Fructose = Fatty Waistline + Fatty Liver

After many decades of Nutri-Spec, we Nutri-Spec practitioners are still asking ourselves, "Which is the most devastating to our health and the health of our patients --- polyunsaturated fatty acids (HOHUM PUFAs = Heated, Oxidized, Hydrogenated, Un-Metabolizable PUFAs = all vegetable oils --- soy, canola, sunflower, safflower, sesame, peanut, walnut --- which includes all salad dressings, mayonnaise, nuts, and nut butters, and all foods grilled or fried in those oils) --- OR --- FRUCTOSE (--- which makes up 50% of what we call "sugar", and more than 50% of the calories in fruit and honey). The devastation inflicted by each of HOHUM PUFAs and Fructose is so severe, there is no point in declaring a "Champion Devastator". Let us just call it a tie, and move forward with this document on the nasty consequences of fructose.

First, we need to resolve the question of "natural" verses "artificial". There is absolutely nothing "natural" about eating fruit or honey. When considering nutrition, it is always wise to use Natural Law as our guide. If fructose were a natural part of the human diet, it would be plentifully available in our natural environment. ----- How many significant sources of fructose can you name? There are absolutely none in the natural world.

Our only substantial sources of fructose are fruits and honey. Honey comprises an insignificant percentage of the human calories consumed over the millennia. And the fruits we have available today that are so unnaturally high in fructose are manmade hybrids. There were never any such fruits available to humanity until the last couple centuries. And until the last couple decades in America and other Western countries, they were extremely scarce --- never making up a significant percentage of human caloric intake.

When my patients try to tell me fruit and honey are "natural sugars," and are therefore far superior to refined sugar, I patiently explain the truth. First, I make it clear to them that the fruits we eat today are agribusiness creations, and never existed in nature. Then, I go on to help them realize that our digestive tract and our liver and our fat cells and our brain are totally incapable of distinguishing between a fructose, glucose, or sucrose molecule that comes from fruit, or honey, or from the sugar bowl. In their mini lesson in food chemistry I make it clear that white refined sugar is exactly 50% fructose and 50% dextrose, and that fruit sugar and honey sugar is even higher in fructose than is sucrose --- the very sucrose that has severely overloaded the livers of those of us consuming the "Western Diet". And so, since fructose is the sugar with disastrous health consequences, that makes fruit and honey even more harmful than sucrose.

I finish my presentation by telling my patients, "You can eat all the fruit you can find growing in nature within 100 miles of your home, and all the honey you can manage to steal from a beehive."

The undeniable truth about fructose? Here are the essentials:

- Fructose is hepatoxic
- Fructose raises triglycerides
- Fructose elevates cholesterol
- Fructose causes weight gain

- Fructose destroys glycemic control, leading to dysinsulinism, then insulin resistance, then Type II Diabetes
- Fructose causes high blood pressure
- Fructose causes gout
- Fructose causes arteriosclerosis
- Fructose causes free radical oxidative damage
- Fructose increases inflammatory cytokines
- Fructose impairs Oxidative Phosphorylation of the Electron Transport Chain in the mitochondria. ATP energy production suffers.
- Fructose promotes the growth of unhealthy microbiota --- with countless ramifications over the Gut-Liver Axis, Gut-Immune Axis, Gut-Brain Axis, and the Gut-Adipose Axis

To complete your ugly picture of fructose, you must realize that these nasty impairments are not caused by ingesting dextrose (glucose). Whether that dextrose derives from digestion of complex carbohydrates, or from ingestion of pure dextrose as part of a meal --- as long as the overall diet is balanced, there are no negative effects from carbs/dextrose.

The evidence: The incidence of obesity and associated complications has closely followed the increased consumption of fructose. Many studies indicate that fructose has greater obesity-generating potential than other sugars.

The liver is the key organ for understanding the deleterious health effects promoted by fructose consumption. Fructose promotes inefficiencies in glucose energetics, accumulation of triglycerides in hepatocytes (Metabolic-Associated Fatty Liver Disease = MAFLD), and alterations in the lipid profile, which, associated with an inflammatory response and alterations in the redox state, leads to insulin resistance.

