SAFE HEALTH REPORT

Scientific Data … Informed Choice … Actionable

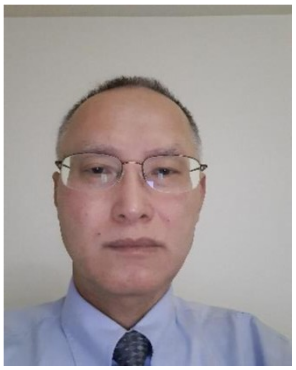
December 2022 *Official Newsletter for MrGineaPig* *Issue 5*

Please repeat once before proceeding: He Can Do It, She Can Do It, I Can Do It!

Inside …

Fructose Toxicity

Your Ticket to Exuberant Health for the next 5 years



Ike Kim, Editor

Main purpose of force-feeding high energy carbohydrate diet in ducks and geese is to produce *foie gras* via fat deposition in the liver. The liver increases in size by 5- to 10-fold in 2 weeks, which is accompanied by reversible hepatic steatosis. Production of triglycerides far exceeds the transport capacity of apo-lipoproteins that transport triglycerides to body tissues for storage as a fat. In addition, fatty acid production exceeds the capacity of mitochondrial beta oxidation of fatty acids.

What does all this mean?

Carbohydrate is a broad term that includes sugar, fruits, vegetables, fibers, and legumes. Carbohydrates are broken down into glucose upon consumption in the digestive tract. The digestive tract begins to break down carbohydrates into glucose. Non-digestible fiber and resistant starches are broken down by gut microbiome into short chain fatty acids (SCFAs) acetate (C2), propionate (C3), and butyrate (C4).

As carbohydrates are consumed, the blood sugar levels in the form of glucose increase, stimulating the pancreas to secrete insulin. Insulin signals the body's cells to utilize the glucose for energy production via mitochondria in under-fed state or storage as fat in hepatocytes and adipocytes in over-fed state. If blood glucose level falls, the pancreas makes glucagon, stimulating the liver to release stored glucose.

Mitochondria are cellular 'power plants' that provide energy via the process of oxidative phosphorylation (OXPHOS), a complex, highly coordinated process that requires the oxidation of NADH or FADH2

generated via glycolysis, Krebs cycle or β-oxidation of fatty acids. Mitochondrial dysfunction is a key mechanism that links obesity and type 2 diabetes (T2D), characterized by insulin resistance. Resulting chronic hyperglycemia, metabolic abnormalities (high glucose and triglyceride) and oxidative stress eventually lead to progressive β-cell loss and failure with subsequent decreased insulin secretion.

Now fructose enters the above scenario. Fructose metabolism by liver is a very lipogenic pathway as it provides carbon atoms for both the glycerol and the acyl portions of triglyceride. Fructose intake causes de novo lipogenesis in the liver, in which precursors of acetyl-CoA are converted into fatty acids without triggering insulin or leptin secretion. The ATP citrate lyase (ACLY) enzyme cleaves cytosolic citrate to generate acetyl-CoA and is upregulated after consumption of carbohydrates. Clinical trials are currently pursuing the inhibition of ACLY as a treatment for metabolic diseases.

Recent study by Zhao et al. published in the Nature on March 2020 edition challenges classical pathway of fructose-induced lipogenesis and reveals a novel pathway of lipogenesis activation by fructose. Using elegant in vivo isotope-tracer approaches (^{13}C labelling) in mice with liver-specific ACLY deficiency, Zhao et al. showed that fructose-derived carbons can be used for lipogenesis even in the absence of hepatic ACLY. They showed that fructo-lysis within hepatocytes provides a signal to promote the expression of cytosolic lipogenic genes (recall epigenetics discussed in September edition), and the generation of acetate made by intestinal microbiome. In summary, the authors showed that dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate.

What does all this mean? In addition to a microbially manufactured metabolite, delta-valerobetaine (VB), that impairs mitochondrial fatty acid β-oxidation (covered on November Issue), we now have another direct hepatic lipogenesis from gut microbiome-derived acetate.

Thus, even if one is not obese, developing central obesity appears to be the path of least resistance with currently widespread practice of dietary fructose consumption. Indeed, it would

be hard to find one single child who is mal- or under-nourished in the US or in any other Western country. It appears every child and adult is being over-fed in most of the developed nations! Yes, fructose would be fantastic way of energy storage every fall season to get ready for long winter months, but it is definitely detrimental to be consuming fructose every single day!

