Published in final edited form as:
Curr Opin Clin Nutr Metab Care. 2012 July ; 15(4): 392–396. doi:10.1097/MCO.0b013e3283544477.

Genetic-related and carbohydrate-related factors affecting liver fat accumulation

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Abstract

Purpose of review—To summarize recent findings that have examined dietary, genetic and gene–diet interactions that contribute to fat accumulation in the liver during growth and development, with particular focus on contributions relating to dietary carbohydrate and sugar consumption. In addition, this review highlights how some of these contributions to liver fat vary across the population in terms of ethnic-specific effects.

Recent findings—Dietary carbohydrate, and especially sugars contribute to increased liver fat accumulation due to the lipogenic potential of fructose during liver metabolism. In addition, recent genome-wide studies have identified several polymorphisms that contribute to increased liver fat accumulation, with some of these genes relating to dietary carbohydrate and sugar consumption. In particular, the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene, which is highly prevalent in Hispanics, contributes to excessive liver fat beginning at a young age, especially in the context of high sugar consumption.

Summary—Dietary sugar contributes to liver fat accumulation, with this being explained by de-novo lipogenesis from fructose in the liver. Certain genetic factors, including PNPLA3, glucokinase regulatory protein and APOC3 contribute to increased liver fat accumulation, with these effects being manifested at an early age. Hispanics in particular are at elevated risk for liver fat accumulation because of the higher frequency of genetic variants such as PNPLA3 and glucokinase regulatory protein as well as an interaction between the PNPLA3 and dietary sugar.

Keywords

fatty liver; genetic; obesity; sugar

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of large droplets of triglycerides within hepatocytes in the absence of chronic alcohol consumption. NAFLD may lead to nonalcoholic steatohepatitis, cirrhosis, and eventually hepatocarcinoma [1, 2]. The purpose of this review is to summarize recent findings that have examined dietary, genetic and gene–diet interactions that contribute to fat accumulation in the liver during growth and development, with particular focus on contributions relating to dietary carbohydrate consumption. In addition, another focus of this review is to highlight how

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Conflicts of interest
There are no conflicts of interest.

some of these contributions to liver fat vary across the population in terms of ethnic-specific effects.

SUGARS AND LIVER FAT ACCUMULATION

Several recent studies support the concept that carbohydrate intake, and more specifically sugar, is a major culprit in liver fat deposition, due primarily to the high lipogenic potential of fructose. Maersk *et al.* [3■■] randomly assigned 47 overweight individuals to receive 1 liter per day for 6 months of cola, milk (same calories as the cola), sugar-free cola or water. There were no changes in total fat mass across groups but the cola group had significant increases in liver fat (~35%) as well as increased visceral fat (~25%) and triglycerides (32%). Le *et al.* [4] conducted a study in 16 male offspring of type 2 diabetes and eight controls who received either 7 days of an isocaloric diet or a hypercaloric diet using fructose to increase daily energy by 35% in a crossover design. The high-fructose diet liver fat increased by 76% in controls and 79% in offspring type 2 diabetes. Stanhope *et al.* [5] examined overweight and obese individuals who consumed glucose or fructose sweetened beverages for 10 weeks at 25% of daily energy requirements under closely controlled conditions. No data on liver fat are available yet from this study, but the results showed that despite similar weight gain in the two groups, the fructose group had a significant increase in visceral fat (14 vs. 3% increase in glucose group), and hepatic de-novo lipogenesis (+75 vs. +27%), both indicating the likelihood of greater liver fat accumulation. Using more invasive liver biopsies, one study has identified a link between dietary fructose and the severity of liver damage [6]. Despite this accumulating evidence, not all studies have demonstrated a relationship between increased dietary fructose and increased liver fat. For example, Silbernagel *et al.* [7] conducted a trial over 4 weeks with 20 healthy nonobese individuals who were placed on a weight maintaining diet and either 150 g per day of fructose or glucose (noncrossover design). There were no significant effects of fructose or glucose on insulin resistance, visceral fat or liver fat, possibly due to the smaller sample size and shorter feeding period of 4 weeks. Even though there were no changes in liver fat, this study did find that circulating triglycerides were 44% higher after fructose with no change after glucose.

