Fructose, Insulin, and Childhood Obesity

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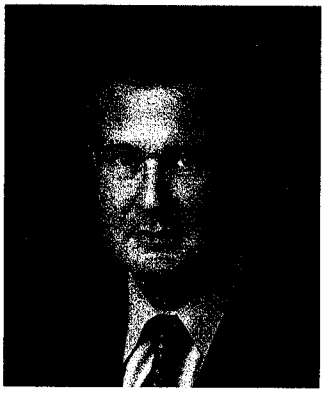

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Introduction:

The obesity epidemic shows no signs of relenting. There is now more obesity globally than there is malnutrition. Not only has the frequency increased, but the severity of obesity in terms of BMI distribution, the prevalence of co-morbidities, and the increases in frequency of bariatric surgery document that obesity is more severe as well. The incidences of obesity-related insulin resistance and its spinoffs ~ metabolic syndrome, non-alcoholic fatty liver disease, and polycystic ovarian syndrome ~ continue to escalate. Worse yet, the greatest increase in prevalence is in the youngest members of society. The 2 - 5 year old demographic is experiencing the most rapid rise in obesity, and metabolic syndrome is even more frequent among obese children than it is among obese adults. We even have an epidemic of obese 6-month olds. Obesity is said to be an interaction between genetics and environment. Our genes haven't changed in 30 years, but our environment sure has. The obese 6-month old is the "exception that proves the rule." While it is easy to ascribe blame to our current dietary and exercise practices, how does this explain the obese 6-month old? What follows is a brief discussion of the actual biochemical alterations that promote obesity, and a suggestion of the changes we can make in the food environment to halt this childhood obesity epidemic.

Insulin and obesity

Insulin is the energy storage hormone. What you don't burn, you store in fat tissue, under the influence of insulin. This is obvious to every physician who treats diabetic patients, as their weights increase with insulin. Things that make insulin go up cause energy storage, and things that make insulin go down promote energy burning. Insulin does three things which put it front and center in obesity physiology. 1) Insulin drives energy into fat for storage. 2) Insulin interferes with leptin signaling at the hypothalamus (the energy control center of the brain). This results in leptin resistance, which results in decreased sympathetic tone, reducing energy expenditure and physical activity, and in increased vagal activity, which promotes further insulin secretion, appetite, and energy storage. 3) Insulin interferes with the clearance of dopamine in the nucleus accumbens (the reward center of the brain), thus increasing the reward of food. Thus, hyperinsulinemia turns the negative feedback system of energy balance into a positive feedback or "vicious cycle," promoting obesity. Externally, this appears as "gluttony and sloth," but it is biochemically driven.

How does this work? A thin, insulin sensitive 13 year old might consume a daily allotment of 2000 kcal, and burn 2000 kcal daily in order to remain weight-stable, with a stable leptin level. However, if that same 13 year old became hyperinsulinemic and/or insulin resistant, perhaps as many as 250 kcal of his daily allotment would be shunted to storage in adipose tissue, promoting a persistent obligate weight gain. Due to the obligate energy storage, the child now only has 1750 kcal per day to burn. The hyperinsulinemia also results in a lower level of hypothalamic leptin signaling, conveying a central signal of energy insufficiency. The remaining calories available are lower than his energy expenditure; the hypothalamus would sense starvation. Through decreased sympathetic tone, he would reduce his physical activity; through increased vagal tone, he would increase caloric intake and insulin secretion, but now at a much higher level. Furthermore, the insulin prevents the extinguishing of the reward pathway, promoting increased intake as well.

Where did the hyperinsulinemia come from?

At least 3 separate reasons for hyperinsulinemia in children can be discerned. 1) Genetics: children from certain racial and ethnic groups have increased insulin dynamics even prior to the development of obesity, which may predispose them to increased weight gain. 2) Epigenetics: the "fetal origins of adult disease" hypothesis states that those born small- and large-for-gestational age at birth are prone to developing obesity; both birth weight extremes are states of hyperinsulinemia and insulin resistance, which may worsen beyond

the neonatal period. 3) Our food environment: our current Western food environment is highly insulinogenic, as demonstrated by its increased energy density, high fat content, high glycemic index, decreased fiber, and decreased dairy content. But in particular, the monosaccharide fructose appears to be a cornerstone of the obesity epidemic, through its effects on insulin.