Take Home Lesson

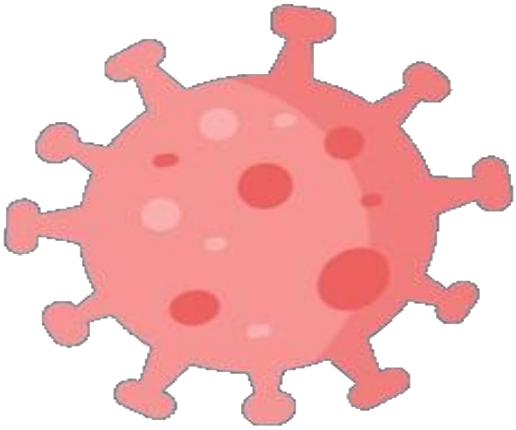
- ✓ **Fructose from sugar (also known as sucrose which is 50% fructose and glucose) and from high fructose corn syrup in carbonated beverages is highly obesogenic.**
- ✓ **Newly discovered direct pathway of fatty acid production via microbiome-derived acetate increases risk of obesity further.**
- ✓ **Minimize table sugar consumption and avoid carbonated beverages that contains high fructose corn syrup sweetener all together!**

- ✓ **You are causing your own little 'foie gras' with fructose!**

Covid19 Update

The virus is known as Severe Acute Respiratory Syndrome Coronavirus 2, abbreviated as SARS-CoV-2. The disease syndrome it causes is called coronavirus disease of 2019 or simply COVID-19. When one refers to COVID-19, it is the disease not the virus. Often, when referring to the virus, it may be referred to as COVID-19 virus rather than SARS-CoV-2. If you are 'Covid 19 Positive', it means you have the infectious viral disease confirmed by blood or

Figure 1. SARS-CoV-2



nasal test. SARS-CoV-2 is the common ancestor to many variants that that is commonly reported as alpha, beta, delta, omicron depending on virus's spike protein changes. All variants of the virus cause COVID-19, the disease. In July of 2022, Omicron BA.5 was the dominant strain, but giving way to Omicron subvariants BQ.1 and BQ.1.1 starting in October 2022 in the US.

Why all the fuss about the COVID-19? Well, about 1 out 6 people have complications, including some that may be life-threatening. The risk of severe complications is higher for older patients and patients with diabetes or heart disease. Complications are caused by a condition known as cytokine release syndrome or a cytokine storm. This occurs when an infection triggers your immune system to flood your bloodstream with inflammatory proteins called cytokines resulting in damages to your lungs, heart, and kidneys and other tissues. Death may result from acute respiratory failure, viral pneumonia, acute respiratory distress syndrome, acute liver injury, cardiac injury, acute kidney injury, septic shock, disseminated intravascular coagulation, blood clots, multisystem inflammatory syndrome in children, chronic fatigue, and rhabdomyolysis (destruction of muscle tissues) .

Latest COVID-19 bivalent booster vaccines were updated to fight **omicron** subvariants **BA.5** and **BA.4**, not specifically to **BQ.1** and **BQ.1.1**. But experts and vaccine manufacturers believe the shots will still provide protection against other omicron subvariants including **BQ.1** and **BQ.1.1**.

If you have any signs of COVID-19 complications, it is recommended to seek emergent medical care to beat the odds of premature death! Remember the virus does not have emotions one way or the other!

Recommendations:

- ✓ **New bivalent COVID vaccines are also expected to help prevent serious illness or death. It is available in many retail pharmacies, free of charge, since**

the US government has already paid for them on your behalf.

- ✓ **Nirmatrelvir/ritonavir (Paxlovid) which works by blocking an enzyme the virus needs to replicate, should work for BQ.1 and BQ.1.11. It is also paid by the US government on your behalf.**

Safety Tip for Nirmatrelvir/Ritonavir (Paxlovid) in Renal, Hepatic Impairments and Drug Interactions

Paxlovid contains nirmatrelvir that inhibits a SARS-CoV-2 protease enzyme, which stops viral replication. Paxlovid also contains ritonavir to prevent metabolism of nirmatrelvir to extend its duration of action. Primary outcome of study that allowed FDA to approve its Emergency Use Authorization (EUA) is that 0.8% of patients on Paxlovid were hospitalized or died by day 28 vs 6% of patients on placebo were hospitalized or died by day 28. Paxlovid reduced proportion of hospitalization/death by 88%.