GENETIC CONTRIBUTORS TO NONALCOHOLIC FATTY LIVER DISEASE

The emergence of genome-wide association studies (GWAS) has led to the identification of several loci associated with NAFLD and/or hepatic inflammation, and some of these loci relate to carbohydrate metabolism. Of the three GWAS studies to date that have been undertaken to specifically identify potential genetic variants that impact hepatic fat content [8■■, 9■, 10■], two have identified specific loci that purportedly play a role in hepatic triglyceride content. The first of these GWAS encompassed over 9000 nonsynonymous sequence variant single nucleotide polymorphisms (SNPs) that were tested in adult Hispanic (n = 383), African–American (n = 1032) and white (n = 696) participants [8■■], from the Dallas Heart Study, for associations with hepatic fat levels measured by spectroscopy [11]. This study revealed that a SNP (rs738409; C > G) in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene was strongly associated with both hepatic fat content and inflammation (as determined by elevated serum liver enzymes) in all three ethnic groups. However, the frequency of the variant allele was highest in Hispanics (49%) with individuals homozygous for the variant having approximately two-fold higher hepatic triglyceride content than noncarriers.

The association of PNPLA3 with NAFLD has been replicated in numerous subsequent studies, thus confirming this gene as an important genetic determinant of hepatic fat accumulation. Of note, several recent studies have also shown that the effect of this gene is

manifested in children [12■, 13, 14]. One study in over 300 Hispanic children showed that liver fat in homozygous variant carriers of the rs738409 SNP was almost 2.5 times higher than noncarriers, and that this effect extended to the youngest children (8–10 years) [12■].

Another more recent GWAS was conducted in over 7100 adult individuals participating in several population-based cohort studies [10■]. A subset of 592 patients, with biopsy-proven non-alcoholic steatohepatitis, were used to validate the 45 loci that were associated with hepatic triglyceride content and five SNPs were found to be associated with NAFLD [computed tomography or histologically defined]; PNPLA3 (rs738409), neurocan (rs2228603), lysophospholipase-like 1 (rs12137855), glucokinase regulatory protein (GCKR; rs780094) and protein phosphatase 1, regulatory subunit 3B (PPP1R3B; rs4240624). The aforementioned effect of the PNPLA3 variant on hepatic fat was replicated in this study with the rs738409 SNP being highly associated with NAFLD as determined by both CT and histology. Novel associations with the remaining four SNPs and NAFLD were also reported but, with the exception of GCKR, have yet to be confirmed in independent studies. For example, GCKR has also been associated with NAFLD in an adult Chinese population [15] as well as in Hispanic children [16]. Analogous to PNPLA3, threat–risk variant is fairly frequent in Hispanics (~36%), suggesting that GCKR may further contribute to the increased genetic risk for high liver fat and NAFLD in this population.

More recently, Petersen *et al.* [17■] carried out a candidate gene study and reported that variants of APOC3 (rs2854117 and rs2854116) were associated with NAFLD in Asian–Indian men, with findings replicated in a larger validation group of white men. Among variant allele carriers, 38% were positive for NAFLD, whereas the prevalence of NAFLD in wild-type homozygotes was 0% [17■]. Several studies thereafter have been unable to replicate these associations with hepatic fat in multi-ethnic adult populations [16, 18–21] and only two studies have been conducted thus far in children [16, 20]. One group was unable to show an association with APOC3 SNPs and the severity of liver damage, independent of the effects of PNPLA3 [20]; however, the study was conducted only in Italian participants. The second study consisted of a larger group of 455 children and also did not observe any associations with liver fat in Hispanics, African–Americans or whites [16]. Further studies with larger sample sizes will be required to better understand the potential contributions of these APOC3 polymorphisms to the complex pathological progression of liver disease [22]. These efforts should also include Hispanics, who are the most at-risk group for developing NAFLD, as the effects of the APOC3 variants may either be ethnic-specific or stronger in certain populations.

