LIV3 HEALTH

The Fructose Model

A unified map of metabolic dysfunction

CELLULAR ENERGY / KHK / RECOVERY CAPACITY

WHITEPAPER SERIES AUGUST 2026

LIV3 HEALTH

The Fructose Model

A unified map of metabolic dysfunction centered on cellular energy, KHK, and recovery capacity.

This hypothesis-forward whitepaper series assembles primary studies, reviews, and consensus evidence into a testable model. It is not a peer-reviewed research article, clinical guidance, or a substitute for medical care.

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Executive Summary

Metabolic disease has many accepted explanations: excess calories, insulin resistance, inflammation, mitochondrial dysfunction, vascular injury, hormones, appetite, and fat storage. Each explains something important. The Fructose Model asks whether they are also parts of one larger story.

Its proposed organizing problem is **cellular energy failure**: a progressive loss of the ability to meet demand, defend, repair, and fully recover. Its primary causal candidate is fructose metabolism through **ketohexokinase**, or KHK-an unusually fast pathway that can create a low-energy signal even while calories are abundant.

The key event has two arms.

First, KHK uses ATP to trap fructose as fructose-1-phosphate. Think of ATP as spendable energy and phosphate as one of the reusable parts needed to keep that energy currency circulating. A large fructose challenge can spend ATP quickly, tie up phosphate, and push AMP toward breakdown. The cell must then do more than recharge; it may need to rebuild part of the currency itself. MECH-P1978

Second, that AMP breakdown produces uric acid. Inside susceptible cells, fructose-related uric-acid signaling can increase oxidative and inflammatory pressure, disturb mitochondrial function, and favor fat production. MECH-U2012 One arm increases the energy bill. The other can make the machinery that pays it work less efficiently.

When the challenge is small and recovery is strong, this can be temporary. When challenges arrive too quickly-or recovery is already slowed by poor sleep, hypoxia, inactivity, illness, toxins, nutrient imbalance, or inflammation-the next demand may begin from a lower starting point. The model calls the accumulating gap **energy debt**.

Energy debt offers a coherent explanation for an apparent paradox: the body can carry more stored energy while its cells behave as though usable energy is scarce. A lower-capacity cell may conserve, divert fuel toward storage, rely more heavily on quick glycolysis, and resist additional substrate. The brain and body may answer the shortage signal with hunger and cravings. More calories then arrive at a system already struggling to use them, reinforcing fat gain and insulin resistance.

This distinction between **stored energy** and **energy capacity** is essential. A warehouse can be full while the delivery fleet is broken. In the same way, fat and circulating fuel can be abundant while mitochondria, blood flow, substrate handling, and repair cannot move that energy to the right place at the right time. The model is not claiming that calories have disappeared. It is proposing that the machinery for using them has become constrained.

This is the central wager of the Fructose Model: KHK is not the only path to cellular energy failure, but it may be a primary, repeatedly activated, and partly modifiable amplifier that helps connect the major arms of chronic metabolic dysfunction.

A New Map Built from Converging Work

The model joins three influential research traditions. Richard Johnson and colleagues developed the fructose-survival hypothesis and the importance of KHK, ATP depletion, uric acid, mitochondrial oxidative stress, and energy storage. Douglas Wallace's work placed mitochondrial energetics near the center of tissue vulnerability and disease expression. Robert Naviaux's cell-danger and healing-cycle research widened the view of mitochondria from power production alone to defense, signaling, resource allocation, and recovery.

The Fructose Model does not claim those researchers proposed this complete synthesis. Its contribution is to place their insights on one map: KHK can initiate or deepen a low-energy state; repeated challenges can outpace recovery; and fragile cells can scale into fragile tissues, organs, and systems.

The case rests on **consilience**. Biochemistry, comparative biology, human physiology, food structure, historical exposure, and the clustering of metabolic diseases are separate lines of evidence. Each is incomplete alone. Together they describe the same landscape.

This matters because a unified theory should do more than rename familiar problems. It should explain why they travel together, identify an upstream intervention point, and make predictions that competing accounts do not. Here the distinctive predictions concern timing and recovery: two people can receive the same load yet experience different effects because one restores capacity before the next challenge and the other does not.

1. Mechanism & Biochemistry

Most fuel pathways are paced by feedback. KHK is different: it can phosphorylate fructose rapidly without waiting for the cell's energy state to catch up. This produces the paired ATP/phosphate and uric-acid/mitochondrial pressures at the center of the model. CORE-J2023

The mechanism paper follows that first biochemical event through energy drawdown, uric-acid generation, mitochondrial stress, and recovery.

2. Fragile Cells to Fragile Systems

A fragile cell is not necessarily damaged beyond repair. It is a cell with too little margin. It can manage ordinary demand, yet falter when demand rises or arrive late to the next challenge because it has not fully recovered.

Organs are built with redundancy, but shared loss of reserve changes the system. Fragile endothelial cells alter blood flow. Fragile liver cells change fuel handling. Fragile immune cells prolong inflammation. Local deficits can therefore reinforce one another until a whole system becomes less resilient.

3. Endogenous Fructose

Fructose is not only eaten. The polyol pathway can convert glucose to sorbitol and then fructose inside the body. This route is well demonstrated in selected high-glucose, diabetic, osmotic-stress, and dehydration models. ENDO-L2013 ENDO-S2018

That expands the model beyond dietary sugar. Different stresses may enter the map at different points, sometimes activating KHK even when little fructose has just been eaten.

4. Fat Gain as a Natural Consequence

Energy balance still governs body mass. The unanswered question is what controls appetite, storage, oxidation, and access to stored fuel.

Fructose metabolism can push several of those controls toward conservation at once. Liver fat production rises; fat oxidation and flexibility can fall; hunger and reward signals may favor another intake. In this model, fat gain is the visible half of a deeper problem: stored fuel increases while usable cellular energy and recovery margin decline.

5. The Burden of Evidence

5.1 Lessons from Nature

Across nature, animals store fuel, conserve water, reduce metabolism, or switch energy pathways to survive fasting, migration, dehydration, and low oxygen. Fructose participates directly in some of these programs and resembles the logic of others. CORE-J2023

The lesson is timing. A survival response can be powerful and beneficial when it turns off. Modern exposure can deliver the signal without the season, fast, or exertion that once completed the cycle.

5.2 The Fruit Paradox

Whole fruit shows why a molecule is not a meal. Water, fiber, intact structure, chewing, and volume slow delivery and increase satiety. Juice and sweetened drinks can deliver a larger dose far faster.

Fruit therefore sharpens the model: dose rate, food matrix, energy demand, and recovery time matter alongside the number of fructose grams.

5.3 From Scarcity to Continuous Exposure

Human fructose biology is ancient; cheap liquid sweetness from breakfast to bedtime is not. Industrial production, transport, retail, advertising, and food formulation removed many natural limits-season, effort, price, structure, and pause.

History cannot prove a molecule caused an epidemic. It does show that the exposure pattern changed in precisely the direction the mechanism predicts would matter most: larger, faster, and more frequent loads with shorter recovery windows.

6. Major Arms of Dysfunction

6.1 Metabolic Dysfunction

Obesity, fatty liver, type 2 diabetes, gout, and kidney disease frequently cluster because liver, adipose tissue, muscle, pancreas, and kidney are managing the same substrate pressure. KHK can reproduce important parts of this pattern in experimental models, and early human inhibition studies show the pathway can be engaged. MET-K2020 MET-K2021

6.2 Cardiovascular Disease

Blood vessels are not passive pipes. They are living, energy-dependent tissues that must dilate, repair, resist clotting, and deliver oxygen precisely. Fructose-linked uric-acid and redox signaling can reduce nitric-oxide biology and add to pressure, lipid, kidney, and metabolic burdens. CVD-Z2008 CVD-R2010

Fragile vessels then worsen the original energy problem by delivering oxygen and fuel less effectively.

6.3 Neurodegeneration

The brain is exceptionally sensitive to failures of energy delivery, mitochondrial reserve, sleep, vascular health, and recovery. Human spectroscopy shows that the brain can produce a fructose-compatible signal during acute hyperglycemia, while mouse studies support local KHK effects in defined diabetic settings.

The model does not reduce dementia to sugar. It proposes that lower metabolic and vascular reserve can make the brain less able to tolerate and repair the disease processes acting upon it.

6.4 Cancer

Cancer adds a different test. Before transformation, repeated energetic, inflammatory, and mitochondrial stress may help create fertile ground. After transformation, some tumors exploit fructose directly; others benefit from fructose-derived metabolites made by the liver. In several preclinical models, blocking fructose transport or KHK reduces growth or improves treatment response.

A smaller precision-oncology branch runs in the opposite direction: tumors unable to complete fructolysis can trap fructose as F1P and be harmed by KHK activity. The exception does not erase the map. It tells us which metabolic markers must be measured before intervention.

6.5 Hormonal Dysfunction

Hormones translate local cellular conditions into body-wide decisions: seek fuel or stop eating, store or spend, grow or repair, reproduce or postpone. This makes the endocrine system the crossroads of the model rather than simply another disease category.

Repeated KHK-related energy challenges may alter that conversation directly in some tissues and indirectly through liver metabolism, insulin, adipose signals, inflammation, vascular delivery, and hunger circuits. The result need not be one universal hormone profile. Men and women, different life stages, and different tissues can translate the same metabolic pressure in different directions.

The hormonal paper asks whether recovery capacity-not one fasting hormone value-better explains when an adaptive reallocation becomes persistent dysfunction.

7. Intervention: Restore Recovery Capacity

If the model is right, intervention has two jobs: reduce repeated loads and improve the ability to recover.

The foundation is familiar-less rapidly delivered added sugar, better food structure, activity, sleep, hydration, treatment of hypoxia, and established medical care. The research frontier is more specific: KHK inhibition, intracellular uric-acid biology, dynamic phosphate and nucleotide recovery, and biomarkers that identify who is actually pathway-dependent.

This is a hopeful model because it points upstream. It does not promise one blocker or supplement. It predicts that when recovery improves, several downstream problems should move together.

It also reframes success. Weight, fasting glucose, blood pressure, and serum urate remain useful, but a restored system should also tolerate a meal, an exercise bout, an infection, or a poor night's sleep without remaining metabolically displaced for days. Resilience is the capacity to leave the low-energy state, not merely the appearance of normality while resting.

8. The Map Comes Together

The closing paper gathers the separate evidence arms into one landscape. It restates the central loop, shows how familiar interventions fit the model, explains why progress may plateau when another entrance remains active, and identifies the measurements that could validate or narrow the theory.

The series ends with a research direction rather than a declaration of settled science: measure pathway engagement, measure recovery, predict responders, and revise the map when the results require it.

Conclusion

The Fructose Model proposes a new unified map of metabolic dysfunction. Cellular energy and recovery are the organizing problem. KHK is a primary causal amplifier. ATP/phosphate loss and uric-acid/mitochondrial stress are parallel arms of the same event. Storage, cravings, insulin resistance, hormonal reallocation, vascular strain, brain vulnerability, and cancer terrain become connected consequences rather than unrelated failures.

The map is not complete. It is complete enough to be challenged.

Its decisive test is whether measuring and changing the proposed upstream pathway improves recovery across the systems that currently fail together.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

1. Mechanism & Biochemistry of Fructose Metabolism

ABSTRACT

Fructose metabolism matters because its first step is unusually fast. The enzyme KHK spends ATP to trap fructose inside the cell before the cell has fully checked its energy balance. A strong challenge can therefore create two problems at once: less immediately usable energy and phosphate, and more uric-acid-linked pressure on mitochondria.

