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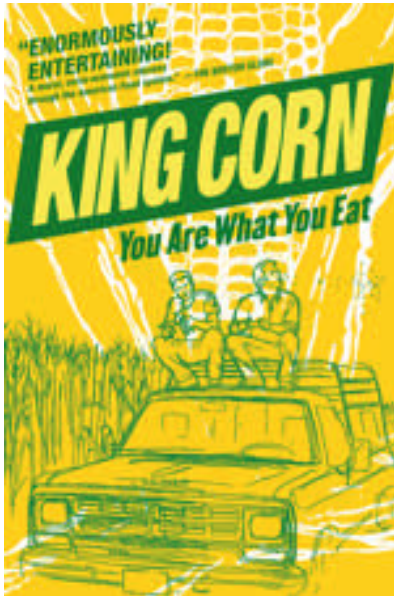
## **“The Perfect Storm” for Fatty Liver Disease in Hispanics: The Role of Diet, Genes, High Fructose Corn Syrup and Global Trade Policies**

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The tongue-in-cheek documentary "KING CORN: You are What You Eat" is a commentary on today's fast food nation and the ubiquity of corn in today's diet in the United States (US). The movie is based around the story of two college buddies who return to where they were raised in Iowa to figure out how corn took over the American diet. Corn does indeed form a significant part of the diet in the US, in many forms. Of particular concern is the chemical transformation of corn into high fructose corn syrup (HFCS), which is part of a major shift in the food supply there, and a contributing factor to the rise in obesity.

One of the co-morbidities associated with obesity is non-alcoholic fatty liver disease, which occurs when excess fat gets deposited in the liver. Over time this can lead to liver diseases and liver cancer. Studies in the US show that Hispanics are more susceptible to deposition of excess fat in the liver, more so for example than other groups such as African Americans who tend to deposit excess fat in peripheral locations such as the legs and buttocks. In fact, fatty liver disease appears to be the most prevalent co-morbidity of obesity in Hispanics. The process of liver fat accumulation begins early in life, and in studies of both children and adults fatty liver is highest among Hispanics compared to other ethnic groups, with almost 40% of obese Hispanics probably having this condition. The underlying explanation of this phenomenon can be traced to multiple factors at the level of diet, genetic susceptibility, increasing amounts of sugar and especially high fructose corn syrup, as well as global trade policy in these dietary components.

From a dietary perspective, it is well known that sugar, and fructose in particular, plays a key role in the accumulation of fat in liver. This is explained by a variety of metabolic factors that are unique to fructose, compared to other sugars like glucose, that ultimately make it more likely for fructose to be converted to fat in the liver. The consumption of total fructose in the US increased by nearly 30% between 1970 and 2000, largely due to the increased use of HFCS in the manufacturing processes of foods and beverages. Although national data do not indicate that Hispanics have a particularly high consumption of sugar or sugar-sweetened beverages, studies do show that as they settle in the US their consumption of sugar and sweetened beverages rises.

The genetic susceptibility to fat deposition in liver was identified several years ago in a genome-wide association study that identified a novel genetic. Individuals carrying this gene which is a single amino acid substitution in the PNPLA3 gene had a >2-fold higher liver fat content. Moreover, the frequency of this polymorphism was highest in Hispanics. One out of two Hispanic adults carry this gene variant compared to 23% of Caucasians and 17% of African Americans. These findings have been replicated in other populations including children, and raise the question of the origins of this particular gene variant among Hispanics.

In addition to the direct effects of fructose and the PNPLA<sub>3</sub> gene on liver fat, there is also evidence of a gene by diet interaction since it has been shown that Hispanic children carrying the genetic risk in PNPLA<sub>3</sub> are even more susceptible to increased liver fat in the context of high dietary sugar. Thus the combination of high sugar consumption (and presumably higher fructose consumption) and the genetic defect in PNPLA<sub>3</sub> that is highly prevalent in Hispanics is particularly problematic for liver fat deposition.

The production of HFCS from corn is a highly processed system that creates a complex mixture of sugars from corn that is higher in fructose than ordinary table sugar. The use of HFCS is highly favored by the food and beverage industry because it has many advantages over table sugar, such as being sweeter, cheaper, and leading to production of foods and drinks that have longer shelf-life and are more appealing due to differences in texture and coloring after baking. HFCS became a major part of the US diet from the 1970s onwards when its production was an alternative use for US-grown corn, at a time when its role as a source of vegetable oil was usurped by the cheaper soy bean. The US is the world's largest producer of corn, and the surpluses diverted into HFCS production from the 1970s were enormous. The consumption of total fructose in the US increased by nearly 30% between 1970 and 2000. Between 1994-1998, the intake of HFCS by US citizens above the age of two years was 318 calories per day, or one sixth of all energy intake and one third of all carbohydrate intake. By the late 1990s, HFCS was the predominant caloric sweetener in soft drinks. Though often estimated at 55% fructose, it is difficult to quantify the actual fructose content of HFCS and of foods and beverages made with it. This is due to lack of industry disclosure on food labels since in the US all sugars are lumped together. One recent study analyzed various beverages and found a much higher than expected fructose content.

The potential problem of obesity and associated co-morbidities like fatty liver are compounded in Hispanics living outside of the US due to dramatic developments in the global sugar trade. Recent data show that dietary sugar consumption is very high and increasing over time in Mexico, especially beverage consumption. Arguably, 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 were made possible through the North American Free Trade Agreement (NAFTA). Between 1993 (when NAFTA was passed) and 2008, the trade of sweeteners was still quite restricted between the two countries. Beginning in January of 2008, these restrictions were removed. Exports of HFCS from the US to Mexico have subsequently increased exponentially over the last 6 years, with most of this increase occurring since the trade restrictions were lifted in 2008. This dramatic shift in the food supply will likely pose an even greater risk for younger generations in Mexico given the heavy marketing of sweet products to Mexican children.

In summary, we are witnessing a confluence of factors that promote the development of excess fat deposition in the liver in Hispanics. These factors cover a spectrum of levels of exposure, from diet to genes and global trade policy. Together, these factors create a "perfect storm" for the conditions of fatty liver disease in Hispanics in the US.