Fructose and insulin

The primary stimulus to insulin release at the pancreas is glucose, found in all forms of carbohydrate (refined starch, legumes). Carbohydrate intake increases insulin release and increases weight gain. However, the other insulin-promoting nutrient is fructose, found in sugar. Fructose does not stimulate insulin directly, but rather promotes insulin resistance.

The most commonly used sweetener in the U.S. diet is the disaccharide sucrose (e.g. table sugar), which contains 50% fructose and 50% glucose. However, in North America and other countries, non-diet soft drinks are sweetened with high-fructose corn syrup (HFCS), which contains up to 55% of the monosaccharide fructose. Thanks to its abundance, sweetness, and low price, HFCS has become the most common sweetener used in processed foods. HFCS is found in processed foods ranging from soft drinks and candy bars to crackers to hot dog buns to ketchup. It's not that HFCS is biologically more ominous than sucrose; it's that its low cost has made it available to everyone, especially low socioeconomic groups. Fructose is fructose, whatever its source. Average daily fructose consumption has doubled over the past 30 years and increased 6-fold in the past century. The growing dependence on fructose in the Western diet may be fueling the obesity and T2DM epidemics.

Both animal and human studies demonstrate that high-fructose diets lead to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance. The hepatic metabolism of fructose differs significantly from glucose. Fructose is absorbed in the intestine and enters the liver without insulin regulation. There, fructose is converted to fructose-1-phosphate (F1P), consuming ATP and increasing the formation of uric acid, which suppresses the action of nitric oxide on vascular smooth muscle and promotes hypertension. F1P enters the glycolytic pathway without regulation. This leads to an accumulation of xylulose-5-phosphate, which stimulates the process of de novo lipogenesis, increasing VLDL production, which promotes atherogenesis. The glycolysis of fructose ultimately leads to an over-accumulation of acetyl-CoA in the hepatocyte, some of which cannot be metabolized through the Krebs cycle; therefore, it is then reassembled into free fatty acids (which promote pancreatic insulin hypersecretion) and triglycerides (some of which precipitate in the liver and cause hepatic insulin resistance and non-alcoholic steatohepatitis). Fructose also does not suppress secretion of the so-called "hunger hormone" ghrelin, levels of which correlate with perceived hunger. Finally, fructose has both direct and indirect effects (through insulin) which activate the reward pathway to foment increased consumption, similar to the process of addiction.

In sum, fructose consumption has metabolic and hormonal consequences different from glucose that facilitate development of obesity and the complications of the Metabolic Syndrome. The highest fructose loads are soda (1.7 gm/oz) and juice (1.8 gm/oz).

What can be done?

As you can see, if our food supply has been adulterated, obesity becomes a public health issue, not a personal responsibility issue. This is going to take an exceptional policy effort addressing the food environment, and will take parent, school, community leader, physician, food industry, and politician education and action. But in the meantime, here are some suggestions.

1) Remove ALL sugar sweetened beverages from schools and school lunches. Juice, sports drinks, and even chocolate milk are as dangerous as soda.
2) Restrict marketing of ANY AND ALL fructose-containing foods to children.
3) Provide parent education at various medical interaction points, e.g. prenatally, at birth, and at doctor office visits.
4) Consider legislation that subsidizes fresh fruit and vegetable (endogenous fructose) consumption while taxing the consumption of fructose-added foods.
5) Change WIC rules so that fresh fruits are covered and juices are not.
6) Most importantly, the Food and Drug Administration has given fructose GRAS (generally regarded as safe) status, allowing the food industry to add as much as they want to our food. This designation must be repealed.

There are many other ways to impact the childhood obesity epidemic, working on the energy expenditure side of the argument. But until our food supply is de-fructosified, don't expect the obesity epidemic to go away.

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