One arm enlarges the recovery bill. The other can weaken the machinery expected to pay it. This coupled event is the biochemical core of the Fructose Model.

1. A Fast Door into Metabolism

Glucose enters a carefully regulated pathway. When energy is plentiful, feedback slows its early processing. Fructose takes a faster entrance.

KHK converts fructose to fructose-1-phosphate, or F1P, using ATP. In tissues with high KHK activity-especially the liver-this can happen rapidly. MECH-P1978

Imagine a factory that pays every incoming invoice immediately, before checking the bank balance. One invoice is easy. A stack arriving at once can drain working cash and tie up resources needed elsewhere. KHK creates a similar **rate problem**: the dose matters, but so does how quickly it arrives and how much capacity is available to clear it.

2. The Energy-and-Recovery Arm

ATP is often called the cell's energy currency. The metaphor is useful, but incomplete: cells also need phosphate and an intact pool of adenine nucleotides to keep that currency circulating.

When KHK makes F1P:

1. ATP is spent quickly.
2. Phosphate becomes temporarily tied up in F1P.

3 ADP and AMP rise as the cell tries to stabilize energy.

4 Under strong flux, AMP can be broken down rather than simply recharged.

The cell must then restore phosphate balance and rebuild the adenine-nucleotide pool. That is why recovery is more than a momentary ATP reading. A cell can return to an acceptable resting level yet have less reserve for the next demand. Human phosphorus-spectroscopy studies also show that an oral fructose challenge can perturb hepatic ATP reserves and that recovery differs with metabolic context. MECH-H2012 MECH-H2016

The Fructose Model calls the gap between challenge and full restoration **energy debt**. It proposes that repeated challenges become important when they arrive faster than a vulnerable cell can repay that debt.

3. The Uric-Acid-and-Mitochondrial Arm

AMP breakdown produces uric acid. This is not a side note; it is the second half of the mechanism.

Uric acid has different roles in different places. In blood it is influenced heavily by kidney handling and can act as an antioxidant. Inside susceptible cells and experimental tissues, fructose-related uric-acid signaling can increase oxidative stress, activate inflammatory pathways, reduce nitric-oxide availability, disturb mitochondrial function, and favor fat production. MECH-U2012 CVD-Z2008

Mitochondria are not simple batteries. They are a flexible network that changes shape, location, and output as demand changes. Oxidative and inflammatory signaling can push that network toward fragmentation and lower efficiency. The result is a reinforcing pair:

1 rapid fructose metabolism leaves more energy capacity to restore;

1 uric-acid/redox pressure can make restoration slower or less complete.

This is why phosphate loss and uric acid should carry equal weight in the model. They are parallel consequences of one event, joined by the cell's recovery task.

The distinction also explains why a serum urate test cannot stand in for the entire mechanism. Blood urate reflects production, kidney clearance, medicines, genetics, and timing. The model is concerned with what happened inside the cell during the challenge: how much ATP was spent, how much phosphate and nucleotide capacity was restored, how much uric-acid/redox signaling occurred locally, and whether mitochondrial performance returned.

4. From One Challenge to a Loop

A single exposure does not equal chronic disease. If fructose arrives slowly, downstream metabolism keeps pace, and the cell has time to rebuild, the disturbance can resolve.

The proposed chronic loop begins when frequency outruns recovery:

1 KHK creates an acute ATP/phosphate drawdown.

2 AMP breakdown produces uric acid and redox pressure.

3. Mitochondrial performance and inflammatory resolution lag.
4. The next load begins from a lower-energy starting point.
5. Fuel is redirected toward storage while the cell resists additional substrate.
6. Hunger and reward systems may answer the apparent shortage with another intake.

This is not merely “too many calories.” It is a mechanism by which abundant calories can create signals of scarcity and make continuing excess more likely.

5. Why Tissue and Timing Matter

KHK expression, fructose delivery, oxygen, disease state, activity, sleep, genetics, and nutritional status differ across tissues and people. The liver receives a large first pass from dietary fructose. The intestine can clear smaller loads. Other tissues may encounter fructose made locally through the polyol pathway.

The model therefore predicts a threshold relationship rather than a universal toxic dose. The relevant question is:

> **How large and frequent is the challenge relative to this cell’s ability to process it and recover?**

That prediction can be tested with dynamic measurements of F1P, phosphate, adenine nucleotides, uric acid, redox state, mitochondrial performance, and the time required to return to baseline after single and repeated challenges.

It also predicts that form matters. A modest load cleared through the intestine and liver during high energy demand may be handled very differently from a large liquid load delivered to a sedentary, insulin-resistant liver. The chemistry begins with the same molecule; the biological result depends on traffic, capacity, and the time until the next arrival.

Conclusion

KHK sits at a consequential metabolic doorway. It can spend energy faster than ordinary feedback can slow it, trap phosphate, expand the nucleotide-recovery task, and produce uric acid that presses on mitochondrial and inflammatory systems.

The Fructose Model proposes that chronic disease begins not with one dramatic collapse but with incomplete recovery repeated often enough to become a new starting point.

One arm increases the debt. The other weakens repayment. Together they turn a temporary survival response into a plausible engine of persistent metabolic dysfunction.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

2. Fragile Cells to Fragile Systems

ABSTRACT

A cell can look normal at rest and still be fragile. Fragility means too little margin: too little reserve for a sudden demand, too little flexibility to switch fuels, or too little time to recover before the next challenge.

The Fructose Model proposes that repeated KHK activation can help create this state through parallel ATP/phosphate loss and uric-acid-linked mitochondrial stress. When many cells share reduced margin-or a critical cell type loses it-small failures begin to scale. Fragile cells become fragile tissues, then fragile systems.

1. What Is a Fragile Cell?

A phone at 40 percent charge may look fine on the desk. Start navigation, video, and a call at the same time, and its true capacity becomes obvious. Cells also reveal vulnerability under demand.

A fragile cell may maintain resting ATP while losing **reserve**: the extra capacity required for contraction, repair, immune defense, electrical signaling, detoxification, or recovery after stress. Resting energy and recovery capacity are not the same measurement.

Repeated fructose metabolism can narrow that margin. KHK spends ATP and ties up phosphate; AMP breakdown produces uric acid; redox and inflammatory signaling can reduce mitochondrial performance. MECH-P1978 MECH-U2012 Other pressures-hypoxia, infection, toxins, nutrient deficiencies, poor sleep, inactivity, aging, and genetic variation-can enter the same energy problem from different directions.

2. The Challenge-Recovery Threshold

Biology is built for challenge. Exercise temporarily disrupts energy balance and then increases capacity. Feeding raises substrate and is followed by clearance. Inflammation protects and then resolves.

The decisive variable is the recovery interval.

If a challenge is cleared, the system may return stronger or unchanged. If another arrives before phosphate balance, adenine nucleotides, redox control, and mitochondrial function are restored, the

next response begins with less margin. Repetition can turn a temporary deficit into a persistent operating state.

The model predicts that vulnerability will depend on **load relative to recovery capacity**, not exposure alone.

3. How Local Fragility Scales

Organs are networks. A liver cell changes what circulates in blood. An endothelial cell changes blood flow. An immune cell changes inflammation. A neuron changes signaling. A kidney cell changes pressure, sodium, and urate handling.

When one cell falters, neighbors usually compensate. When many cells share the same energetic limitation, compensation itself becomes costly. The tissue starts borrowing from other systems:

- the liver exports more lipid or glucose;
- the pancreas raises insulin;
- adipose tissue stores more fuel and releases inflammatory signals when overloaded;
- vessels raise pressure to preserve delivery;
- immune responses remain active longer;
- the brain increases hunger or reduces expenditure.

Each response can be rational in the short term. Together they can create a body that survives today by making tomorrow's recovery harder.

This is a scaling problem. A city does not fail because one delivery truck needs repair. It becomes fragile when many trucks share the same defect, spare vehicles are already in use, and every delayed delivery creates another emergency elsewhere. Chronic disease can emerge in the same way: not from universal cellular collapse, but from shrinking redundancy across connected systems.

4. Insulin Resistance as a Systems Response

Insulin resistance is often described as a broken lock. The Fructose Model adds another possibility: sometimes the cell is pushing back because it already has more substrate than it can safely oxidize or store. This remains an integrative interpretation rather than a single experimentally settled mechanism. CORE-J2023

That brake may initially protect the cell. At whole-body scale it raises insulin, leaves more glucose and lipid in circulation, and transfers the burden to liver, pancreas, muscle, vessels, and kidney. A local defense becomes systemic dysfunction.

This does not make every form of insulin resistance protective or KHK-driven. It explains why blocking fuel entry can emerge alongside energy shortage: the shortage is in **usable capacity**, not calories available outside the cell.

5. From Energy Debt to Chronic Disease

The major disease arms in this series can be read as different expressions of the same scaling problem:

- **metabolic dysfunction:** storage rises while flexibility falls;
- **cardiovascular disease:** vessels lose the reserve to match delivery to demand;
- **neurodegeneration:** high-demand networks become less able to signal, repair, and recover;
- **cancer:** stressed tissue may become more permissive, while transformed cells exploit whatever fuels and signals support growth.

The tissue determines the visible disease. The shared feature is shrinking energetic margin.

6. Why Recovery Changes the Question

Traditional measurements are often snapshots: fasting glucose, serum urate, resting ATP, blood pressure, weight. They matter, but they may miss how a system behaves after a load.

The Fructose Model predicts that a more revealing test will ask:

1. How far does a defined challenge push the system?
2. How quickly does it return?
3. Does a second challenge produce the same response, or a larger one?
4. Which interventions restore the original recovery curve?

This approach turns “metabolic health” from a static number into a measure of resilience.

Conclusion

Chronic disease rarely begins when an organ suddenly stops. It begins when margin quietly disappears.

KHK provides one concrete route into that loss of margin: it can create an immediate energy withdrawal while uric-acid/redox signaling makes mitochondrial recovery more difficult. Repeated often enough, a cell built to absorb occasional stress may begin operating permanently near its limit.

Fragile cells do not stay isolated. They change the conditions around them. When those changes spread through blood flow, hormones, inflammation, and fuel handling, cellular energy debt becomes system-wide disease.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

3. Endogenous Fructose Production

ABSTRACT

Fructose is not only something we eat. Under certain conditions, the body makes it from glucose through the **polyol pathway**. That discovery changes the model from a simple sugar-intake story into a broader account of metabolic stress.

High glucose and concentrated body fluids can activate this route in defined experimental settings. The fructose produced inside a susceptible tissue can then reach KHK and create the same paired event: ATP/phosphate drawdown alongside uric-acid, redox, and mitochondrial pressure.

Different triggers do not all act identically, but they may converge on the same energetic landscape.

1. A Sugar Made Inside the Body

The polyol pathway has two steps:

1. **Glucose becomes sorbitol** through aldose reductase, using NADPH.
2. **Sorbitol becomes fructose** through sorbitol dehydrogenase, changing the cell's redox balance.

If the tissue expresses KHK, that new fructose can be converted to F1P and enter the mechanism described in Paper 1. ENDO-L2013

This is important because “I did not eat fructose” does not always mean “my cells did not encounter fructose.” The pathway can be activated from inside.

The first step also spends NADPH, a resource used in antioxidant defense and cellular maintenance. The pathway can therefore add redox pressure even before its fructose product reaches KHK. This makes endogenous fructose a particularly interesting bridge: the route that creates the substrate may already be weakening the conditions needed to process it safely.

2. High Glucose: The Clearest Trigger

When intracellular glucose rises, more substrate becomes available to aldose reductase. In diabetic kidney and brain models, sorbitol and fructose rise alongside injury, and disrupting KHK reduces selected redox, mitochondrial, cognitive, or tissue effects.

