Editorial

Genetic predisposition and increasing dietary fructose exposure: The perfect storm for fatty liver disease in Hispanics in the U.S.

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1. Predisposition to NAFLD in Hispanics

As the prevalence of overall obesity has increased in much of the developed and developing world, non-alcoholic fatty liver disease (NAFLD) is of increasing concern. A study of autopsy samples found that 38% of obese children had NAFLD [1], showing that NAFLD is a critical issue for obese children as well as for adults. NAFLD may lead to non-alcoholic steatohepatitis, cirrhosis, and eventually hepatocarcinoma, and is also associated with the development of type 2 diabetes.

Previous studies show that NAFLD is particularly prevalent in Hispanics, and Hispanics constitute the fastest growing segment of the U.S. population. According to data from the 2010 census, the most represented ethnic groups in the United States are non-Hispanic whites (64%), Hispanics (16%), and blacks (13%) [2]. However, the percentage of Hispanics in the United States is increasing rapidly. Between 2000 and 2006, the growth rate among Hispanics was 24.3% as compared to the rate of 6.1% in the total population [3]. In a study of 2287 adults in the U.S., NAFLD prevalence was highest in Hispanics (45%) and lowest in African Americans (24%), as compared to 33% in whites [4]. In our ongoing studies in Los Angeles, we have shown that 38% of obese Hispanic children and adolescents have liver fat accumulation >5.5% by magnetic resonance imaging (MRI) [5], indicating likely NAFLD. The prevalence of NAFLD in our non-clinical pediatric cohorts is higher than for pre-diabetes and metabolic syndrome (~30%), suggesting that NAFLD may be the most common co-morbidity in overweight/obese Hispanic youth. Perhaps not surprisingly, Hispanics have a >5-fold higher risk of liver cancer mortality compared to other ethnicities [6], which may be due, in part, to the high prevalence of NAFLD in this population and its long term pathogenesis.

A recent genome-wide association study in adults identified a novel genetic factor explaining some of the striking ethnic difference in liver fat accumulation [7]. An amino acid substitution (I148M; rs738409) in the PNPLA3 gene was associated with over 2-fold higher liver fat content in adults, with the strongest effect observed in Hispanics in whom the frequency of the variant was much higher (49%) than Caucasians (23%) or African Americans (17%). Importantly, these associations were not confounded by genetic admixture, lending support for the consistent effects observed across populations [7]. The function of this gene is not entirely known but has been reported to affect triglyceride hydrolysis in the liver. In addition, this variant is associated with severity of steatosis and fibrosis in patients with NAFLD [8]. We have recently documented the prevalence and impact of PNPLA3 on variation on liver fat in younger Hispanic children and adolescents [5].

2. Role of dietary sugar in promoting NAFLD

Several studies have shown that carbohydrate, and more specifically dietary fructose, is a major culprit in liver fat deposition, due primarily to the higher lipogenic potential of this sugar through de novo lipogenesis in the liver. In addition to this direct effect of higher sugar (and specifically fructose) on liver fat deposition, we also now have evidence of a gene-diet interaction, such that in Hispanic children, liver fat fraction is positively related to total sugar intake but only in subjects carrying the GG risk allele in PNPLA3 [5]. These findings suggest that Hispanics carrying the GG genotype are particularly susceptible to increased liver fat in the context of high dietary sugar. This finding is consistent with our current, though limited, understanding of PNPLA3 function. These findings support the hypothesis that dietary sugar reduction might be a useful strategy in NAFLD patients homozygous for the G allele of PNPLA3, although this concept remains to be tested.

3. Trends of sugar consumption in Hispanics

High consumption of sugar, especially fructose, is of particular concern for Hispanics given the genetic predisposition for NAFLD and the interaction of this gene with dietary sugar. The consumption of total fructose in the United States increased by nearly 30% between 1970 and 2000, largely due to the increased use of high
fructose corn syrup (HFCS) [9]. Soft drinks in the United States, as well as some other popular sugar-sweetened beverages, are sweetened primarily with HFCS, but it is difficult to quantify how much fructose is actually ingested from HFCS due to lack of industry disclosure on food labels. In a recent exploratory study, we found that fructose in some soft drinks, especially the most popular, was about 20% higher than expected, suggesting that some manufacturers might be using HFCS with more fructose than previous estimates [10]. Furthermore, some products, such as Coca-Cola® from Mexico, that do not list HFCS on the labelling, were found to have high fructose levels. In essence, these data suggest that consumers may be ingesting more fructose than has been previously estimated and calls for clearer labelling on foods and drinks related to sugar composition. Although national data does not indicate that Latinos have a higher consumption of sugar or sugar-sweetened beverages than other ethnic groups [11,12], studies do show that as Latinos become more acculturated in America, their consumption of sugar and sugar-sweetened beverages rises [13].

Increasing sugar and fructose consumption is of concern in Mexico as well. Recent studies show that dietary sugar consumption is very high and increasing over time in Mexico, especially beverage consumption [14,15]. In a company report, Coca-Cola® showed that in 2010, Mexico had the highest per capita consumption of company beverage products (675 products per capita, as compared to 394 products per capita in the US) [16]. Furthermore, consumption of Coca-Cola® beverage products in Mexico has risen dramatically over the past few decades; between 1988 and 2008 there was a near threefold increase in consumption. Comparatively, there was a 1.5 fold increase in the United States over the same period [17]. Data show that in Mexico, much of the advertising for sugar-sweetened products is directed to children, making children especially vulnerable to industry influence. Pérez-Salgado et al. found that food advertising in Mexico is greater during children’s television than during programming targeted to the general audience (25.8 vs. 15.4%) and that the more frequently advertised products were sweetened beverages, sweets, and cereals with added sugar [18].

The rise in sugary beverage consumption in Mexico, and specifically products sweetened with HFCS, can be largely attributed to partnerships with the United States that have been made possible through the North American Free Trade Agreement (NAFTA). Between 1993 (when NAFTA was passed) and 2008, the trade of sweeteners was still restricted between the two countries, but beginning January of 2008, these restrictions were removed. Mexico is now one of the most important markets for American-produced HFCS, and exports to Mexico have spiked almost 4 fold in the last 10 years, with most of this increase occurring since the trade restrictions were lifted in 2008 [19]. These policies and trade sanctions should be reviewed and reconsidered, in order to moderate the fructose content in the food supply and prevent increases in NAFLD rates, particularly in youth who will arguably be most affected by the shifts in fructose availability.

4. Summary

We are witnessing a confluence of factors that promote the development of NAFLD in Hispanics. These factors cover the spectrum of levels of exposure from individual genes to global trade policy (see Fig. 1) and include: genetic predisposition with a gene apparently specific to Hispanics, increased consumption and exposure to dietary sugar and especially fructose, and agricultural policies that promote the use of HFCS (Fig. 1). These conditions create a perfect storm which should be both monitored and prevented to ensure the health of future generations of Hispanics in both the U.S and Mexico. Public health strategies could include genetic screening for predisposition to NAFLD, culturally tailored educational campaigns to promote reductions in added sugar intake, and policies to limit the production and trade of HFCS.

Conflict of interest statement
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References
[10] Ventura EE, Davis JN, Goran MI. Sugar content of popular sweetened beverages based on objective laboratory analysis: focus on fructose content. Obesity (Silver Spring) 2011;19:866–84.