For healthy patients without any kidney or liver impairment, 2 pink tablets and 1 white tablets for total of 3 tablets is taken twice daily as shown in the picture below. For patients with Creatinine Clearance between 30 and 60 ml/minute, the dose needs to be reduced to 150 mg nirmatrelvir (one pink 150 mg tablet) with 100 mg ritonavir (one white 100 mg tablet), with both tablets taken together twice daily for 5 days. Patients with creatinine clearance less than 30 ml/minutes or with liver disease, Paxlovid is contra-indicated and should not be taken. Taking Paxlovid is also contra-indicated or caution is advised for patients taking the following drugs due to drug-drug interaction. Please consult your healthcare provider for specific recommendations.

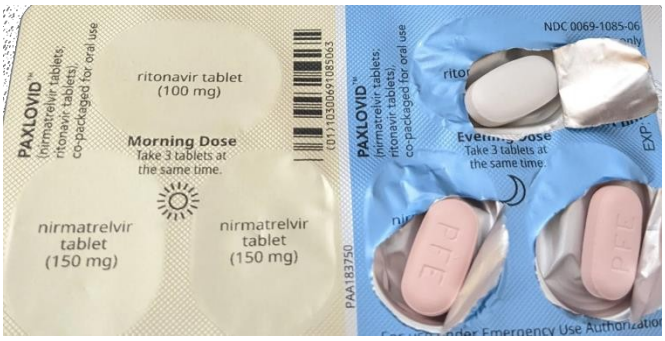


Table 1. Contra-indicated with Paxlovid

Contraindicated Medications	
• Alfuzosin • Amiodarone • Apalutamide • Apixaban • Carbamazepine • Clozapine • Colchicine • Cyclosporine • Dihydroergotamine • Disopyramide • Dofetilide • Dronedarone • Elbasvir/Grazoprevir • Eplerenone • Ergotamine • Everolimus • Flecainide • Glecaprevir/Pibrentasvir • Ivabradine • Lurasidone • Meperidine • Methylergonovine • Midazolam	• Phenobarbital • Phenytoin • Pimozide • Piroxicam • Primidone • Propoxyphene • Propafenone • Quetiapine • Quinidine • Ranolazine • Rifampin • Rifapentine • Rivaroxaban • Sildanafil • Sirolimus • St. John's Wort • Tacrolimus • Tadalafil • Ticagrelor • Triazolam • Voriconazole • Warfarin (Coumadin)

- ✓ **Make sure to tell your provider if you have renal or hepatic impairment.**

- ✓ **Check to see you are on any of the medications on the contra-indicated drug list. You may potentially not be a candidate for Paxlovid. Or your provider may have to make changes to your current drug regimen on the list.**
- ✓ **Retail pharmacies may charge you a flat fee of $40-60 for clinical assessment since there is no allowed dispensing fee for the free drug.**

FDA Medication/Food November Recall

Brand Name(s)	Product Description	Product Type	Recall Reason Description	Company Name
Giant	Smoked Salmon	Food & Beverages	Potential Listeria monocytogenes contamination	Seven Seas International USA, LLC
Gamesa	Arcoiris Marshmallow Cookies	Food & Beverages	Potential presence of Salmonella	Comercializadora PepsiCo S. de R.L. de C.V.
Adam's Polishes	Hand sanitizer	Drugs	Presence of methanol	Adam's Polishes, LLC
Insulet Corporation Omnipod DASH	Personal Diabetes Managers	Medical Devices	Battery issue: battery swelling, leakage, and in rare cases, extreme overheating, which has resulted in reports of fire.	Insulet Corporation
Gibeck® and Iso-Gard®	Bacterial and viral filters	Medical Devices	Filter may split or detach during use	Teleflex Incorporated
Kalera	Fresh Lettuce Products	Food & Beverages, Foodborne Illness	Salmonella	Kalera Public Limited Company

NESTLÉ® TOLL HOUSE®	Edible Chocolate Chip Cookie Dough	Food & Beverages	Potential for Soft Plastic Film	Nestle USA
Cedar Creek Popcorn	Old-Fashioned Caramel Holiday Popcorn Box	Food & Beverages, Allergens, Snack Food Item	Undeclared Wheat	Cedar Creek Popcorn

Case Number 4 Continued from November

Can this 51-year-old male be saved at least next 5 years?