This creates a plausible bridge from repeated glucose pressure to fructose biology. Glucose and fructose are not metabolically identical, yet high glucose can feed a route that ends at KHK.

In 2026, that bridge moved beyond animal models. During a 75-gram oral glucose tolerance test, serum fructose rose at 30 and 60 minutes in fourteen people with hereditary fructose intolerance and fourteen matched healthy controls-even though the challenge contained glucose, not fructose. This is direct human evidence consistent with internal fructose production after a glucose load. The human study did not isotope-label the glucose, locate the producing tissue, or measure how much fructose reached KHK, so it establishes the response without yet defining its full physiological importance. ENDO-B2026

The same study supplied a second piece of the map in mice. Isotope-labelled glucose carbon appeared in hepatic F1P, and blocking aldose reductase lowered liver fructose under fructose-free conditions. This directly strengthens the route-level case that excess glucose can become fructose inside the liver. Liver fat did not fall during the short nine-day intervention, but that experiment was not evidence that switching off an upstream contributor should rapidly reverse established fat. The result is most relevant to how metabolic stress may begin or be reinforced-not as a test of treatment for existing disease. ENDO-B2026

The practical implication is not that every carbohydrate becomes fructose. It is that persistent hyperglycemia may keep the pathway relevant even when added fructose is reduced.

3. Salt, Dehydration, and Osmotic Stress

When body fluids become more concentrated, cells activate osmotic-defense programs. In sustained hyperosmolar and recurrent-dehydration models, polyol-pathway fructose rises and selected metabolic or kidney effects become KHK-sensitive. ENDO-S2018

The survival logic is compelling. An animal facing drought benefits from conserving water, storing fuel, and making metabolic water when fat is later burned. A temporary water-saving program can be adaptive. Continuous osmotic pressure can turn the same logic into a burden.

Salt and dehydration also act through other pathways, so KHK is not their universal explanation. It is a tested point of convergence in particular tissues and conditions.

4. Alcohol, Hypoxia, and Stress

Alcohol appears to recruit the fructose pathway from within. In mice, ethanol raised portal-vein osmolality, activated aldose reductase and the polyol pathway in the liver and intestine, and increased tissue sorbitol and fructose. The response depended partly on concentration: diluting the ethanol markedly weakened the osmotic and aldose-reductase response. ENDO-A2025

This was more than a biochemical resemblance. Removing aldose reductase or KHK reduced alcohol seeking in several mouse paradigms, while global or liver-specific KHK deletion protected against alcohol-associated steatosis, inflammation, and fibrosis under matched exposure. Human alcoholic-liver-disease tissue also points in the same direction, but the decisive interventions remain animal experiments. The pathway is therefore established in experimental models; what remains uncertain is how much it contributes across different patterns of human drinking.

Low oxygen is also tissue-specific. It reduces oxidative energy production directly and can alter KHK expression or fructose use in some heart and tumor models. The pathway does not respond the same way in every organ.

Stress hormones raise glucose and change fuel allocation, making a connection to the polyol pathway plausible. Direct evidence that psychological stress produces clinically important fructose flux remains a research question.

These are not retreating caveats. They are a useful map: high glucose, osmotic stress, and alcohol are established roads in experimental models; hypoxia and hormonal stress are important intersections whose exact traffic still needs measuring.

Tissue identity matters throughout. A kidney under diabetic pressure, a heart adapting to low oxygen, and a liver processing alcohol do not express the same enzymes or face the same demands. A useful unifying model should predict shared logic without demanding identical molecular traffic in every organ.

5. A Self-Reinforcing Cycle

Endogenous fructose can make metabolic dysfunction feed itself:

1. Hyperglycemia or osmotic stress increases polyol-pathway activity.
2. Locally made fructose reaches KHK.
3. ATP and phosphate fall while AMP breakdown generates uric acid.
4. Redox and mitochondrial stress make recovery harder.
5. Liver fat, insulin resistance, or kidney stress increase future substrate pressure.
6. The next challenge produces still more endogenous fructose.

The loop explains why changing one food may help without fully resolving the underlying state. Once the system is generating its own trigger, recovery also requires improving glucose control, hydration, sleep, oxygenation, activity, and the health of the affected tissue.

6. Why Different Approaches Can Work-and Then Plateau

This map helps explain why very different diet and lifestyle programs can produce overlapping benefits. They may be closing different entrances into the same stressed system:

- **reducing added sugar or refined carbohydrate** lowers direct fructose delivery, glucose spikes, and substrate available to the polyol pathway;
- **choosing intact, minimally processed food** slows delivery and makes repeated overload less likely;
- **leaving genuine space between substantial meals** gives ATP, phosphate, redox balance, and hormonal signals more time to recover;
- **improving hydration and avoiding excessive sodium** can reduce osmotic pressure;

- **reducing alcohol** removes a demonstrated experimental trigger of endogenous fructose as well as alcohol's independent toxic burden;
- **movement, sleep, and treatment of sleep apnea** improve glucose handling, mitochondrial capacity, and oxygen availability around the pathway.

This does not mean that every benefit of a Mediterranean, low-carbohydrate, whole-food, fasting, exercise, or sleep program is mediated by KHK. It means these approaches can converge: each reduces one or more challenges, improves recovery, or does both.

The same map explains why progress can stall. A low-sugar diet may leave alcohol, hyperglycemia, dehydration, poor sleep, or inactivity untouched. Better sleep may improve recovery without removing rapid dietary loads. Once fatty liver, insulin resistance, vascular dysfunction, or mitochondrial damage has become self-reinforcing, removing the original trigger may no longer be enough to restore the system quickly.

A plateau is therefore not necessarily evidence that an approach was wrong. It may mean that one entrance has been closed while another remains open-or that the downstream system now needs time and additional support to rebuild capacity. That is a more useful question than arguing over which single diet is universally correct.

7. Why This Broadens the Fructose Model

The polyol pathway unifies debates that otherwise seem unrelated. Sugar intake, high glucose, salt balance, dehydration, alcohol, and hypoxia can all affect cellular energy, although not always through the same route or with the same strength.

The model's stronger claim is not that every stressor secretly becomes fructose. It is that KHK can sit inside a larger stress network, receiving fructose from both diet and internal production while other pressures simultaneously reduce the capacity to recover from it.

That idea also creates a practical research strategy. Instead of asking only how much fructose a person ate, investigators can ask where fructose was produced, whether it reached KHK, how large the F1P and uric-acid response became, and how long the affected tissue took to restore its energy state.

Conclusion

Endogenous fructose is the bridge between the food environment and the cell's internal stress response.

It shows how a pathway used for short-term adaptation can remain active after the obvious dietary trigger has been removed. It also explains why recovery must be broader than avoidance: reduce major external loads, but also change the internal conditions that keep generating the signal.

The Fructose Model becomes more unified at this point. Different challenges can arrive by different roads and still meet at the same energetic bottleneck.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

4. Fat Gain as a Natural Consequence

ABSTRACT

Fat gain requires excess energy. That is the accounting. It does not explain why hunger, storage, fatigue, and insulin resistance often rise together.

The Fructose Model proposes that rapid KHK activity can create a signal of low usable energy while calories are abundant. ATP and phosphate are spent; uric-acid-linked oxidative pressure can slow mitochondrial recovery; the liver turns more substrate into fat; and the body may seek more fuel.

Fat gain is therefore the visible half of a deeper mismatch: stored energy rises while the ability to use and recover from energy falls.

1. Calories Are the Accounting, Not the Whole Explanation

Energy balance determines whether body mass rises or falls. Biology determines the variables inside that equation: hunger, satiety, heat production, spontaneous movement, storage, and access to stored fat.

Those controls respond to sleep, stress, hormones, medicines, genetics, activity, food structure, and the social environment. Fructose metabolism is important because it can push several of them toward conservation at the same time.

The model does not suspend physics. It tries to explain why sustained surplus becomes easier to create and harder to reverse.

2. The Conservation Signal

When a large fructose load reaches KHK, the cell experiences two linked pressures: MECH-P1978 MECH-U2012

1. ATP is spent and phosphate is tied up in F1P;
1. AMP breakdown produces uric acid, which can amplify oxidative, inflammatory, and mitochondrial stress.

The cell receives abundant carbon at the same moment its immediately usable energy falls. In the liver, fructose also favors lipid production and can reduce metabolic flexibility in relevant models. MET-K2020

The rational short-term response is conservation: store incoming fuel, limit costly oxidation, and signal for more energy. In an animal preparing for scarcity, that can be lifesaving. In continuous abundance, it can become self-reinforcing.

3. Why Stored Energy Can Feel Unavailable

Someone can carry a large energy reserve and still feel tired or hungry because stored quantity and usable capacity are different things.

If mitochondrial performance, blood flow, sleep, or insulin signaling is impaired, fuel may not reach the right tissue or be oxidized at the right time. A cell already facing substrate pressure may resist additional entry. The pancreas answers with more insulin, which further favors storage and restrains fat release.

The body then occupies an uncomfortable middle state: plenty of fuel in storage, too much fuel circulating after meals, and too little flexible energy where demand is rising.

Fructose is not the only cause of this state. KHK matters because it offers a direct route from nutrient arrival to the low-energy signal that makes conservation seem necessary.

Adipose tissue is initially protective in this story. It keeps surplus lipid away from organs that are less able to store it safely. Disease accelerates when that buffer becomes inflamed, fibrotic, or simply unable to expand fast enough. Lipid then accumulates in liver, muscle, pancreas, and other tissues, where it further disrupts insulin action and energy use.

4. Appetite, Reward, and the Next Load

Hunger is not a calorie counter. The brain integrates learned reward, food availability, sleep, stress, hormones, and signals from the liver, gut, and adipose tissue.

Experimental work supports fructose-related effects on appetite, reward, and metabolic signaling, but no single pathway explains human eating. NEURO-P2013 NEURO-L2015 The stronger proposition is systemic: if energy use and recovery are impaired, signals that encourage another intake become easier to understand.

Modern foods intensify that loop. Sweetened drinks deliver energy rapidly with little chewing. Highly processed foods combine sugar, refined starch, fat, salt, and flavor in forms designed for repeated intake. The next challenge can arrive before the last one has been cleared.

Sleep loss and stress make the same environment harder to resist by shifting appetite, reward, and glucose control. Social conditions decide how often a person must choose between time, cost, convenience, and recovery. The biology is therefore personal, but it is never only a matter of personal will.

5. The Fat-Gain Loop

The proposed sequence is:

1. Rapid KHK activity creates ATP/phosphate drawdown and uric-acid pressure.
2. Mitochondrial recovery and fat oxidation become less flexible.
3. The liver redirects more substrate toward lipid.
4. Hunger, reward, and the food environment make another intake likely.
5. Adipose tissue stores the surplus until its buffering capacity is strained.
6. Insulin resistance limits further entry but raises circulating fuel and insulin.
7. Greater substrate and inflammatory pressure make the next recovery harder.

Calories explain the stored mass. The loop proposes why the system may keep asking for more while becoming worse at using what it already has.

6. A Less Blaming, More Useful Model

This view shifts the practical question from “Why did this person fail to eat less?” to “What is driving intake, storage, and low energy together?”

The answer may include food access, shift work, medications, sleep apnea, stress, pain, hormonal disease, inactivity, and many other pressures. Reducing rapidly delivered sugar is one upstream step. Restoring sleep, movement, satiety, oxygenation, and recovery capacity addresses the wider system.

If KHK is genuinely upstream for a subgroup, pathway reduction should improve liver fat or fuel handling before major weight loss. That is a testable prediction-not a demand that every person follow the same diet.

