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Cohen CC, Li KW, Alazraki AL, et al. Dietary sugar restriction reduces hepatic de novo lipogenesis in adolescent boys with fatty liver disease. *Journal of Clinical Investigation*. 2021;131(24):e150996.

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

In a previous Research Lecture on non-alcoholic fatty liver disease [NAFLD], the title of the presentation was deliberately framed as "moving beyond sugar". This is because up until more recent controlled interventions, sugar was deemed to be particularly deleterious for liver fat due to a process known as *de novo lipogenesis* [DNL], i.e., the synthesis of new fats from non-fat sources, and result in upregulation of new triglyceride synthesis in the liver [(1)].

However, we also know that the magnitude of DNL responses to dietary sugars is mediated by the metabolic health status of the person, and can be up to 2-3-fold higher in persons with fatty liver compared to healthy controls [(2)].

NAFLD is now a substantial concern in paediatric populations; in general population studies the prevalence of paediatric NAFLD is ~7.6%, however, in childhood obesity clinics the prevalence is 34.1% [(3)]. The relationship with dietary sugars is worth considering given that children and adolescents may be more likely to consume excessive free sugars [(4)].

While it is known that excess free sugars can increase hepatic fat and DNL in adults [(5)], little is known on the effects of dietary manipulations in children. In 2019, an exploratory study found that a low-sugar diet lowered liver fat levels in children with NAFLD over 8-weeks [(6)]. The present study is a recent intervention investigating the effects of a low-sugar diet in adolescents with NAFLD.

The Study

40 adolescent boys aged 11–16 years old completed an 8-week randomised trial comparing a low-sugar intervention diet to participants' usual habitual diet as the control diet.

All participants had liver fat levels of >10% [a diagnosis of NAFLD being 5%]. All participants also had a minimum weekly consumption of sugar-sweetened beverages/fruit juices of three 240ml servings.

The intervention diet was designed to have <3% added sugars, and investigators visited the homes of participants in the intervention group to remove all added sugar products and replace them with low/no-sugar alternatives. Foods and meals for the entire family were provided by the research team.

DNL was assessed using stable isotope tracers* [see ***Geek Box**, below], and liver fat was assessed using MRI. DNL was assessed before and at the end of the 8-week study period.

The primary outcome was change in DNL between diets, and the secondary outcome was change in liver fat levels between diets.

*Geek Box: Stable Isotope Tracers

So, what is a "stable isotope"? When talking about chemical elements, like nitrogen, carbon, or hydrogen, these elements exist in a form that is abundant in nature. For example, about 99% of the carbon is ^{12}C, which reflects the fact that it has 6 protons and 6 neutrons [adding the protons and neutrons give the element its 'atomic mass', in this carbon has an atomic mass of 12, thus '^{12}C'. However, around 1% of the carbon on Earth has an extra neutron, i.e., with 7 neutrons and 6 protons it has an atomic mass of 13 and is written as ^{13}C.