Case examples present real life patient cases from the ground floor as we send these folks to palliative care or hospice care settings. Frailty score is often considered when making major placement decisions to optimize patient care. It is also used to see whether patient can withstand major surgical interventions. It is due to poor frailty score that patients often do not survive 5 years after major health crisis.

Eye of the Tiger Test for Thomas Gillen

*All patient data is fictional. Safe Health Report complies fully with US HIPPA regulations.

Clinical Frailty Score

- **1 – Very Fit: Very fit for their age with no disease symptoms, very active and exercise regularly- 5 days a week**
- **2 – Fit: Still no active disease as in 1 but exercise only occasionally – three times a week or only seasonally**
- **3 – Managing Ok: Disease symptoms are well managed. Not able to exercise at all other than walking.**
- **4 – Very Mild Frailty: Symptomatic disease. Not dependent on others for daily activities but disease symptoms slow down their activities. May need cane for walking occasionally for example**
- **5 – Mild Frailty: Symptomatic disease limit daily activities. Needs walkers. Needs help with walking and shopping.**
- **6 – Moderate Frailty: Needs helps with walking, shopping, climbing stairs, bathing with disease progression.**
- **7 – Severe Frailty: Completely dependent for personal care and daily activities but seem stable and at risk of death within the next 6 months.**
- **8 – Very Severe Frailty: Same as 7 but unstable and even mild illness is likely to cause death.**
- **9 – Terminally Ill: As in 8 but not likely to live next 3-6 month.**

*Adapted from Rockwood & Theou 2020

Thomas Gillen's Frailty Score 3

Thomas Gillen is a 51-year-old male with type 2 diabetes now on diabetic medications glipizide, metformin, and insulin regimen as well as atorvastatin for cholesterol, and amlodipine/carvedilol for high blood pressure. He has recently undergone right shoulder rotator cuff surgery. He has recently been diagnosed with benign prostate hypertrophy (BPH) for which he is taking tamsulosin. His blood pressure is 145/90, heart rate of 82. Just looking at the Eye of Tiger test and ADL score, his chance of living next 5 years looks promising but not guaranteed since uncontrolled diabetes can progress rapidly with life-altering macrovascular complications such as coronary artery disease, peripheral arterial disease, and stroke and microvascular complications such as kidney failure, blindness, and limb amputations. He is seeking advice on how to lose weight.

We discussed the difficulty of weight loss in the November Issue. To

summarize, there is no magical formula for weight loss.

Obesity in Diabetes Summary

First, insulin not only causes glucose to be utilized by cellular mitochondria for energy production, but also promotes lipogenesis, resulting in the triglycerides storage in fat cells. Second, leptin secreted by white fat cells usually sends a signal to your brain that you are full and not interested in further food intake but also causes obesity in congenital leptin deficiency and in mutations in the leptin gene or extreme leptin resistance due to mutations of the leptin receptor genes. Third, lipoprotein lipase (LPL) activity in fat cells increases in favor of energy storage in order to provide fat for insulation over the long winter months. Fourth, microbially manufactured metabolite, delta-valerobetaine (VB), impairs mitochondrial fatty acid β-oxidation resulting in excess fat accumulation. Finally, there is a direct hepatic lipogenesis from gut microbiome-derived acetate with excess fructose consumption.

Hyperinsulinemia and Obesity

In hyperinsulinemia, the amount of insulin in the blood is higher than considered normal amongst non-diabetic patients. The association of insulin and obesity was first published in December 5th, 2012, edition of Cell Metabolism. Mehran A and Johnson J et al in 2012 discovered that too much insulin may be detrimental. The researchers split mice into two groups and provided both with a high-fat diet. The control group consisted of normal insulin secreting mice and the other consisted of mice which were bred to have only half the regular amount of insulin. The results were surprising in that **the mice that had low levels of insulin remained skinny and did not gain any weight due to the fact that their fat cells burned more energy while storing less** and did not develop diabetes. The conclusion, according to the authors, is that the cause of obesity was from the additional insulin, which was induced by the high-fat diet in the normal mice. The discoveries were completely unanticipated. Not only did the majority of mice with significantly reduced insulin levels **not** develop diabetes but also did not gain any weight. Insulin is hormone that permits the body to store blood sugar as glycogen so that it can be used as energy later, and lack of insulin causes diabetes, a chronically high blood sugar state. This is first definitive study to show hyperinsulinemia first causes obesity which in turn causes insulin resistance.