Conclusion

Fat is not simply a mistake. It is the body's safest place to store surplus energy until storage itself becomes strained.

The deeper problem is a program that keeps choosing storage because cells are signaling low usable energy and incomplete recovery. Fructose metabolism can help create that contradiction: abundance outside the cell, scarcity inside its working energy system.

Breaking the loop means making healthy intake easier, stored energy more accessible, and cellular recovery more complete.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

5.1 Lessons from Nature: Fructose as a Survival Tool

ABSTRACT

Nature repeatedly solves the same problem: how to survive when food, water, or oxygen will soon become scarce. Animals store fat, reduce energy use, change insulin sensitivity, conserve water, and switch fuels.

Fructose metabolism participates directly in some of these strategies and follows the survival logic of others. The important lesson is not that one enzyme explains every adaptation. It is that storage and metabolic slowdown can be intelligent, reversible biology-when the signal is timed and the recovery phase arrives.

1. Survival Changes the Meaning of "Dysfunction"

Insulin resistance before a long fast can preserve glucose for selected tissues. Rapid fat gain before migration can carry an animal across an ocean. Lower metabolism during dehydration can conserve both water and energy.

The same traits become harmful when they are continuous or separated from the short-term conditions they help manage. Comparative biology therefore adds a powerful line to the Fructose Model: some features of modern metabolic disease resemble survival states that have lost their off-switch. CORE-J2023

2. Seasonal Fat: The Importance of the Unloading Phase

Bears accumulate enormous fat stores before hibernation, then fast for months while their metabolism changes with the season. Other mammals and birds also alternate between intense feeding, storage, migration, fasting, and recovery.

Fructose-rich foods may contribute to some pre-scarcity diets, but photoperiod, hormones, temperature, behavior, and many foods coordinate the full program. The analogy is strongest at the level of rhythm.

Natural fattening has an unloading phase. Human metabolic disease often combines storage signals with uninterrupted access, producing accumulation without the long interval that would draw down the reserve.

That difference may explain why large seasonal changes can remain reversible while smaller year-round changes accumulate. The animal does not merely stop eating; its hormones, behavior, temperature, movement, and tissue metabolism shift together. Recovery is a coordinated phase of the program, not an accidental gap between meals.

3. Water Conservation

Fat is more than stored calories. When later oxidized, it also yields metabolic water. Animals facing drought benefit from strategies that promote drinking, conserve sodium and water, lower expenditure, and build fat before scarcity.

In experimental mice, recurrent heat dehydration activates renal polyol metabolites and produces KHK-sensitive kidney injury. Sustained hyperosmolar conditions also connect endogenous fructose to metabolic changes. ENDO-S2018

These experiments do not mean every desert animal relies primarily on KHK. They show that the fructose pathway can join a genuine water-conservation program-and that repeated activation can become damaging outside the original ecological context.

4. Uric Acid and the Water Economy

Birds and reptiles excrete nitrogen mainly as uric acid, conserving water compared with dissolving urea. Mammalian uric acid after fructose metabolism is not the same process, but both reveal how purine biology intersects with survival under limited water.

In humans, uric acid can be useful in one compartment and harmful in another. It is an antioxidant in plasma, a crystal-forming cause of gout when sufficiently concentrated, and a redox or inflammatory signal inside selected cells. The Fructose Model focuses on that intracellular arm without reducing the molecule to a simple toxin.

5. Oxygen Conservation: The Naked Mole Rat

The naked mole rat provides a striking example of fructose as an emergency fuel. During severe low oxygen, it can mobilize fructose and drive glycolysis in vital tissues, bypassing a regulatory bottleneck that normally limits glucose use. NAT-P2017

That emergency pathway helps the animal survive conditions that would quickly kill most mammals. It also makes the model's central distinction vivid: a short, purposeful low-oxygen response is not equivalent to chronic fructose exposure during abundance.

6. Capacity Changes the Meaning of Exposure

Hummingbirds can burn recently consumed sugars at extraordinary rates. Their flight muscles have extreme demand and rapid throughput. They demonstrate that high sugar flux is not automatically disease.

The relevant variable is challenge relative to capacity. A small animal immediately turning sugar into flight is in a different energetic state from a sedentary person repeatedly drinking sugar while liver, muscle, and adipose stores are already full.

This is why the Fructose Model is not a theory of fructose toxicity alone. It is a theory of dose, rate, demand, and recovery.

Comparative examples should therefore be read in layers. Naked-mole-rat fructose use and experimental osmotic activation are direct mechanistic evidence. Bears and hummingbirds provide parallel physiology: they show what reversible storage and extreme throughput look like. The synthesis is the hypothesis that human KHK retains part of the same survival logic. Nature makes that proposal plausible; controlled experiments decide where it is literally shared.

7. Humans: The Signal Without the Season

Modern humans can combine several ancient signals continuously:

- concentrated sweetness without seasonal scarcity;
- salt and refined starch in the same foods;
- low movement despite constant energy access;
- shorter sleep and recurrent stress;
- alcohol, dehydration, hypoxia, and other metabolic burdens.

The pathway may be ancient. The exposure pattern is new.

Conclusion

Nature shows why the fructose pathway exists. It can help an organism store, conserve, and survive a temporary emergency.

The modern problem is not that the program is irrational. It is that the signal can remain on while the fast, migration, drought, or winter never arrives.

The most important feature of a survival response may not be how powerfully it turns on, but how reliably it turns off.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

5.2 The Fruit Paradox: How Nature Packages Fructose

ABSTRACT

If fructose metabolism can produce a storage-and-conservation signal, why is whole fruit consistently associated with health?

Because a molecule is not a meal. Whole fruit delivers fructose inside water, fiber, intact structure, vitamins, minerals, and plant compounds. It takes time to chew, occupies volume, and usually reaches the intestine and liver more gradually than juice, syrup, or a sweetened drink.

Fruit does not contradict the Fructose Model. It demonstrates the importance of **packaging, pace, and recovery**.

1. Why Fruit Becomes Sweet

Fruit helps plants recruit animals to disperse seeds. As fruit ripens, its color, aroma, texture, acidity, and sugars change. Ripe fruit advertises accessible energy.

In seasonal environments, that signal may arrive when animals benefit from eating and storing more. The exact chemistry varies widely among species, so fruit should not be reduced to one script. The broader ecological point is enough: sweetness is a message that energy is available now.

2. Whole Fruit Is a Delivery System

An orange and an orange-flavored drink may contain some of the same sugar molecules, but they do not create the same eating event.

Whole fruit brings several natural brakes:

1. **intact structure and fiber** slow eating and intestinal delivery;
1. **water and volume** lower energy density and increase fullness;
1. **chewing** gives satiety signals time to develop;
1. **micronutrients and plant compounds** support health through pathways that extend beyond fructose;
1. **physical capacity** makes consuming the equivalent of several fruits at once less likely.

No antioxidant magically cancels fructose. The food matrix changes the size and speed of the challenge.

That difference is visible at the level of behavior as well as digestion. Eating three or four apples demands time, chewing, and stomach volume. Drinking the equivalent carbohydrate can take minutes. The second exposure can outrun satiety before the body has fully registered the first.

3. What Processing Changes

Processing progressively removes those brakes.

1. **Juice** makes several fruits drinkable in minutes and removes much of the intact structure.
1. **Dried fruit** retains fiber and nutrients but compresses the portion and makes larger carbohydrate loads easier.
1. **Smoothies and purées** vary, preserving some components while reducing chewing and often increasing speed.
1. **Added sugars and syrups** separate sweetness from the fruit matrix almost entirely. FRUIT-G2024

The model predicts a continuum, not a moral divide. A whole orange, smoothie, orange juice, and sweetened orange drink differ in dose rate, satiety, context, and recovery demand even when all taste like fruit.

This is consistent with the broad human evidence: whole fruit generally belongs within healthy dietary patterns, while sugar-sweetened beverages carry a clearer metabolic burden. One-hundred-percent juice sits between those endpoints, with mixed findings that vary by dose, age, energy compensation, and outcome. The distinction is not “natural sugar versus chemical sugar.” It is a whole delivery system versus concentrated, rapidly repeatable sweetness. FRUIT-G2024 FRUIT-N2024

4. Fruit in an Always-Sweet World

For most of human history, ripe fruit was constrained by place, season, effort, spoilage, and appetite. Modern transport has made whole fruit available year-round-a major nutritional benefit. At the same time, food manufacturing can reproduce concentrated sweetness in nearly every setting and at every hour.

The metabolic problem is less “fruit exists” than “the sweet signal never stops.” Natural pacing is replaced by beverages, snacks, desserts, sauces, and refined foods that allow one challenge to overlap the next.

Seasonality also changes meaning in a modern life. A physically active person eating intact fruit as part of meals is not recreating the metabolic conditions of continuous sweetened drinks. The Fructose Model is strongest when it distinguishes those contexts rather than treating every gram as interchangeable.

5. A Practical Hierarchy

For most people, the implications are straightforward:

1. Prefer intact whole fruit as the default.
2. Treat juice and large dried-fruit portions as concentrated carbohydrate, not unlimited equivalents of fruit.
3. Let activity, appetite, metabolic health, and tolerance guide amount and timing.
4. Focus first on added sugars and sweetened beverages, where rapid delivery is greatest and nutritional buffering is smallest.

Specific conditions-including hereditary fructose intolerance, gastrointestinal intolerance, and individualized diabetes needs-require specific advice. They do not change the general role of whole fruit in a healthy dietary pattern.

6. Fruit as a Test of the Model

Fruit makes a useful prediction possible. If delivery rate and recovery matter, then equal labeled sugar should not always produce equal downstream effects. Intact structure, chewing, meal context, activity, and time between exposures should change the F1P, uric-acid, appetite, and recovery response. That is more informative than arguing whether fruit is simply “good” or “bad.”

Conclusion

Fruit makes the Fructose Model more precise.

The relevant exposure is not simply grams of fructose. It is the dose, delivery rate, food matrix, tissue destination, current energy demand, and time available to recover.

Nature's buffer is not magic. It is context-and context is part of the mechanism.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

5.3 Historical Context: From Scarcity to Continuous Exposure

ABSTRACT

Human fructose biology is old. Continuous access to refined sweetness is not.

Over several centuries, sugar moved from a costly luxury to a global commodity, then into inexpensive drinks and packaged foods available at almost every hour. History cannot prove that sugar caused the modern metabolic epidemic. It can show that the exposure pattern changed faster than bodies and institutions could accommodate.

The natural limits-season, effort, structure, price, and pause-were progressively removed. The Fructose Model predicts that this is exactly the kind of change that would turn an intermittent survival pathway into a chronic burden.

1. When Sweetness Was Intermittent

Before refined sugar became cheap, most fructose came from fruit, honey, and limited local sources. Exposure varied by season, climate, trade, and wealth. Whole foods required gathering, growing, preserving, chewing, and sharing.

Preindustrial diets were not universally healthy or sugar-free. The crucial difference was constraint. For most people, sweetness could not arrive in a large liquid dose at breakfast, between meals, with dinner, and again at night.

Scarcity built a recovery interval into daily life.

2. How Sugar Became Ordinary

Cane and beet production, colonial trade, slavery, industrial refining, tariffs, transport, and mass retail lowered the cost of sugar in many markets. HIST-M1986 The human cost belongs inside the health story: mass sweetness was built partly through extraction and forced labor before it was normalized as an everyday commodity.

Branded packaging, confectionery, tea culture, advertising, and later supermarkets changed sugar from an ingredient into an always-available experience. High-fructose corn syrup was a later chapter, not the beginning of the transition.