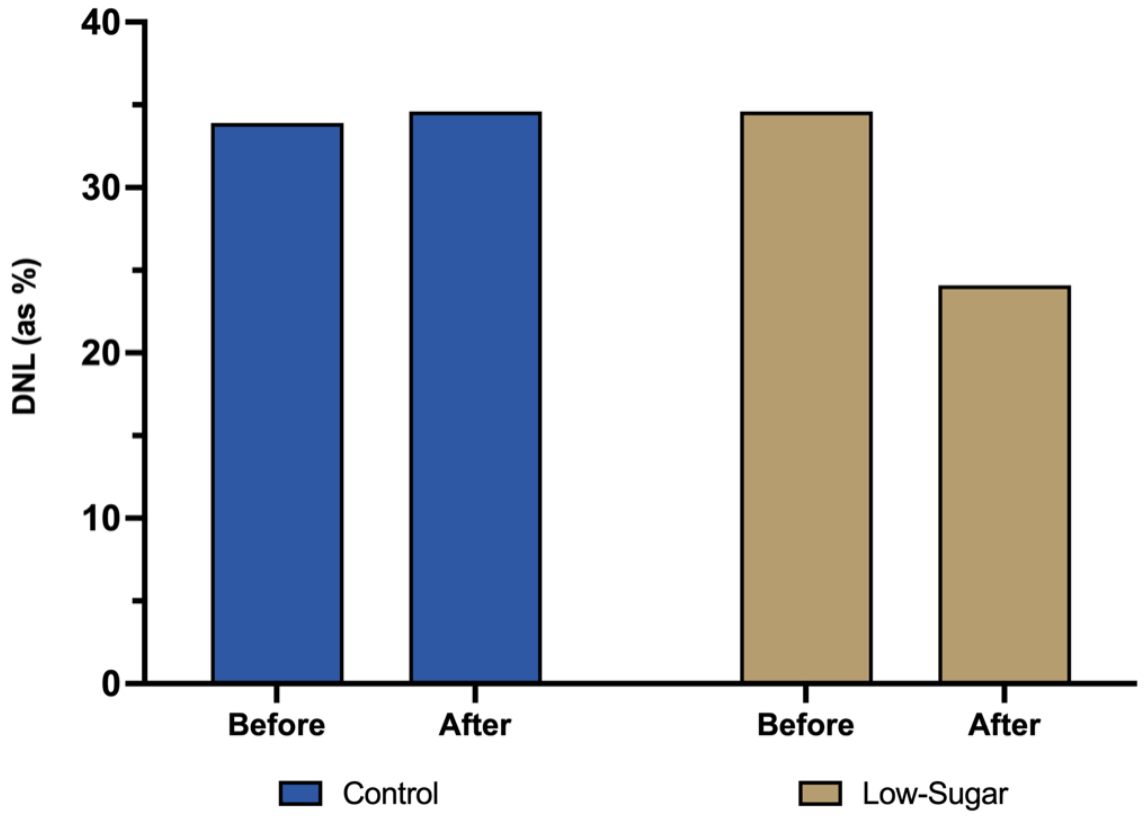
Now, what does this have to do with nutrition research? Well, recall that carbon is an element in each macronutrient; fats, carbohydrates, and proteins. As such, it is possible to chemically enrich nutrients with less abundant stable isotopes. For example, you could take a fatty acid, and substitute the ^{12}C for a ^{13}C isotope [this would all be done in the lab]. Substituting the more abundant ^{12}C for the less abundant ^{13}C in the fatty acid would then create a 'tracer', meaning that it has the same chemical properties of the original compound, but the appearance of the ^{13}C in the body is much more readily identifiable because of its scarcity.

You could do this for leucine, if the substrate you intended to 'trace' was a protein, and you could do it for glucose if the substrate you intended to 'trace' was a carbohydrate. There are other methods, too, that depend on the type of measurement being undertaken. For example, in the present study, doubly-labelled water was used to determine the contribution of DNL to triglycerides.

The use of stable isotopes in nutrition research is a fascinating area and provides nutrition science with a highly accurate methodology to precisely trace the metabolic fate of nutrients through the body.

Results: Average age of participants was 13.3yrs and 12.6yrs in the intervention and control groups, respectively. 16 participants in the intervention group and 13 from the control group completed the study. The treatment group lost 1.9kg compared to the control group.

- ***DNL*:** DNL decreased from 34.6% to 24.1% after 8-weeks in the intervention group, while there was no change in the control group. There was a 10.6% [95% CI, 2% to 19.1%] decrease in DNL between groups [see **figure**, below]. The results were similar when adjusted for weight change in both groups.
- ***Liver Fat*:** Liver fat levels decreased by 6.3% [95% CI, 2.6% to 10.1%] between groups.
- ***Correlations*:** The reduction in DNL correlated modestly with the reduction in added sugar intake, however, there was no correlation between the reduction in hepatic fat and DNL.



