Combatting the Fructose Epidemic

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 non-communicable 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 children[10], 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 challenging[11-14], 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.

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