Common HFCS formulations are not metabolically alien to sucrose; both deliver fructose and glucose. FRUIT-G2024 The larger shift was economic and practical: sweetness became cheap, stable, drinkable, and easy to add to almost anything.

That distinction matters because public debate often became trapped in a contest between sweeteners. The model points to a more durable issue: sucrose and HFCS both make a rapid fructose-plus-glucose load inexpensive and repeatable. Glucose can raise insulin and, under some conditions, feed endogenous fructose production; fructose can enter KHK directly. The package delivers overlapping pressure from both sides.

3. The Loss of Season and Structure

Railways, shipping, refrigeration, and global agriculture brought enormous nutritional benefits, including reliable access to fresh foods. They also dissolved seasonality.

Food manufacturing went further. Sugar became useful for texture, browning, shelf life, flavor balance, and repeat purchase. Refined starch, fat, salt, and sugar increasingly appeared together in highly palatable products.

In energy-recovery terms, the challenge became:

1. **larger**, because concentration and portions increased;
1. **faster**, because calories became liquid or highly processed;
1. **more frequent**, because eating opportunities multiplied;
1. **harder to recover from**, because movement and sleep often declined while stress remained high.

The exposure curve became taller and wider while the gap between loads became shorter.

At the same time, daily energy demand changed. Motor transport, mechanization, office work, and labor-saving devices reduced the need to oxidize incoming fuel immediately. More substrate arrived into a system that was being asked to do less physical work, while sleep and circadian regularity often deteriorated.

4. History as a Natural Experiment

Long-run food-availability records show major increases in caloric-sweetener supply, followed by plateaus or declines in some countries and periods. These are exposure proxies-not measurements of what each person ate-and they cannot assign chronic-disease trends to sugar alone. They do show how radically the food environment changed during the broader transition to industrial abundance. HIST-USDA2025

Timelines alone cannot establish causality. Lifespan, smoking, physical activity, pollution, sleep, medicines, diagnosis, and the entire food supply also changed.

History becomes persuasive when placed beside the other evidence arms:

1. KHK provides a mechanism capable of turning rapid fructose exposure into an energy-and-storage signal.
2. Experimental models show KHK-dependent metabolic effects.
3. Industrial systems greatly increased the speed and frequency of exposure.
4. Diseases marked by liver fat, insulin resistance, vascular strain, and low metabolic flexibility rose in the same environment.

History supplies the exposure experiment. Mechanism and intervention studies must decide what it means.

The strongest historical claim is therefore about mismatch, not monocausality. The environment changed several variables in the direction of continuous energy storage and incomplete recovery. Fructose exposure is unusually relevant because its biochemistry predicts exactly that conservation-oriented response.

5. The Socioeconomic Inversion

Sugar was once a sign of privilege. Today, the heaviest burden of diet-related disease often falls on people with the least control over time, food access, housing, sleep, healthcare, and environmental stress.

Cheap shelf-stable calories can be rational under constraint. Shift work shortens sleep. Long commutes and unsafe neighborhoods reduce activity. Targeted marketing shapes preferences. Chronic stress and pollution can add independent inflammatory and mitochondrial burdens.

This is why the Fructose Model must not become a story of individual blame. Biology operates inside systems that determine who receives the most frequent challenges and the least opportunity to recover.

6. Restoring the Missing Constraints

The historical lesson points beyond personal restraint. If the problem was created partly by removing friction, solutions can restore healthier defaults:

1. water and minimally processed food that are easy to access;
1. smaller and less concentrated sweetened products;
1. clearer marketing and labeling;
1. work and school schedules that protect meals, sleep, and recovery;
1. neighborhoods that make movement practical;
1. product reformulation that reduces repeated hidden loads.

Conclusion

The historical mistake was not inventing fructose. It was removing nearly every natural constraint around its delivery.

An intermittent biological signal can now arrive from morning to night, often paired with glucose, salt, fat, alcohol, poor sleep, and stress. The Fructose Model predicts that the cost depends not only on how much arrives, but whether the cell has time and capacity to recover.

History cannot prove the model. It explains why a once-useful pathway has become important enough to test.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

6.1 Metabolic Dysfunction: The Primary Fingerprint

ABSTRACT

Obesity, fatty liver, type 2 diabetes, gout, and kidney disease often travel together. They are not one disease, but their clustering resembles the output predicted by repeated fructose/KHK activation: ATP and phosphate are spent, uric acid and redox pressure rise, liver fat production increases, and metabolic flexibility falls.

This makes metabolic dysfunction the clearest proving ground for the Fructose Model. The pathway can be measured, genetically disrupted, and pharmacologically inhibited. The evidence already supports important pieces. The next question is whether dynamic energy recovery ties them into the proposed loop in people.

1. Why the Cluster Matters

Each condition shows a different face of the same substrate problem:

1. **obesity** records long-term storage;
1. **fatty liver** places surplus fuel in the organ coordinating metabolism;
1. **type 2 diabetes** reflects failing insulin control under sustained pressure;
1. **gout** reveals excessive urate and crystal inflammation;
1. **kidney disease** disrupts pressure, sodium, acid-base, and urate handling while receiving injury from the same environment.

The Fructose Model proposes that KHK can contribute to several at once, helping explain why they cluster more often than chance would predict.

2. The Energy-Debt Loop

The central sequence is straightforward:

1. Fructose reaches KHK faster than a susceptible cell can clear and recover from it.
2. ATP and phosphate fall while AMP breakdown produces uric acid.
3. Uric-acid/redox signaling increases inflammatory and mitochondrial pressure.

4. The liver converts more incoming carbon to fat.
5. Cells facing excess substrate reduce further insulin-stimulated uptake.
6. The pancreas raises insulin; circulating fuel and storage increase.
7. Another meal arrives before full recovery.

Insulin resistance is not only a broken signal. It can begin partly as a cell's attempt to limit more substrate entering when oxidation and storage are already crowded. A local brake then becomes a whole-body problem.

This helps explain a central paradox of diabetes: blood contains too much fuel while some tissues behave as though energy is insecure. Raising insulin can force more substrate into storage for a time, but it does not necessarily restore the capacity to oxidize fuel, resolve redox stress, or recover before the next load.

3. Fatty Liver as the Keystone

The liver sits at the crossroads of dietary fructose, endogenous fructose, lipid synthesis, glucose output, uric acid, and insulin signaling.

Mouse studies show that liver KHK can drive important sugar-associated liver-fat and metabolic effects. MET-K2020 Early human KHK-inhibitor studies demonstrate target engagement, and a small six-week trial reported lower liver fat at the higher tested dose, though the lower dose was ineffective. Other programs have shown acute F1P/phosphate target engagement or entered first-in-human testing. These findings do not prove that KHK inhibition reverses metabolic disease, but they show that the pathway is real and modifiable in humans. MET-K2021 MET-HFI2025 MET-F2025

Liver fat is not the whole disease. Genetics, alcohol, medicines, activity, diet, and adipose capacity change who develops it and who progresses. It is a useful junction because several parts of the model meet there.

It may also be an early readout. If a pathway-directed intervention lowers liver fat or improves post-meal handling before major weight change, that would support the claim that metabolic partitioning-not body mass alone-is being altered.

4. Uric Acid Is More Than a Marker

Fructose-driven AMP breakdown generates uric acid. Above saturation, urate crystals cause gout. In blood, urate also reflects kidney handling, genetics, medicines, and metabolic state.

Inside selected cells, the role is different. Uric-acid-linked redox signaling can promote inflammation, mitochondrial stress, and fat production. MECH-U2012 This is the model's main bridge from purine breakdown to impaired recovery.

Lowering blood urate is proven for gout, but it has not become a universal treatment for hypertension, kidney disease, or metabolic syndrome. That distinction does not demote uric acid. It tells us that preventing local production, lowering circulating concentration, and reversing an established cellular state are different interventions.

5. Endogenous Triggers Keep the Pathway Relevant

High glucose can feed the polyol pathway. ENDO-L2013 Sustained hyperosmolarity and severe recurrent dehydration activate it in selected models. ENDO-S2018 Alcohol can also recruit the pathway in selected mouse models, while hypoxia, sleep disruption, and inflammation can add independent energy stress even when their KHK contribution is uncertain. ENDO-A2025

This helps explain why reducing added sugar can be valuable without being sufficient. Once hyperglycemia, liver fat, sleep apnea, kidney stress, or inactivity is established, the body may keep generating the conditions that prolong energy debt.

6. What the Model Predicts

If KHK sits upstream for a meaningful subgroup, then:

1. pathway reduction should improve liver handling before large weight loss;
1. recovery after a standardized challenge should improve before every fasting marker normalizes;
1. the benefit should be greatest when rapid loads are reduced and sleep, activity, oxygenation, and nutrition improve together;
1. disease stage should matter, because a deeply remodeled system may not reverse when one trigger is removed.

These predictions turn a broad theory into an experimental program.

They also separate prevention from reversal. Reducing KHK pressure before extensive fibrosis, beta-cell failure, vascular remodeling, or kidney loss may have a larger effect than removing the same pressure after the system has reorganized around disease. An upstream cause can remain important even when late disease no longer depends on it alone.

Conclusion

Metabolic dysfunction is the clearest fingerprint of the fructose pathway running too often and recovering too slowly.

KHK links a rapid energy withdrawal to uric acid, mitochondrial pressure, liver fat, insulin resistance, and storage. Other causes matter, but few offer such a direct route through so many features of the cluster.

If the model is right, the earliest sign of recovery may not be less fuel in the body. It may be a better ability to use and recover from the fuel already there.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

6.2 Cardiovascular Disease: Fragile Vessels from Fragile Energy

ABSTRACT

The cardiovascular system delivers energy, but it must also power itself. Vessel linings regulate flow and clotting. The heart contracts without pause. The kidneys continuously adjust pressure and volume. Each depends on mitochondrial reserve, redox balance, nitric oxide, and recovery.

Fructose metabolism can press on this network from several directions at once: ATP/phosphate drawdown, uric-acid-linked oxidative stress, impaired nitric-oxide biology, liver lipid production, insulin resistance, and kidney strain.

The Fructose Model does not replace cholesterol, smoking, blood pressure, diabetes, or genetics. It proposes an upstream amplifier that can make those established insults harder to tolerate and repair.

1. Blood Vessels Are Living Tissue

An artery can be open and still unhealthy. Long before blockage, its endothelial lining may lose some ability to dilate, resist inflammation, control clotting, and match blood flow to demand.

A heart can also maintain resting output while losing reserve for exertion or illness. Cardiovascular fragility is ordinary function preserved at the cost of shrinking margin.

That margin is easy to overlook because routine medicine often measures the system while a person is sitting still. Exercise, a meal, heat, infection, or emotional stress demands rapid changes in flow and output. A vessel that cannot dilate or a heart that cannot increase efficient ATP production reveals its weakness only when asked to respond.

2. From KHK to Vascular Stress

Fructose-driven AMP breakdown produces uric acid. In selected experimental systems, uric-acid and oxidative signaling reduce nitric-oxide availability and can narrow endothelial mitochondrial reserve. CVD-Z2008 CVD-R2010

Nitric oxide helps vessels relax and helps coordinate redox and mitochondrial biology. When oxidative stress consumes it, vessels stiffen and lose the ability to increase flow precisely when tissues need more oxygen.

The energy problem then becomes circular:

1. KHK creates metabolic and redox stress.
2. Vessel reserve and nitric-oxide signaling decline.
3. Oxygen and substrate delivery become less responsive.
4. Tissues recover more slowly.
5. Slower recovery increases the cost of the next demand.

Smoking, high blood pressure, LDL particles, hyperglycemia, pollution, infection, and aging can all enter this loop independently. KHK is important because it can connect nutrient pressure to several of them at once.