Wiebe et al, as published on March 12, 2021, JAMA Network, carried out a systematic review and meta-analysis of 5603 participants in 112 cohorts from 60 studies to answer temporal associations between higher body mass index (BMI), hyperinsulinemia and chronic inflammation. The authors found that "the association between period 1 (preceding) levels of fasting insulin and period 2 (subsequent) BMI was positive and significant: for every unit of standard deviation change in period 1 insulin level, there was an ensuing associated change in 0.26 units of standard deviation in period 2 BMI." The findings suggest that adverse consequences currently attributed to obesity could be attributed to hyperinsulinemia in humans before diabetes set in.

There are two intense academic debates to explain obesity. The energy balance model (EBM) considers overeating

(intake > expenditure) as the primary cause of obesity and attributes rising obesity prevalence to inexpensive, convenient, energy-dense, "ultra-processed" foods high in fat and sugar. An alternative view, the carbohydrate-insulin model (CIM), proposes that hormonal responses (hyperinsulinemia) to highly processed carbohydrates shift energy partitioning toward deposition in adipose tissue, leaving fewer calories available for the body's metabolic needs. In CIM model, energy is being stored as fat and causes further food intake to compensate for the less available calories for the body's metabolic needs. Despite these two long-standing scientific controversies, processed carbohydrates remains major drivers of obesity and/or hyperinsulinemia in non-diabetics.

If indeed hyperinsulinemia is the true cause of obesity in non-diabetic patients, then the same is likely to be true for diabetic patients. Since, hyperglycemia, a high blood sugar, causes life-threatening medical conditions, not using insulin would **not** be an option at this time for Mr. Gillen. He would need a very close collaboration with endocrinologist to navigate this difficult process of weight loss, hyper- and hypoglycemia and possible hyperinsulinemia (?) due to insulin resistance in diabetes. There are two types of diabetic medications may be beneficial for Mr. Gillen's weight loss program. First class will be GLP-1 agonists such as dulaglutide, exenatide, semaglutide, liraglutide and SGLT-2, and the second class, SGLT2 inhibitors that includes canagliflozin, dapagliflozin, and empagliflozin.

Will Insulin Therapy Disappear in Type 2 Diabetes?

"Will insulin therapy disappear in Type 2 diabetes?" was the topic of a debate at the recent European Association for the Study of Diabetes 2022 Annual Meeting. At the meeting, Apostolos Tsapas, MD, PhD, argued that newer approaches will eventually render insulin treatment unnecessary for people with type 2 diabetes. His argument was that there is recent shift away from glucose-lowering to cardiovascular outcomes as the main focus of treatment.

Bruce H.R. Wolffenbuttel, MD, PhD, at the meeting argued the insulin-free diabetic treatment is a nonsense due to the heterogeneity and progressive nature of type 2 diabetes. He argued "insulin will always be necessary for some patients with type 2 diabetes because the condition is characterized by both increased insulin resistance and reduced insulin secretion." Diabetes is indeed complex disease and has 5 different sub-types as delineated in the March 1, 2018, *Lancet Diabetes & Endocrinology* by Ahlqvist et al. rather than traditionally classified type 1 or type 2.

In summary, depending on the nature and type of diabetes, Mr. Gillen may potentially benefit from further consultation with an academic endocrinologist.

Take Home Lesson

- ✓ **Discuss with endocrinologist about diabetic drugs that may be helpful in weight loss.**
- ✓ **GLP-1 agonists and SGLT-2 inhibitors may be beneficial in the case of Mr. Gillen.**

MrGineaPig's Core Long-Term Trial

LONG-TERM TRIAL	SUPPLEMENT	START DATE	
Muscle Weakness	Hyaloronic Acid	07/01/2019	50 mg-1 capsule daily
Digestive Aid	Bacillus coagulans	10/4/2022	take one gummy bear daily after dinner
Back Pain	Pantothenic acid	09/1/202	500 mg 1 capsule daily
	Pantethine	09/01/2022	450 mg 1 capsule daily

Purpose of Safe Health Report

If you feel you are used by someone or somebody or institution or institutionalized philosophy or even by your parents or siblings or your coworkers or even your boss, you are a GineaPig. This newsletter is designed to empower GineaPigs in the area of human health.

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