In contrast, physical exercise has been indicated for the treatment of several chronic diseases. Much research has investigated how various exercise protocols (aerobic, strength, or a combination of both) promote improvements in the obesity created by fructose consumption --- by improving serum and liver lipid profile (increasing HDL, decreasing triglycerides and LDL cholesterol), as well as reduction of the inflammatory markers caused by fructose .

Simply replacing fructose by glucose for 4 weeks results in improvement in insulin sensitivity in adipose tissue in young subjects diagnosed with MAFLD.

The harmful effects of fructose are also found in the first months of life, as newborns breastfed by mothers who ingested fructose during pregnancy or lactation present metabolic alterations that may last throughout the infant's life. Children of mothers who consume fructose have increased body weight, food intake, and circulating levels of leptin, and decreased insulin sensitivity.

It is also shown that each glass of fructose-containing beverage ingested daily by a child increases by up to 6 times the probability that child will become obese during adulthood.

Many studies show fructose consumption leads to accumulation of adipose tissue, systemic inflammation, obesity, oxidative stress, and insulin resistance in multiple tissues. The systemic inflammation includes elevation of the proinflammatory cytokines Interleukin-1ß, Interleukin-6, and TNF-α.

Test animals consuming fructose solutions show higher levels of ghrelin than animals consuming an equal amount of glucose. In animals fed a high fructose diet for eight weeks, the leptin levels are approximately 100% higher than in test animals fed the chow diet. One important study with primates shows that diets rich in fructose induce fatty liver, with lipid droplet size positively correlated to length of exposure to the diet. High fructose consumption induces liver damage even without intake of excess calories or excess fat.

In human adolescents, high fructose consumption results in higher fasting insulin, serum uric acid, and abdominal weight gain. Many human studies show an elevation of triglycerides caused by fructose consumption. One notable study finds that subjects consuming only 150 g of fructose for 4 weeks show a triglyceride elevation to 350, while subjects who consume the same amount of glucose (dextrose) show no elevation whatsoever in triglycerides. The elevation of triglycerides begins after only 7 days of fructose supplementation.

Increased fructose intake also increases lactic acid production and hampers mobilization of lipids from fat cells.

Leptin levels are increased by 48% after 4 weeks of fructose supplementation.

Only 9 days of a fructose-rich diet is enough to raise liver lipid accumulation and cause a significant increase in postprandial de novo lipogenesis, plus complications in control of hepatic glucose production.

Supplementing the diet with equal calories of fructose or saturated fat for only 7 days shows no increase in VLDL in those eating excess saturated fat, but shows significant elevation of VLDL in the fructose-rich supplement group, thus indicating liver fat accumulation and the development of hepatic insulin resistance. (Note that saturated fat (demonized by the medical/pharmaceutical establishment for decades) causes zero adverse effects associated with MAFLD. ----- It is HOHUM PUFAs that rival fructose for the title “Champion Devastator.”)

Intestinal absorption of glucose is via GLUT5, releasing it into the bloodstream. Assimilation of fructose occurs mainly in the liver, which has a high level of GLUT2. In contrast, virtually no fructose is absorbed by pancreatic beta cells since they lack GLUT2 and GLUT5 transporters. This is the critical distinction for understanding the pathogenesis of obesity from fructose . While glucose triggers the release of insulin from the pancreas, fructose does not. Neither does fructose activate leptin release nor suppress the release of ghrelin in the fasting state.

Insulin, leptin, and ghrelin are the 3 peptide hormones that fundamentally control food intake and basal energy expenditure, acting both in the central nervous system and peripheral tissues. Insulin and leptin reduce the hunger signal and hepatic gluconeogenesis, and contribute to energy expenditure. In contrast, fructose causes increased food intake, while glucose decreases it.

In addition to the anti-metabolic effects on satiety and energy expenditure and the inhibition of glucose uptake for energetics, fructose also activates extremely harmful signaling pathways in the liver. Again, since most tissue cells have low GLUT2 content, the overwhelming burden of fructose is placed on the liver with its high GLUT2. The immediate effect on the liver is to decrease energetic availability in hepatocytes and increase the content AMP. This in turn activates mitochondrial energetics pathways that increase the NAD+/NADH ratio, which in turn leads to increased Sirtuin-1 and PPCK.

