

Combatting the Fructose Epidemic

Citation for published version (APA):

Buziau, A. M. (2023). Combatting the Fructose Epidemic: Fruitful or Fruitless? [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20231113ab

Document status and date: Published: 01/01/2023

DOI: 10.26481/dis.20231113ab

Document Version: Publisher's PDF, also known as Version of record

Please check the document version of this publication:

 A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.

• The final author version and the galley proof are versions of the publication after peer review.

 The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these riahts.

Users may download and print one copy of any publication from the public portal for the purpose of private study or research.

- You may not further distribute the material or use it for any profit-making activity or commercial gain
 You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Impact paragraph

Non-alcoholic fatty liver disease (NAFLD) is a major health burden worldwide (with a prevalence of 25% in the adult population).¹ NAFLD is a risk factor of other noncommunicable diseases including type 2 diabetes mellitus (T2DM), chronic kidney disease, cardiovascular disease, and cancer.²⁻⁴ Intrahepatic lipid (IHL) accumulation (the first stage of NAFLD) is, among others, driven by the conversion of simple sugars into fatty acids via hepatic *de novo* lipogenesis (DNL).⁵⁻⁷ However, which simple sugar – fructose or glucose – plays the greater role in the augmentation of DNL has been the subject of much debate.⁸ Therefore, the overall aim of this thesis was to determine the role of fructose in the pathophysiology of NAFLD, and the possible underlying mechanisms. This chapter describes how the findings of this thesis may impact scientific research, society, policy, and clinical practice.

Implications for the prevention of fructose-induced non-alcoholic fatty liver disease at the population level – Societal measures

IHL accumulation is an asymptomatic disease with low awareness among patients and clinicians, despite the increasing prevalence and the associated morbidity and mortality. An understanding of disease etiology is essential to adequately treat NAFLD patients. This thesis has gained (additional) insight into the causal relationship between fructose and NAFLD and provides evidence that fructose causes IHL accumulation in humans. Furthermore, findings in this thesis imply that fructose from fruit juice and sugar-sweetened beverages (SSB) may be more prone to cause IHL accumulation than fructose from fruit. Therefore, implementation of societal measures to reduce fructose intake at the population level (in particular from fruit juice and SSB) are an important goal for the foreseeable future.

National dietary recommendations should be updated, especially since various nutritional recommendations have currently not established a place for fruit juice.¹ We showed in this thesis that fruit, fruit juice and SSB possibly have different effects on liver health and should be considered in the establishment of future nutritional recommendations.⁹ Specifically, it should be advised to avoid fruit juice and SSB, rather than to completely refrain from fructose since other fructose-containing foods like fruit and vegetables contain essential nutrients (e.g. vitamin C and fibers). In addition, fruit juice is still perceived as healthy by both adults and children¹⁰, which demonstrates the need for education to improve health literacy with a view to the adoption of a healthy diet.

Nonetheless, long-term compliance to dietary guidelines is challenging¹¹⁻¹⁴, and, thus, additional societal measures are warranted to reduce the intake of fructose at the

population level. We should redesign our living environment by disincentivizing unhealthy food products and nudging consumers towards healthy food choices (e.g. warning labels, in-store promotions of healthier beverages, fruit, and vegetables, price increases on SSB [and possibly fruit juices], and increasing the availability of low-calorie beverages^{15,16}), which can to a large degree be accomplished by legislation. For example, the implementation of an excise tax on SSB has a beneficial, reducing effect on fructose intake^{17,18} and, therefore, has been advocated by the World Health Organization.¹⁹ Notably, fruit juice (without added sugar) is currently exempted from all these levies.^{17,18} Furthermore, the excise tax on SSB incentivizes manufacturers of SSB to reduce the sugar content in their products.¹⁸ Although together these changes are modest at the individual level, they can have substantial health effects at the population level (=prevention paradox).²⁰

Implications for the treatment of non-alcoholic fatty liver disease in patient groups – Pharmacological measures