The Critical Breakdown

Pros: Participants were randomised using computer-generated assignments. Randomisation was conducted in blocks of 2-4 participants to maintain balance between groups, and stratified according to study site. DNL was assessed by stable isotope tracers both before and after, rather than just at baseline. This is pretty impressive given the level of compliance involved [drinking doubly-labelled water for 7-days for each assessment]. Both DNL and liver fat were assessed using advanced, accurate laboratory methods. Although 24 h recalls were used to assess diet, there were multiple repeated measures at different timepoints throughout the study. The participants were also from a minority ethnic population relevant to the demographics of the U.S. [97% were Hispanic].

Cons: The study sample only included boys, so the findings may not extrapolate to adolescent girls. There was imbalanced intensity of intervention between groups, with the treatment group receiving dietetic support and bi-weekly telephone calls to bolster adherence; this may have introduced bias toward the intervention group. The study was open label, and so all researchers were aware of the dietary assignment. The sample was small, and the study would require confirmation in a larger paediatric sample.

Key Characteristic

Although the sample size was small, the fact that stable isotope labelling was undertaken both before and after is a major strength of the present study. The method used in this study requires both the 7-day period of doubly-labelled water intake together with the use of mathematical modelling to determine the contribution of triglycerides that are actually derived from DNL, and not derived from other pathways of triglyceride synthesis or delivery to the liver.

Importantly, it provides an assessment of liver DNL that integrates a full week, thus minimising day-to-day variation. And it is clear that the reduction in sugar intake correlated with the change in DNL, with an r of 0.48 in the total study group and $r = 0.42$ in the intervention group, indicating a moderate positive correlation between change in sugars and change in DNL [remember the scale for these correlations is -0.1 to 1.0].

Interesting Finding

If there was a decrease in DNL from free sugars, why did the change in DNL not correlate with changes in hepatic fat? It could be that the actual levels of liver fat were high in both groups and, although there was a significant reduction between groups in hepatic fat. For example, in the intervention group liver fat levels at baseline were 25.5% and decreased to 17.9%.

While this would be good return on investment, it may not correlate strongly with DNL given that these processes are not necessarily mutually dependent. For example, in the adult research it has been shown that although free sugars will increase DNL, there are still greater increases in liver fat levels from overfeeding saturated fats [(5)]. Other research has also shown that in response to sugar feeding, DNL may only contribute 4-8% to triglycerides in either participants with NAFLD or healthy controls [(7)].

None of this is intended to downplay either finding; the decrease in DNL or the reduction in liver fat. Merely to highlight the pathways of liver fat accumulation are complex, and DNL is just one of three main pathways of liver fat accumulation.

Relevance

The level of sugar reduction achieved in the present study is impressive for a paediatric setting, and added sugars intake in the intervention group was estimated at 1.1%, well below the <3% target of the study. To be fair, achieving this required substantial intervention by the research team, removing added sugar products from the participants' homes and providing foods and meals. Nevertheless, it does indicate what is possible to achieve in the paediatric context with targeted effort.

The results are encouraging, and highlight the relationship between added sugars and DNL in adolescents with NAFLD. This relationship between sugars and DNL, of course, is nothing new and is a well-established impact of added sugars on metabolism [1,2].

One important consideration, however, is the fact that participants in the present study were 97% Hispanic, and ethnic differences in the role of DNL in fatty liver have been observed [8]. Thus, further paediatric research will need to consider potential ethnic differences in the pathways of liver fat accumulation.

Overall, the fact that DNL is significantly higher in the presence of fatty liver makes the present findings relevant, if not somewhat predictable from the achieved restriction in added sugars, for paediatric NAFLD.

Application to Practice

Most guidelines now recommend reduction in sugar levels to <5% energy, particularly for children and adolescents where other negative impacts such as dental caries show associations with sugar. For those working with paediatric populations, attention in the present study should be given to the lengths that were taken to facilitate the reduction in added sugars; a whole-family affair could likely provide the best odds to achieve the desired outcome. Either way, at this juncture in the wider evidence of what we know, reducing dietary added sugars is hardly a controversial recommendation for diet. But for adolescents, particularly those at higher levels of adiposity, the benefit of earlier risk reduction and improved cardio-metabolic health warrants an emphasis on added sugar reduction.

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