The Sirtuin-1 ultimately results in increased rates of hepatic gluconeogenesis and hyperglycemia. Additionally, the increase in AMP triggered by fructose activates the hypoxanthine pathways, which increase inflammation and produce uric acid. The uric acid inhibits nitric oxide synthase, thus causing vasoconstriction of the arteries. Elevated systemic blood pressure can result. This explains the contribution of fructose to diabetes, gout, endothelial inflammation, and hypertension.

Fructose compared to glucose also increases fatty acid synthesis. As fructose progresses through its unique form of glycolysis, it alters the Krebs Cycle to produce an excess of malonyl-coA, thus inhibiting the carnitine transport of lipids in the mitochondria and stopping beta oxidation of fatty acids. The excess fatty acids now are diverted into triglyceride production leading to fatty liver disease.

Fructose also activates ApoB to produce VLDL, or simply releases the Free Fatty Acids into the bloodstream, triggering elevation of cholesterol and triglyceride. The excess influx of lipids generates hypertrophy of White Adipose Tissue, and triggers insulin resistance in skeletal muscle, while inhibiting pancreatic secretion of insulin.

There are other mechanisms by which fructose increases hepatic insulin resistance, and increases hepatic gluconeogenesis, leading to significant elevations in blood sugar and contributing to weight-gain. Insulin signaling is reduced by nearly 72% in the livers of test animals exposed to a fructose-rich diet.

As fructose activates reactive oxygen species formation and the expression of inflammatory cytokines in the hepatocyte, there is tissue damage and inflammation identical to the liver damage caused by alcohol. The hypertrophy of White Adipose Tissue also triggers an increased release of inflammatory cytokines by the adipocyte. TNF-α is particularly elevated. Another family of inflammatory receptors, toll-like receptors (TLRs), magnify the inflammatory response in the liver and in skeletal muscle, exacerbating insulin resistance. In the central nervous system these inflammatory cytokines prevent efficient signaling of leptin and insulin by inhibiting the effect of these peptides on food consumption, energy expenditure, and central control of the hepatic gluconeogenesis.

Interestingly, the harmful effects of fructose are the polar opposites of the beneficial effects of exercise. We can look at that phenomenon in two ways …

EITHER EXERCISE MITIGATES SOME OF THE DAMAGE OF FRUCTOSE, OR, FRUCTOSE DESTROYS THE BENEFITS OF YOUR EXERCISE REGIMEN.

At rest, GLUT4 is stored in the liver's intracellular vesicles. But shortly after exercise, GLUT4 is distributed throughout the hepatic plasma membrane, just as it is stimulated by insulin after a meal. The distribution of GLUT4 in the plasma membrane in response to exercise involves activation of AMPK, which is essential for control of energy balance. AMPK activates the phosphorylation that promotes the release of GLUT4 via a mechanism that is independent of insulin action.

Note that all your patients with either Glucogenic or Ketogenic Imbalance desperately need activation of AMPK --- and your Energetics G and K are formulated to do just that.

Obese individuals who are sedentary show insulin resistance, but when the obese exercise aerobically, the insulin signaling pathway is similar to non-obese individuals. The mechanism at work here may be the reduction of proinflammatory proteins by aerobic exercise as well as the inhibition of PTP-1B, which is involved with insulin resistance. Therefore, aerobic exercise increases both insulin action in skeletal muscle, and, glucose uptake by a mechanism independent of insulin action. Aerobic exercise can thus be called an insulin agonist. The benefits are not limited to skeletal muscle, but extend to the liver, hypothalamus, and adipose tissue.

Even a single aerobic exercise session reduces the level of PTP-1B and thus increases insulin signal transduction. And that exercise session also decreases the proteins involved in gluconeogenesis such as PEPCK and glucose-6-phosphatase. Aerobic exercise also decreases the markers of endoplasmic reticulum stress. Simultaneously, we have the activation of Protein Kinase B accompanied by decreased inflammation.

In the hypothalamus, aerobic exercise helps decrease hunger and satiety. Adipose tissue is also a target of aerobic exercise. Aerobic training decreases hypertrophy of adipocytes in obese animals, while simultaneously improving the systemic inflammatory status associated with obesity. Once insulin activity in metabolically active tissues is enhanced, serum proinflammatory proteins and fasting glucose are reduced. After 8 weeks of endurance training there is a decrease in TNF-α accompanied by a decrease in oxidative stress and an increased antioxidant capacity.