Uric acid deserves careful placement here. Serum urate is an imperfect reflection of intracellular production, and vascular trials of urate lowering have not yielded one universal answer. Yet the local mechanism remains relevant: fructose-derived purine breakdown can produce oxidative pressure precisely where nitric oxide and mitochondrial reserve are needed for adaptation.

3. The Kidney and Blood Pressure

The kidney helps set long-term blood pressure through sodium, water, hormonal, and vascular control. It is also responsible for most urate excretion in people. CVD-K2012

Experimental fructose, diabetic, dehydration, and osmotic-stress models show KHK-sensitive kidney effects in particular settings. Salt can raise pressure through KHK-independent mechanisms as well. The unifying point is not that salt and sugar are the same. It is that sodium balance, uric acid, kidney function, and metabolic stress can reinforce one another.

High blood pressure may initially preserve perfusion. Over time it damages the vessels, heart, brain, and kidneys it is trying to supply. A compensation becomes another source of fragility.

The sodium-to-potassium balance matters within this system because the kidney and vessel wall respond to both. A systematic review found that higher potassium intake lowered blood pressure in adults with hypertension, though not in those with normal pressure; impaired renal potassium handling requires individualized guidance. CVD-A2013 The Fructose Model does not reduce potassium to a KHK intervention. It recognizes mineral balance as part of the recovery environment.

4. The Liver-to-Artery Link

Hepatic fructose metabolism can increase fat production and contribute to triglyceride-rich lipoprotein output in relevant settings. MET-K2020 That can add to the burden of apoB-containing particles circulating through stressed vessels.

LDL-containing apoB particles are established causal drivers of atherosclerosis through their cumulative exposure and retention in the artery wall. CVD-B2020 The Fructose Model does not weaken that conclusion. It asks what raises particle burden while also reducing the vessel's ability to withstand, clear, and repair injury.

Fructose/KHK may therefore matter on both sides: more adverse metabolic cargo and less resilient delivery infrastructure.

Atherosclerosis still requires its own causal chain: apoB particles enter and are retained in the artery wall, immune responses follow, and plaques progress. The unifying claim is that fructose-related metabolism can increase the supply of harmful particles and worsen the tissue conditions into which they arrive. It adds terrain to the particle story rather than competing with it.

5. A Systems View of Prevention

Cardiovascular risk remains clinically actionable now. Blood pressure, LDL/apoB, smoking, diabetes, sleep apnea, kidney disease, activity, and diet should be treated according to established evidence.

The model adds a shared upstream question: does an intervention merely improve a resting marker, or does it restore the ability of vessels and tissues to respond to demand?

That suggests future studies of flow-mediated responses, exercise reserve, post-meal vascular recovery, redox state, and KHK target engagement-not just one fasting urate value.

Conclusion

Cardiovascular disease is where energy production and energy delivery meet.

Fructose metabolism can add to pressure, particles, kidney strain, oxidative stress, and loss of nitric-oxide signaling. Fragile vessels then deepen the original cellular energy problem by delivering oxygen and fuel less effectively.

The target is not one molecule in isolation. It is the loop between metabolic stress and failing delivery-and KHK may be one of its most modifiable entry points.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

6.3 Neurodegeneration: The Brain on Fragile Energy

ABSTRACT

The brain is expensive tissue. It must maintain electrical gradients, recycle transmitters, move cargo, remodel connections, regulate blood flow, and coordinate immune defense without stopping.

A brain can preserve basic function while losing the reserve needed for learning, stress, sleep loss, infection, or aging. The Fructose Model proposes that systemic metabolic disease, fragile vessels, and locally produced fructose may converge on that shrinking energy margin. It also asks a more provocative question: could KHK help place the brain into an energy-triage state-temporarily favoring food-seeking and immediate survival over memory, restraint, and long-range thought?

This does not reduce Alzheimer's disease to sugar. It places fructose/KHK on a broader map of brain vulnerability that can now be tested.

1. The Brain's Energy Margin

Neurons signal; astrocytes manage substrates and transmitters; microglia respond to injury; oligodendrocytes maintain myelin; vessels regulate delivery. Brain function depends on all of them coordinating under changing demand.

Resting ATP can look adequate while synaptic reserve or recovery is poor. The more revealing question is how well the network responds when demand rises-and how completely it returns afterward.

Sleep, oxygen, blood flow, glucose regulation, mitochondrial function, and inflammation all shape that margin. Fructose biology can intersect with each.

2. Fructose Made in the Brain

Dietary fructose is handled substantially by the intestine and liver. The stronger brain hypothesis is local production from glucose through the polyol pathway.

In a small human spectroscopy experiment, a brain fructose-compatible signal increased during several hours of controlled hyperglycemia even though plasma fructose did not explain the rise. This supports the ability of the human brain to make fructose acutely from glucose. NEURO-H2017

In a diabetic mouse model, hippocampal sorbitol, fructose, and KHK rose alongside lower ATP. Reducing KHK in the hippocampus improved selected redox, mitochondrial-protein, neural, and cognitive outcomes. NEURO-LI2023

Together, these findings provide a credible bridge: high glucose can create local fructose, and local KHK can matter in a defined disease model. They do not yet tell us which human brain cells carry the most flux or how much it contributes to long-term neurodegeneration.

That is already a meaningful advance over a purely dietary argument. It suggests that years of poor glucose regulation could expose the brain to fructose biology from within, even when little dietary fructose crosses directly into brain tissue.

3. KHK as an Energy-Triage Switch

Dr. Richard Johnson's Alzheimer's hypothesis adds a crucial layer to this story. It does not treat cerebral fructose metabolism as random damage alone. It proposes that the pathway may help coordinate a short-term survival state. NEURO-J2020 NEURO-J2023

The logic is simple. When food or water is scarce, the brain does not need every function operating at full power. It needs attention directed toward finding resources. A temporary program that heightens hunger, makes food cues harder to ignore, relaxes restraint, and reduces energy spent on less urgent work could improve the odds of getting through the immediate problem.

KHK is a plausible switch for that program because it changes both energy and behavior-facing signals. Its rapid use of ATP and phosphate lowers the cell's immediate energy state. AMP disposal and uric-acid production make ATP recovery harder while adding redox, inflammatory, and mitochondrial pressure. In the brain, that combination could help shift priorities away from expensive functions such as memory formation, sustained attention, and executive control and toward appetite, reward, and foraging.

Human feeding studies point in the same direction. Compared with glucose, fructose produced less suppression of appetite-related brain activity and less satiety in one small crossover study. In another, it produced stronger responses to food cues, greater hunger and desire for food, and a greater willingness to trade a delayed monetary reward for immediate high-calorie food. NEURO-P2013 NEURO-L2015

These studies did not manipulate brain KHK, so they do not prove that KHK caused the response. They show that fructose can shift human brain and appetitive behavior in the direction the triage hypothesis predicts. The direct KHK evidence remains preclinical.

The pathway is also unlikely to act as a single dimmer switch across the whole brain. Fructose-handling machinery has been mapped to selected regions, including the hippocampus and cortex. NEURO-O2017 That raises a sharper possibility: the brain may be reprioritizing networks, preserving the circuits most useful for immediate resource-seeking while allowing higher-order functions to become temporarily less dominant.

4. When Triage Becomes a Trap

A brief shift in priorities is not Alzheimer's disease. The danger is repeated activation without complete recovery.

If KHK repeatedly draws down ATP and phosphate while uric acid sustains mitochondrial and inflammatory pressure, the brain can become less able to restore the energy it has spent. The next challenge then arrives before the previous one has been fully repaid. What was useful as a temporary state can become a chronic operating condition.

That is where Johnson's hypothesis gains its explanatory power. Early cerebral glucose hypometabolism, mitochondrial dysfunction, insulin resistance, reduced blood flow, and neuroinflammation need not be disconnected findings. They may be different faces of a brain that has remained in energy triage too long. Postmortem Alzheimer's tissue has also shown higher glucose and polyol-pathway intermediates, including sorbitol and fructose, although this does not establish that the pathway initiated the disease. NEURO-X2016

The model does not ask us to choose between energy failure and familiar Alzheimer's pathology. A brain with less ATP-producing and recovery capacity may be less able to maintain synapses, regulate immune cells, clear damaged material, preserve blood flow, and withstand amyloid, tau, vascular injury, or infection. The energy state may help determine whether those stresses are tolerated, contained, or allowed to spread.

5. Two Routes to a Fragile Brain

Fructose biology may reach the brain by two routes.

The systemic route: liver fat, insulin resistance, hypertension, kidney disease, sleep apnea, and vascular dysfunction change the blood, oxygen, and signals arriving at the brain. Even modest local fructose metabolism could become important in a network already receiving poor support.

The local route: endogenous fructose reaches KHK, drawing down ATP and phosphate while generating uric-acid/redox pressure. In susceptible cells, that could narrow the energy available for signaling, repair, and inflammatory resolution.

The systemic route is likely broader. The local route is a more specific research target. Both fit the same cellular-energy model.

They can also reinforce one another. Metabolic disease can impair vessels and raise glucose; impaired delivery and high glucose can increase local stress; a less resilient brain may then regulate appetite, sleep, and autonomic function less effectively, feeding pressure back to the rest of the body.

6. Metabolic Disease and Neurodegeneration

Type 2 diabetes and metabolic dysfunction are associated with higher dementia risk. Vascular disease, inflammation, altered insulin signaling, and mitochondrial stress can all contribute. NEURO-J2023

The phrase “type 3 diabetes” is memorable but incomplete. Alzheimer's disease also involves amyloid, tau, immune responses, synaptic loss, vascular injury, and genetics. The Fructose Model offers a connecting question rather than a replacement diagnosis:

> **Does lower metabolic and vascular reserve make the brain less able to tolerate and repair these other disease processes?**

If so, improving recovery may change the terrain on which neurodegeneration progresses, even when it does not remove every initiating cause.

This may help explain why apparently different risks-diabetes, hypertension, sleep disruption, inactivity, and vascular disease-converge on cognitive decline. They need not share one origin to subtract from the same reserve.

7. What Should Be Tested

The next research questions are concrete:

1. Which human brain cells produce and metabolize fructose under hyperglycemia?
1. Does local F1P or KHK activity track cognitive or vascular recovery?
1. Does blocking KHK change the predicted shift between executive-memory networks and appetite-reward networks?
1. Do sleep, exercise, glucose control, or pathway inhibition change the recovery curve?
1. Is the pathway important only in a metabolically defined subgroup?

These questions are narrower than saying fructose causes dementia-and much more useful.

They also preserve hope. A vulnerability factor is not destiny. If part of brain risk comes from the metabolic terrain rather than an irreversible initiating lesion, improving that terrain may extend the period in which neural networks can compensate and repair.

Conclusion

The brain sits at the end of every metabolic supply line. It inherits the health of the liver, vessels, kidneys, sleep, and whole-body energy system.

Fructose/KHK can plausibly narrow brain-energy margin both indirectly and locally. Johnson's hypothesis goes further: KHK may help triage brain energy toward immediate resource-seeking, and chronic activation may trap vulnerable networks in the very low-power state that once served a short-term purpose.

That proposed function is not yet settled human biology. But it connects appetite, behavior, glucose hypometabolism, mitochondrial dysfunction, inflammation, and cognitive decline in a way that is

specific enough to test. A brain with less reserve is more vulnerable, and restoring recovery may be as important as removing any single insult.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

6.4 Cancer: Fragile Cells, Fertile Ground

ABSTRACT

Cancer begins when genetic and epigenetic changes allow cells to survive and grow outside normal control. But every transformed cell still has to solve an ordinary physical problem: where will it get the energy and raw material to build a tumor?