Findings presented in this thesis show that reduced fructose metabolism protects from IHL accumulation (and T2DM, hypertension, myocardial infarction, and colorectal cancer). These findings provide therapeutic opportunities, namely blocking ketohexokinase (KHK) activity. Indeed, previous studies have shown that the blocking of KHK-C ameliorated fructose-induced IHL accumulation in rodents.^{21,22} In addition, pharmaceutical companies have recently initiated programs aimed at developing novel and specific KHK inhibitors. For example, a potent reversible KHK inhibitor (i.e. PF-06835919; tested in a Phase 2 clinical trial), was well tolerated, resulted in pronounced fructosuria (~4.5 g/day), and reduced IHL by ~19% at the background of their normal diet in adults with NAFLD.²³ Of interest, the elevated urinary fructose levels due to pharmacological KHK inhibition appear clinically asymptomatic and benign (similar to individuals with essential fructosuria who have a loss of *KHK* [EC 2.7.1.3; OMIM #229800]).

Moreover, treatment with a pharmacological KHK inhibitor is of particular interest for patients with hereditary fructose intolerance (HFI). Patients with HFI cannot metabolize fructose due to a genetic defect (and thus accumulate hepatocellular fructose 1-phosphate [F1P]). Dietary treatment with complete fructose, sorbitol and sucrose restriction has been effective in preventing acute HFI manifestations.²⁴ However recent studies have shown that, despite this diet, HFI patients still suffer from hepatic steatosis^{25,26}, which may even evolve in non-alcoholic steatohepatitis and fibrosis.²⁷ These studies also identified hepatocellular F1P (or concomitant hepatocellular ATP and phosphate depletion) as culprit in the pathogenesis of HFI, which may be due to the trace amounts of fructose in the diet and/or endogenous fructose production.^{22,28} This

illustrates that dietary treatment may be insufficient to prevent long-term chronic liver manifestations and that novel therapeutic approaches to HFI are an emerging need. It is expected that pharmacological KHK inhibitors – by preventing F1P accumulation – may be a complementary therapy to ameliorate clinical manifestations in HFI patients.

Implications for future scientific studies

Results of this thesis provide starting points for future research. First, future studies should identify the key molecular mechanisms by which fructose participates as signalling molecule in the pathogenesis of IHL accumulation, and the role of F1P herein. Second, future studies should investigate the effects of different fructose sources in relation to IHL accumulation in humans, and the role of intestinal and hepatic fructose metabolism herein.

Conclusions

Taken together, based on this thesis we can conclude that it is FRUITFUL to combat the current fructose epidemic, as it will result in a lower risk of IHL accumulation, T2DM, hypertension, myocardial infarction, and colorectal cancer. The findings of this thesis may have implications for several stakeholders, such as the general population, certain patient groups (e.g. HFI), health care professionals (including dieticians and clinicians), the pharmaceutical industry, insurance companies, policy makers, and the food industry, as they support measures to reduce fructose intake at the population level (by societal efforts such as updated dietary guidelines and an excise tax on SSB) and to reduce/impair fructose metabolism in certain patient groups (by pharmacological KHK inhibitors), in order to combat the current fructose-induced NAFLD epidemic and its sequelae.