NUTRIGENETIC INTERACTIONS

Given the adverse effects that dietary sugar has in promoting accumulation of fat in the liver, an interesting extension of genetic studies with NAFLD has been the identification of gene–dietary interactions. For example, a nutrigenetic analysis with the PNPLA3 rs738409 variant in Hispanic children revealed that hepatic fat was positively related to carbohydrate ($r = 0.38$, $P = 0.02$) and total sugar ($r = 0.33$, $P = 0.04$) intakes but only in the homozygous variant group [23■■]. These findings suggest that Hispanic children with two copies of the PNPLA3 variant (GG) are particularly susceptible to increased liver fat in the context of high dietary sugar, whereas such a nutrigenetic effect is not apparent in CC and CG individuals. Notably, the results of a recent short-term intensive dietary intervention are consistent with the observed nutrigenetic association with PNPLA3 [24■]. In this study, 18 adults with NAFLD (matched for elevated liver fat content) were preselected on the basis of PNPLA3 genotype and placed on a 6-day hypocaloric, low-carbohydrate diet. Although hepatic fat content significantly decreased in both GG ($n = 8$) and CC ($n = 10$) individuals, the reduction in liver fat was 2.5-fold greater in GG homozygotes. This differential effect

was observed even though weight loss was similarly marginal in the two genotype groups (~3%). Thus, this latter study demonstrates that PNPLA3 variant homozygotes respond better to a low-carbohydrate diet with respect to liver fat reduction, which can be observed in as few as eight individuals.

BIOLOGICAL MECHANISMS

One important consideration in genetic studies of NAFLD is an understanding of the underlying biological mechanisms, particularly for genes whose functional role in hepatic triglyceride metabolism is not initially evident. In this regard, APOC3 is thought to potentially influence NAFLD by delaying the metabolism of triglyceride-rich lipoprotein particles, which increases their uptake by the liver [17■]. GCKR inhibits glucokinase activity, thereby regulating glucose storage/disposal and increasing substrate availability for de-novo lipogenesis [25]. PPP1R3B, a serine/threonine phosphatase involved in hepatic glycogen synthesis could thus modulate risk of NAFLD through a similar mechanism as GCKR. Thus, it is possible that the association of these genes with NAFLD is mediated through their effects on adiposity, lipid metabolism and/or glucose homeostasis.

By comparison, less is known about the function of PNPLA3 and, as this gene is the most strongly associated genetic risk factor for NAFLD, we will focus most of our discussion on functional studies of this protein. PNPLA3, or adiponutrin, encodes a protein in hepatocytes that has been reported to have lipase-like activity and promote hepatic triglyceride hydrolysis [26, 27]. In addition, PNPLA3 has been shown to have specific hydrolase activity against triglycerides but not other lipid substrates, such as phospholipids, cholesteryl ester and retinyl esters [27]. On the basis of these studies, this putative enzyme does not appear to promote de-novo hepatic triglyceride synthesis, although it is possible that PNPLA3 has other functional properties that have yet to be determined [27]. Animal studies have also shown that expression of hepatic PNPLA3 mRNA levels is low during fasting and increases approximately 90-fold in response to carbohydrate feeding [28■]. This effect occurs as a secondary effect of insulin-mediated upregulation of sterol regulatory element binding protein 1 (SREBP-1) and liver X receptor, which are important transcription factors responsible for fat metabolism in the liver. Although this transcriptional effect would presumably not differ across genotypes, recent studies have shown that the G variant substitutes a methionine at position 148 in the protein and abolishes PNPLA3 hydrolase activity [26], which would presumably increase risk of NAFLD by inhibiting hepatic fat mobilization. This notion would also be consistent with the nutrigenetic interactions described above because homozygous GG individuals would consequently be more susceptible to the effects of dietary sugar as transcriptional upregulation of PNPLA3 would still result in a protein with severely reduced function.