The Warburg effect describes one common answer: many cancer cells take up large amounts of sugar and rely heavily on fast glycolysis even when oxygen is available. The Fructose Model proposes that KHK can help create this fertile ground before cancer and help feed or support it afterward. In several preclinical models, more fructose availability or pathway activity promoted tumor growth, while reducing fructose transport or KHK slowed growth or improved treatment response.

A smaller precision-oncology branch runs in the opposite direction: tumors that cannot finish fructolysis may trap fructose as F1P and be harmed by KHK activity. That exception refines the map. It does not erase the broader pattern.

1. The Warburg Effect: Why Cancer Has a Sugar Problem

Healthy cells usually extract much of their usable energy by sending fuel through mitochondria. Many cancer cells do something strikingly different: even when oxygen is present, they pull in glucose at high rates and turn much of it into lactate. This is the **Warburg effect**. CANC-N2020

At first glance, that looks wasteful. Glycolysis yields less ATP from each molecule of glucose than complete mitochondrial oxidation. But it is fast, and a growing cell needs more than ATP. It needs carbon for membranes, nucleotides, proteins, antioxidants, and every other component of a new cell. Rapid sugar processing can keep those construction lines supplied.

The Warburg effect does not mean every tumor has broken mitochondria. Many cancers use glycolysis and mitochondria together, then switch according to oxygen, treatment, and available fuel. The shared theme is metabolic flexibility: tumors redirect fuel toward whatever best supports growth.

Fructose fits this picture in two ways. In defined tumor models, it can supply carbon or growth signals to cells able to use it. Separately, KHK metabolism can draw down ATP and phosphate while generating uric-acid-linked redox pressure that can impair mitochondrial work in susceptible

experimental tissues. CANC-N2020 MECH-P1978 MECH-U2012 The hypothesis is that these mechanisms can help reinforce a low-energy, high-glycolysis terrain that selected cancers are unusually able to exploit; that complete bridge has not been demonstrated as one universal tumor sequence.

The useful question is not “Does sugar cause every cancer?” It is “At what stage, and in which tumors, does fructose metabolism create an advantage?”

2. Fertile Ground Before the Tumor

Before there is a tumor, tissue still has to police itself. Cells must repair DNA, maintain mitochondria, resolve inflammation, and remove damaged neighbors.

Repeated KHK activation may make those jobs harder in two parallel ways. First, it spends ATP, temporarily ties up phosphate in F1P, and disposes of AMP that could otherwise help rebuild ATP. Second, it generates uric acid, which can increase oxidative and inflammatory signaling and impair mitochondrial performance in susceptible tissue. One arm reduces the resources available for repair; the other burdens the machinery doing it.

Over time, liver fat, insulin resistance, poor perfusion, inflammation, and disturbed redox control may make tissue less able to repair damage or remove abnormal cells. Fructose/KHK is not the only route to this terrain; age, inherited risk, smoking, infections, radiation, hormones, environmental carcinogens, and chance remain major causes. The model's claim is that KHK can help create a metabolically permissive background in which those causes act.

That background may matter most where metabolic dysfunction already increases cancer risk: liver, colorectal, pancreatic, endometrial, breast, and other obesity-associated settings. The claim is not that KHK creates the first mutation. It is that KHK may make the neighborhood more hospitable to a damaged cell that has begun to escape normal control.

3. Tumor Advantage After Transformation

Once a tumor exists, the direction is usually easy to state: in the preclinical cancer systems summarized here, **more usable fructose or more helpful fructose-pathway activity generally means more tumor support; reducing that access generally slows the tumor or makes treatment work better.** The mechanism differs by cancer:

1. **direct fuel:** cells expressing the required transporters and enzymes can use fructose carbon for energy and building material;
1. **growth signaling:** KHK isoforms and F1P-related pathways can influence cancer-specific signaling networks;
1. **treatment resistance:** selected colorectal models link fructose transport and metabolism to poorer oxaliplatin response, while blockade improves response;
1. **support from the liver:** dietary fructose can be converted by liver KHK into circulating lipids that feed tumors unable to metabolize fructose efficiently themselves.

In a 2024 mouse study, this liver-mediated route accelerated melanoma, breast, and cervical tumor growth, and pharmacologic KHK inhibition prevented the fructose-associated effect. CANC-F2024

This makes KHK relevant beyond the tumor cell. A cancer can benefit from fructose metabolism occurring in another organ.

It also broadens what a biomarker must capture. Measuring tumor KHK alone may miss a liver-mediated dependency; measuring diet alone may miss endogenous production. The relevant unit may be a whole-body metabolic circuit rather than a single biopsy.

4. A Tumor-Type Map

The current preclinical landscape is not uniform, but a broad direction is visible:

1. **colorectal and intestinal cancer:** fructose has accelerated tumor growth in APC-deficient mice; GLUT5/KHK-related pathways have also been linked to growth and chemotherapy resistance CANC-I2019 CANC-S2022;
1. **pancreatic ductal adenocarcinoma:** loss of KhkC delayed disease and extended survival in a KPC mouse model, alongside reduced growth signaling CANC-G2023;
1. **lung adenocarcinoma:** GLUT5-dependent fructose use has supported proliferation, invasion, and xenograft growth CANC-L2018;
1. **acute myeloid leukemia:** selected cells have used GLUT5-mediated fructose metabolism to support growth under glucose-poor conditions CANC-A2016;
1. **melanoma, breast, and cervical tumors:** liver-derived lipids have supported fructose-associated tumor growth in mice CANC-F2024;
1. **colorectal liver metastasis:** ALDOB-dependent fructose metabolism has supported metastatic growth in preclinical models CANC-M2018.

These are research leads, not a clinical treatment table. Most evidence comes from cells and animals. The important point is that fructose advantage now appears across several cancer types and through more than one mechanism.

The repeated pattern gives the thesis its force. Direct fuel use, growth signaling, metastasis, chemotherapy resistance, and liver-derived support are different routes to the same outcome: fructose metabolism can improve the tumor's ability to acquire resources or survive stress.

This is also why examining only glucose misses part of the picture. The Warburg effect describes the tumor's appetite for rapid carbon flow. Fructose can join that flow directly, alter the signaling around it, or be processed by the liver into material the tumor can use.

5. The F1P Trap: Where the Direction Reverses

Some tumor cells express KHK but lack enough downstream aldolase B to complete fructolysis. They phosphorylate fructose, accumulate F1P, and lose usable phosphate and ATP without efficiently harvesting the carbon. In that setting, fructose can suppress growth-and KHK inhibition can rescue the tumor. CANC-T2022 A newer HCC study identified a different F1P-dependent growth brake in ALDOB-deficient models. CANC-H2026 After chemotherapy-induced senescence, however, ovarian-cancer models have shown KHK-dependent dissemination, underscoring that direction depends on tumor state. CANC-O2026

This appears to be a narrower, context-dependent branch, but it matters because the treatment implication reverses. Candidate markers include KHK isoform, GLUT5, aldolase B, F1P accumulation, tissue of origin, and whether the tumor depends on direct or liver-mediated fructose metabolism.

The exception reveals a simple rule: fructose benefits the tumor that can complete or exploit the pathway and punishes the tumor that becomes trapped in its first step.

6. Why Reducing Added Sugar Makes Sense

Advice to limit sugar-sweetened drinks is common in cancer-prevention guidance. The usual reasons are already sound: it can help control excess energy intake, weight gain, and the wider metabolic conditions associated with several cancers. The Fructose Model adds a mechanistic reason to take that advice seriously without pretending it is a tumor treatment. CANC-WCRF2025

The Fructose Model offers a deeper possible reason. Reducing repeated glucose and fructose exposure may lower endogenous fructose production, reduce KHK pressure on ATP and mitochondria, and remove one source of fuel or liver-derived support from tumors that can exploit it. It may improve the terrain around the cancer even when it does not starve the cancer directly.

That last distinction matters. “Cancer eats sugar” is memorable but too simple. Every healthy tissue also needs glucose, the body can make glucose when carbohydrate intake falls, and cancer patients can be harmed by weight loss and poor nutrition. Human studies have not shown that removing sugar by itself makes an established cancer shrink. CANC-NCI2026 This paper does not justify an extreme diet or replacing oncology care. It explains why limiting rapidly delivered added sugars is biologically coherent-and why future trials should ask which tumors and patients benefit most.

7. What This Means for Prevention and Treatment Research

The evidence supports an ambitious but disciplined program:

1. reduce the metabolic terrain associated with obesity-related cancers;
1. identify tumors that depend on GLUT5, KHK, or liver-derived fructose metabolites;
1. test whether pathway inhibition improves chemotherapy response;
1. distinguish KHK-dependent tumors from F1P-trap tumors before intervention;

1. test whether protecting healthy tissue and improving recovery can widen the therapeutic window.

KHK inhibition is not established cancer therapy. Its value is to identify a metabolic dependency that standard tumor classification may miss.

Conclusion

Cancer is many diseases, but every cancer must solve the same practical problem: how to acquire energy and material, survive stress, and continue growing.

KHK may matter twice. Repeated activation can help create fertile ground before transformation. After transformation, a growing set of tumors can use fructose, fructose-related signaling, or liver-derived metabolites as an advantage.

The less-documented reverse branch makes the model more precise, not less compelling. The next step is to map pathway competence by tumor type-and remove the advantage where it exists.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

6.5 Hormonal Dysfunction: When Energy Availability Redirects the Endocrine System

ABSTRACT

Hormones are the body's allocation system. They help decide whether energy should be spent, stored, sought, used for growth, invested in reproduction, or reserved for repair.

That makes hormones a natural bridge between cellular energy and whole-body behavior. If cells repeatedly receive more fuel than they can safely use-or repeatedly lose energy and fail to recover-the endocrine system does not simply watch. It changes appetite, insulin, stress responses, metabolic rate, and reproductive priorities.

The Fructose Model proposes that repeated fructose/KHK challenges can contribute to this redirection. The claim is not that fructose controls every hormone. It is that a pathway capable of creating both an acute low-energy signal and a longer metabolic burden can influence the signals that coordinate the organism.

1. Hormones Turn Cellular Conditions into Body-Wide Decisions

A cell can respond only to its immediate surroundings. Hormones allow tissues to coordinate.

Insulin tells tissues that fuel has arrived. Leptin reports long-term energy storage. Ghrelin and hypothalamic circuits influence hunger. Cortisol reallocates resources during stress. Thyroid hormones help set energy expenditure. Sex hormones coordinate growth, body composition, and reproduction.

These systems do not measure calories in a warehouse. They respond to delivery, storage, oxygen, inflammation, circadian timing, and whether tissues can actually use the available substrate. A body can therefore contain abundant energy while signaling that usable energy is insecure.

This is the endocrine face of the Fructose Model's central distinction: **stored energy is not the same as energy capacity**.

2. How KHK Can Enter the Hormonal Conversation

Rapid KHK activity spends ATP, ties up phosphate in F1P, and can push AMP toward uric-acid production. In susceptible tissues, the result is a paired pressure: less immediate energy and more redox, inflammatory, and mitochondrial work.

That first event does not need to touch every endocrine gland directly. The liver can change circulating glucose, lipids, urate, ketones, and binding proteins. Adipose tissue can change leptin and inflammatory signals. The brain can change hunger and autonomic output. Blood vessels can change delivery. Each becomes a messenger carrying local energy strain to the rest of the body.

This is why the hormonal paper belongs late in the series. It gathers the earlier arms into one coordinating layer: metabolism creates conditions; hormones decide how the organism responds.

3. Appetite: Abundant Fuel, Persistent Seeking

The brain does not wait for the body's total calorie count. It estimates whether energy is available now and whether more should be sought.