References

- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
- 2. Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. Diabetes Care. 2018;41(2):372-82.
- 3. Brouwers M, de Graaf J, Simons N, Meex S, Ten Doeschate S, van Heertum S, et al. Incidence of type 2 diabetes in familial combined hyperlipidemia. BMJ Open Diabetes Res Care. 2020;8(1):e001107.
- 4. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65(3):589-600.
- Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. Gastroenterology. 2014;146(3): 726-35.
- Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. J Clin Invest. 2020;130(3):1453-60.
- Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005;115(5):1343-51.
- Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, Carleton AJ, et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr. 2014;68(4):416-23.
- 9. Avignon A. Protecting the Liver: Should We Substitute Fruit Juices for Sugar-Sweetened Beverages? Diabetes Care. 2022;45(5):1032-4.
- 10. Bucher T, Siegrist M. Children's and parents' health perception of different soft drinks. Br J Nutr. 2015;113(3):526-35.
- Alkerwi A, Sauvageot N, Nau A, Lair ML, Donneau AF, Albert A, et al. Population compliance with national dietary recommendations and its determinants: findings from the ORISCAV-LUX study. Br J Nutr. 2012;108(11):2083-92.
- 12. de Abreu D, Guessous I, Vaucher J, Preisig M, Waeber G, Vollenweider P, et al. Low compliance with dietary recommendations for food intake among adults. Clin Nutr. 2013;32(5):783-8.
- Malon A, Deschamps V, Salanave B, Vernay M, Szego E, Estaquio C, et al. Compliance with French nutrition and health program recommendations is strongly associated with socioeconomic characteristics in the general adult population. J Am Diet Assoc. 2010;110(6):848-56.
- 14. Serra-Majem L, Ribas-Barba L, Salvador G, Serra J, Castell C, Cabezas C, et al. Compliance with dietary guidelines in the Catalan population: basis for a nutrition policy at the regional level (the PAAS strategy). Public Health Nutr. 2007;10(11A):1406-14.
- von Philipsborn P, Stratil JM, Burns J, Busert LK, Pfadenhauer LM, Polus S, et al. Environmental Interventions to Reduce the Consumption of Sugar-Sweetened Beverages: Abridged Cochrane Systematic Review. Obes Facts. 2020;13(4):397-417.
- 16. World Health O, Rios-Leyvraz M, Montez J. Health effects of the use of non-sugar sweeteners: a systematic review and meta-analysis. Geneva: World Health Organization; 2022 2022.
- 17. Falbe J, Thompson HR, Becker CM, Rojas N, McCulloch CE, Madsen KA. Impact of the Berkeley Excise Tax on Sugar-Sweetened Beverage Consumption. Am J Public Health. 2016;106(10):1865-71.
- Pell D, Mytton O, Penney TL, Briggs A, Cummins S, Penn-Jones C, et al. Changes in soft drinks purchased by British households associated with the UK soft drinks industry levy: controlled interrupted time series analysis. BMJ. 2021;372:n254.
- 19. WHO. Health taxes: a primer (a WHO policy brief). World Health Organization; 2019.
- Rose G. Strategy of prevention: lessons from cardiovascular disease. Br Med J (Clin Res Ed). 1981;282(6279):1847-51.
- 21. Gutierrez JA, Liu W, Perez S, Xing G, Sonnenberg G, Kou K, et al. Pharmacologic inhibition of ketohexokinase prevents fructose-induced metabolic dysfunction. Mol Metab. 2021;48:101196.

- 22. Lanaspa MA, Andres-Hernando A, Orlicky DJ, Cicerchi C, Jang C, Li N, et al. Ketohexokinase C blockade ameliorates fructose-induced metabolic dysfunction in fructose-sensitive mice. J Clin Invest. 2018;128(6):2226-38.
- 23. David J. Kazierad KC, Veena R. Somayaji, Arthur J. Bergman, Morris J. Birnbaum, Roberto A. Calle. Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: A randomized phase 2 trial. Med. 2021:1-14.
- 24. Demirbas D, Brucker WJ, Berry GT. Inborn Errors of Metabolism with Hepatopathy: Metabolism Defects of Galactose, Fructose, and Tyrosine. Pediatr Clin North Am. 2018;65(2):337-52.
- 25. Di Dato F, Spadarella S, Puoti MG, Caprio MG, Pagliardini S, Zuppaldi C, et al. Daily Fructose Traces Intake and Liver Injury in Children with Hereditary Fructose Intolerance. Nutrients. 2019;11(10):2397.
- 26. Simons N, Debray FG, Schaper NC, Kooi ME, Feskens EJM, Hollak CEM, et al. Patients with aldolase B deficiency are characterized by an increased intrahepatic triglyceride content. J Clin Endocrinol Metab. 2019;104(11):5056-64.
- Zheng M, Huang DQ, Konkwo C, Agrawal S, Khera AV, Loomba R, et al. Genomic analysis of lean individuals with NAFLD identifies monogenic disorders in a prospective cohort study. JHEP Rep. 2023;5(4):100692.
- Simons N, Debray FG, Schaper NC, Kooi ME, Feskens EJM, Hollak CEM, et al. Patients With Aldolase B Deficiency Are Characterized by Increased Intrahepatic Triglyceride Content. J Clin Endocrinol Metab. 2019;104(11):5056-64.