in clients about dietary sugars being "toxic" or otherwise. The present study may provide some help to dismantle this, and indicate that some honey on the toast is not worth sweating over. Conversely, the present study also provides another piece of evidence which demonstrates that, indeed, the bacon and butter brigade are unlikely to rewrite the dietary history books just yet. Not that they will listen to you.

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