Aerobic exercise is also a strategy for preventing MAFLD. Sedentary obese animals have a 72% increase of fat accumulation in the liver with 48% more lipid vacuoles. However, aerobic exercise during an obesity induction period decreases the development of MAFLD. Exercise improves the oxidation of fatty acids in the liver. Exercise decreases the liver triglyceride level. Twelve weeks of aerobic exercise decreases triglyceride by 3.7%, while HDL increases by 4.6%, and LDL decreases by 5%.

[Note, however, these numbers, while statistically significant, are not clinically of major importance. A 3.7% decrease in triglycerides of an individual with a TG of 200 only drops it from 200 down to 192.]

Far more significant than the small benefits to lipid profile and insulin levels from aerobic exercise is the anti-fructose benefit of resistance exercise. Strength training is far more effective than aerobic training as a means to improve both glycemic control and normal lipid profile.

After 10 weeks of isotonic training with weights, participants show no change in fasting glucose, but plasma insulin is dramatically decreased from 10.8 to 6.8. During a glucose tolerance test the area under the insulinemic curve is significantly lower than the sedentary control group, thus demonstrating major improvement in insulin sensitivity.

The other benefit of strength training is that there is a major increase in muscle mass, which has a strong negative correlation with insulin levels during a Glucose Tolerance Test. Another study shows that after 16 weeks of strength training, body weight does not change significantly (as muscle mass is increased), but abdominal adipose tissue is significantly reduced.

GLUT4 gene expression is also increased by strength training. TNF-α and Interleukin-6 are decreased with training, accompanied by an increase in adiponectin. Interestingly, however, obese subjects undergoing strength training show improved insulin sensitivity independent of changes in proinflammatory cytokines. Another study shows that after a single strength exercise session the triglyceride level decreases, while sensitivity to insulin in hepatic tissue is improved by 8%, and there is a 12% decrease in hepatic glucose production.

Regarding liver tissue, strength training decreases fat accumulation and leads to a greater reduction in the level of the powerful proinflammatory NF-kB, yet another indication that strength exercise decreases inflammation --- including inflammation induced by a high-fructose diet.

One important study tested participants after their very first day of strength training. Fifteen hours after the training session, participants were fed a meal containing 0.75 g/kg body weight of fructose, then blood samples were taken for the next 6 hours. Insulin and lactate levels did not differ significantly between the training group and the non-training group after the fructose rich meal, but the postprandial triglyceride level was significantly lower in the group undergoing a single strength training session. In other words, a strength training workout performed prior to fructose-rich food attenuates the rise in triglyceride caused by fructose .

Regrettably, many studies show that in individuals on an exercise regimen that combines strength training with aerobic training ---

AEROBIC TRAINING NEGATES SOME OF THE BENEFITS OF STRENGTH TRAINING.

While an exercise regimen combining aerobic and strength training still yields benefits, it is particularly interesting that it yields zero improvement in waste circumference and waste to hip ratio, while strength training alone specifically reduces abdominal fat.

THE ULTIMATE EXERCISE PLAN ---

--- to yield health benefits by reversing all the damage done by dietary fructose (and also dietary HOHUM PUFAs) --- is a combination of strength training plus High-Intensity Interval Training. ----- But the intervals must be ultra short --- as brief as 8 seconds, and with a rest between sprints of only the time it takes to briskly walk back to the starting line. ----- Imagine the health benefits and youth-preserving effects you and your patients can achieve by combining a nearly zero fructose eating plan with an exercise plan that includes strength training and sprint interval training.

As destructive as is the direct metabolic damage inflicted by fructose, that harm is compounded by its disruption of the microbiome. It is critical that you understand the devastation of the microbiota from eating fructose. You have at your disposal the two synbiotic products (Immuno-Synbiotic Immune Restore, and Immuno- Synbiotic Immune Power) that are unmatched for their benefits to the Gut-Immune Axis, Gut-Liver Axis, as well as all the other Gut-Metabolic Axes. But eating fructose is enough to severely limit the benefits from Immuno-Synbiotic supplementation.