Other animal studies, however, do not support this biological model. For example, two groups have independently knocked out PNPLA3 in mice using gene targeting and do not observe any effects on hepatic triglyceride accumulation, glucose homeostasis, lipid levels or body composition [29■■, 30■■]. These surprising results were observed even after the mice were placed on either a genetically induced obesity background (i.e. leptin deficiency) or on a variety of diets, including those with high sucrose content. Two other interesting observations from these studies were that expression of PNPLA3 is regulated in a nutrient-specific manner, consistent with previous observations, and that PNPLA5 is upregulated several fold in adipose tissue of PNPLA3-deficient mice. The latter findings suggest that the increased expression of PNPLA5 in adipose, which is a paralog of PNPLA3, may serve as a compensatory mechanism for the lack of PNPLA3, although it was also observed in both studies that PNPLA5 expression was either very low or not detectable in liver. By comparison, another study used the adenovirus system to perturb PNPLA3 expression [31].

Whereas overexpression of PNPLA3 in mouse primary hepatocytes increased intracellular triglycerides, knockdown of PNPLA3 suppressed SREBP-1-stimulated lipid accumulation. Thus, despite the strong and compelling genetic evidence in humans that PNPLA3 influences the development of NAFLD, these important animal studies suggest that species-specific differences may exist with respect to how this putative triglyceride hydrolase mediates liver fat accumulation and that additional studies will be needed to understand the precise role that PNPLA3 (and the rs738409 variant) plays in hepatic lipid metabolism.

CONCLUSION

New studies point to the contributing role of dietary sugar in the accumulation of fat in the liver, with this being explained by the potential of fructose to serve as a substrate for de-novo lipogenesis in the liver. In addition, genetic variants associated with liver fat accumulation are being identified with mechanism of action in some cases being closely related to carbohydrate metabolism. Hispanics in particular are at elevated risk for liver fat accumulation due to the higher frequency of variants such as PNPLA3 and GCKR. Given the high frequency of the PNPLA3 rs738409 variant and the increasing prevalence of NAFLD and obesity in Hispanic children and adolescents, high levels of added sugar intake likely play a vital role in the pathogenesis of the disease in Hispanics. This gene–diet interaction is a specific example with translational implications, as this finding suggests that specific interventions based on reducing dietary sugar intake in genetically predisposed individuals may lead to more effective therapeutic outcomes for fatty liver. Although previous studies have shown that weight loss alone can lead to significant and rapid reduction in liver fat in children and adults, this strategy may not be sustainable and may not be effective in certain subgroups depending on genotype. Therefore, other adjunct strategies are required that may need to target individual genotype, to prevent and/or treat the accumulation of fat in the liver for overall improvement of metabolic health.

Acknowledgments

None.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 407).

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KEY POINTS

- New studies point to the contributing role of dietary sugar in the accumulation of fat in the liver, with this being explained by the potential of fructose to serve as a substrate for de-novo lipogenesis in the liver.
- Hispanics in particular are at elevated risk for liver fat accumulation because of the higher frequency of genetic variants such as patatin-like phospholipase domain-containing protein 3 (PNPLA3) and glucokinase regulatory protein (GCKR).
- The combination of greater frequency of liver fat gene variants and high dietary sugar, as well as an apparent interaction between the PNPLA3 rs738409 variant and dietary sugar is of particular concern among Hispanics.
- Other adjunct strategies in addition to weight loss are required to prevent and/or treat the accumulation of fat in the liver for overall improvement of metabolic health, and these strategies may need to be specific to ethnicity and genotype.