Consider these studies:

Microbiota and Fructose Intake

Thomas Jensen, et al. Fructose and Sugar: A Major Mediator of Non-alcoholic Fatty Liver Disease. Hepatol. 2018.

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of Metabolic Syndrome. Its rising prevalence parrels the rise in obesity and diabetes. Diets in high in fructose not only increase the risk of NAFLD, but also non-alcoholic steatohepatitis (NASH). Fructose precipitates fat accumulation in the liver due to both increased lipogenesis and impaired fat oxidation. (The same aberrant metabolism causes excess uric acid production.)

Alterations to gut permeability, the microbiome, and associated endotoxemia contribute to the risk of NAFLD and NASH associated with Fructose ingestion.

Jelena Todoric, et al. Fructose stimulated denovo lipogenesis is promoted by inflammation. Nat Metab. 2020.

Hepatosteatosis, affected by lipid intake, denovo lipogenesis and fatty acid oxidation, progresses to non-alcoholic steatohepatitis (NASH) on stress and inflammation. A key macro nutrient proposed to increase hepatosteatosis and NASH risk is fructose . Intake of fructose, causes intestinal barrier deterioration and endotoxemia. That deterioration depends on endoplasmic-reticulum stress and subsequent endotoxemia. The endotoxin triggers TNF production by liver macrophages, thereby inducing lymphogenic enzymes that convert acetyl-CoA to fatty acids in liver cells.

Young-Eun Cho, et al. Fructose promotes leaky gut, endotoxemia, and liver fibrosis through ethanol-inducible Cytochrome P450-mediated oxidative and nitrative stress. Hepatology. 2021.

Fructose intake is known to induce obesity, insulin resistance, metabolic Syndrome, and non-alcoholic fatty liver disease (NAFLD). This study evaluated the effects of fructose on gut leakiness, endotoxemia, and NAFLD to determine the underlying mechanism.
fructose ingestion caused microbiome change, leaky gut, and hepatic inflammation/fibrosis --- with increased levels of nitro-oxidative stress, inducible nitric oxide synthase, and nitrated proteins in the small intestine and the liver. Fructose significantly elevated plasma bacterial endotoxin levels, likely resulting from decreased intestinal tight junction proteins. In obese humans, consistently decreased intestinal TJ/AJ proteins and increased hepatic inflammation with fibrosis were observed on autopsy compared to lean individuals. Furthermore, there is markedly elevated hepatic fibrosis marker proteins in fructose-exposed rats compared to controls.

Ran Jin, et al. Fructose -induced endotoxemia in pediatric non-alcoholic fatty liver disease. Int J Hepatol. 2014.

In Fructose-induced NAFLD, endotoxin plays an important role. Adolescents with hepatic steatosis had elevated endotoxin levels compared to obese controls, and the endotoxin level correlated with insulin resistance and with several inflammatory cytokines. In a 24-hour feeding study, endotoxin levels in NAFLD adolescents increased after Fructose beverages (consumed with meals) as compared to healthy children. Similarly, endotoxin was significantly increased after adolescents consumed Fructose beverages for 2 weeks, and endotoxin remained high at 4 weeks.

Peng Zhou, et al. High Dietary Fructose Promotes Hepatocellular Carcinoma Progression by Enhancing O-GlcNAcylation Via Microbiota-derived Acetate. Cell Metab. 2023 Nov 7;35(11):1961-1975.e6.
https://pubmed.ncbi.nlm.nih.gov/37797623/

Emerging studies have addressed the tumor-promoting role of fructose in different cancers. The study shows that high dietary Fructose promotes liver cancer progression through microbiota-derived acetate-induced hyper-O-GlcNAcylation.

Rodrigo Martins Pereira, et al. Fructose Consumption in the Development Obesity and the Effects of Different Protocols of Physical Exercise on the Hepatic Metabolism. Nutrients. 2017 Apr 20;9(4):405. https://pubmed.ncbi.nlm.nih.gov/28425939/

Zheng J, et al. Early Life Fructose Exposure and its Implications for Long-Term Cardio-Metabolic Health in Offspring. Nutrients. 2016 Nov 1;8(11):685.
https://pubmed.ncbi.nlm.nih.gov/27809266/