In an acute mouse experiment, centrally delivered fructose lowered whole-hypothalamus ATP and malonyl-CoA and increased feeding relative to glucose. HORM-C2008 The route and dose were artificial, but the experiment demonstrates the principle: fructose can create a low-energy feeding signal inside the brain even while it is itself a fuel.

Longer exposure can also change the circuitry. High-fructose feeding remodeled inputs and excitability in NPY/AgRP hunger neurons in mice, with sex-dependent effects that persisted after withdrawal for selected measurements. HORM-P2025

The proposed loop is straightforward: repeated challenge narrows energy margin; hunger circuitry interprets the state as fuel insecurity; another intake arrives; and the added substrate makes recovery harder. Hormones and neural signals turn a cellular problem into behavior.

Leptin and ghrelin make this paradox easier to see. **Leptin reports longer-term energy stores; ghrelin helps announce that it is time to seek and begin a meal.** If the brain becomes resistant to leptin, a full fuel tank no longer closes the appetite gate reliably. In one male-rat model, a very high-fructose diet produced leptin resistance before body weight, fat mass, insulin, or circulating leptin had risen. HORM-S2008

Human ghrelin findings are less uniform. In a controlled one-day crossover study of twelve women, high-fructose meals produced lower insulin and leptin responses and weaker post-meal ghrelin suppression than matched high-glucose meals. HORM-T2004 Shorter acute comparisons have not always found a fructose-glucose difference in leptin or ghrelin. NEURO-P2013

The strongest claim is therefore not that fructose always raises ghrelin or directly controls leptin. It is that repeated fructose/KHK pressure may help create a state in which stored-energy and meal signals are generated or interpreted less reliably. Because leptin-sensitive AgRP circuitry also communicates with the kisspeptin reproductive gate, that appetite disturbance can plausibly reach beyond eating behavior.

4. Reproduction Is Energy-Gated

Reproduction is expensive. Biology therefore links fertility to energy state.

AgRP neurons-best known for promoting hunger during energy shortage-form direct inhibitory connections with Kiss1 neurons, a key gate controlling reproductive signaling. Sustained AgRP activation delayed reproductive cycling and fertility in female mice. HORM-P2017

That gate can also matter during excess. In a separate female-mouse obesity model, inhibiting AgRP neurons restored reported hormone, ovulation, and fertility outcomes even though the experiment did not involve fructose. HORM-B2022

That does not prove a complete fructose-to-Kiss1 pathway. It establishes something more fundamental: the circuit exists for perceived energy shortage to postpone reproductive investment.

The Fructose Model asks whether repeated KHK-related energy challenges can sometimes recruit that gate even in caloric abundance. The connecting evidence remains incomplete, so this is a testable hypothesis rather than a settled mechanism. Its prediction is clear: reproductive disruption should track the energetic intermediaries and recovery curve-not fructose exposure alone.

5. Kisspeptin Helps Explain Why the Endpoints Diverge

Kisspeptin is a reproductive permission gate, not a dial that determines one universal sex-hormone level. In the Fructose Model, repeated KHK activation is one proposed upstream source of disturbed energy sensing. The endocrine network then translates that pressure according to where the dominant bottleneck lies:

1. **central bottleneck:** AgRP or NPY signaling restrains Kiss1 output, lowering GnRH/LH drive;
1. **gonadal bottleneck:** LH may rise because the brain is asking an impaired gonad to do more;
1. **insulin-liver-ovary bottleneck:** insulin raises ovarian androgen production while lower SHBG increases free exposure;
1. **feedback bottleneck:** androgen and metabolic signals distort the timing and sensitivity of the reproductive circuit.

This can resolve low testosterone in men and the PMOS pattern in women at the same time. In men, altered leptin-insulin signaling may reduce central drive, while testicular energy strain can lower testosterone even when LH rises to compensate. Obesity-related repression of hypothalamic Kiss1 signaling has been reversed experimentally in male rodents, supporting the central route.

HORM-A2024 A fructose-fed rat study found lower testosterone with higher LH, supporting a peripheral testicular branch. HORM-S2013

In women, the same pressure can travel through hyperinsulinemia, lower hepatic SHBG, ovarian androgen production, and altered feedback. PMOS can therefore produce higher free-androgen exposure while coordinated ovulation remains impaired-not a simple global shutdown. HORM-PMOS2026 HORM-S2007 Human hyperinsulinemia has amplified stimulated ovarian steroid production in women with PCOS. HORM-T2012

Observational human data fit this branching pattern: higher sugar-sweetened-beverage fructose estimates have been associated with lower testosterone indices in men but higher free-androgen exposure in women, although adiposity explains much of the relationship. HORM-C2024 A small randomized comparison found no fructose-versus-glucose difference in SHBG or testosterone over six weeks. HORM-N2025

The prediction is not one "fructose hormone profile." Low testosterone and PMOS may be parallel sex-specific expressions of the same failure to match abundant substrate with secure usable energy. Direct KHK-to-Kiss1 causation has not yet been shown; that is the resolving hypothesis to test.

6. Stress and Thyroid Signals Can Enter the Loop from Either Direction

Cortisol and catecholamines raise glucose and redirect fuel during stress. Thyroid hormones influence mitochondrial activity, heat production, substrate use, and recovery. Sleep loss and circadian disruption can alter both systems while also changing appetite and insulin sensitivity.

These hormones can worsen the conditions that favor endogenous fructose production or incomplete recovery. They can also change as consequences of illness, nutrient deficiency, medication, adiposity, or energy strain. The loop is therefore bidirectional.

The evidence does not yet justify a simple KHK-to-thyroid or KHK-to-cortisol pathway in humans. Their importance is broader: endocrine state helps determine how hard a fructose challenge lands and how quickly the system recovers.

7. A Hormonal Recovery Model

The model predicts that endocrine health will be better understood dynamically than through one fasting measurement.

A useful study would ask:

1. How does a defined metabolic challenge change ATP/phosphate balance, uric-acid/redox signaling, and the relevant hormone axis?
2. How quickly do those signals return to baseline?
3. Does a second challenge produce the same response or a larger one?
4. Does verified KHK engagement change the hormone only when it also changes the proposed energetic intermediary?

5 Do sex, life stage, sleep, liver function, and insulin state predict different branches?

This approach avoids the vague promise of “hormone balance.” It asks which signal is changing, in which person, for what reason, and whether restoring energy capacity restores appropriate endocrine choice.

Conclusion

Cellular energy is local. Hormones scale it into life strategy.

They help the organism decide whether to seek fuel, store it, spend it, defend, repair, grow, or reproduce. Repeated fructose/KHK challenges may influence those decisions by creating a mismatch between abundant substrate and insecure usable energy.

Hormonal dysfunction is therefore not an isolated fifth disease arm. It is the crossroads through which the other arms communicate.

The most powerful version of the Fructose Model does not predict one endocrine outcome for everyone. It predicts that a shared energetic pressure will be translated differently by sex, tissue, life stage, and metabolic state-and that the ability to recover will determine whether adaptation remains flexible or becomes disease.

THE FRUCTOSE MODEL / WHITEPAPER SERIES

7. Intervention Strategies: Restoring Recovery Capacity

ABSTRACT

If metabolic dysfunction is partly a repeated-challenge and incomplete-recovery problem, intervention has two jobs: reduce the load and rebuild the ability to recover.

That means addressing both arms of the model. Cells need time and resources to restore ATP, phosphate, and adenine nucleotides. They also need lower uric-acid/redox pressure and healthier mitochondria to do that work.

The foundation is practical and available now. Direct KHK inhibition and other pathway-specific tools are a promising research frontier, not yet a universal therapy.

1. Why Restriction Is Only Half the Strategy

Reducing rapidly delivered fructose can lower an important load. Yet hunger, habits, sleep, stress, medicines, hormones, food access, and endogenous fructose can keep the wider system active.

A plan based only on avoidance also leaves recovery untreated. A person may remove one trigger while remaining sleep-deprived, inactive, hyperglycemic, hypoxic from sleep apnea, or exposed to continuous stress.

The Fructose Model therefore asks two questions:

1. What keeps creating the challenge?
2. What keeps the system from fully recovering?

Those questions change the tone of intervention. The goal is not lifelong vigilance against a forbidden molecule. It is to lower the frequency and intensity of the largest challenges while rebuilding enough capacity that ordinary life no longer produces an outsized response.

2. Reduce the Fastest Loads

Sugar-sweetened beverages are the clearest starting point: large doses, rapid delivery, weak satiety, and little nutritional buffering. Whole fruit is a different exposure and usually belongs in a healthy dietary pattern. FRUIT-G2024

Fiber-rich minimally processed foods, adequate protein, and structured meals can slow delivery and improve satiety. The goal is not fear of every carbohydrate. It is to reduce repeated peaks that arrive faster than the intestine, liver, and whole body can comfortably handle.

Meal timing is individual, but constant caloric grazing leaves little recovery interval. A genuine pause between substantial loads may matter as much as the ingredients of the next meal.

The appropriate interval will not be identical for everyone. A healthy active person may recover quickly; someone with fatty liver, diabetes, poor sleep, or mitochondrial disease may require a different pattern. The model predicts that recovery time can eventually be measured rather than guessed.

3. Rebuild Capacity

Movement

Physical activity creates an energy challenge followed by adaptation. It improves glucose disposal, vascular function, insulin sensitivity, and mitochondrial capacity. The contrast is central: demand followed by recovery can build reserve; nutrient loading without use can erode it.

Sleep and oxygen

Sleep coordinates appetite, glucose control, inflammation, and repair. Treating sleep apnea restores oxygen during a period meant for recovery. Neither works because of KHK alone, but both can reduce the background pressure that makes KHK challenges harder to repay.

Hydration and mineral balance

Avoiding recurrent dehydration and excessive sodium may reduce osmotic stress, while potassium-rich foods support vascular and kidney health when medically appropriate. Heart and kidney disease require individualized fluid and potassium guidance.

Alcohol and nutritional adequacy

Alcohol adds hepatic redox burden, can worsen sleep and appetite, and overlaps with fructose metabolism in the liver. Adequate nutrition supplies the cofactors and building materials needed for energy metabolism and repair. Recovery cannot be built from restriction alone.

These foundations are powerful because they act at several points in the loop. Exercise creates useful demand, sleep coordinates repair, oxygen supports oxidative phosphorylation, and minimally processed food slows substrate delivery. None must be proved to work through KHK alone to support the recovery state that makes KHK exposure easier to handle.

4. Directly Targeting KHK

KHK is no longer only a theoretical target.

Human essential fructosuria offers a bounded natural clue that KHK function can be markedly reduced. Biallelic KHK variants were identified in three affected siblings from one characterized family. MET-EFG1994 In a separate physiological report, one adult with diagnosed essential fructosuria

showed none of the hepatic F1P accumulation or ATP and phosphate drawdown seen in controls after intravenous fructose. MET-EF1994 These small reports demonstrate a human functional boundary; they do not establish population-wide safety, long-term protection, or equivalence to a drug.

Drug programs have also demonstrated human target engagement. PF-06835919 reduced liver fat at the higher dose in a small six-week phase 2 study; a lower dose was ineffective. MET-K2021 KHK inhibition has reduced the acute F1P/phosphate response in hereditary fructose intolerance, and other inhibitors have entered early human testing. MET-HFI2025 MET-F2025

These results validate KHK as druggable. They do not establish long-term metabolic, cardiovascular, neurological, or cancer benefit. Safety must be assessed molecule by molecule, including liver, thyroid, kidney, and reproductive effects.

The ideal result would not be permission for unlimited sugar. It would be a lower upstream burden that helps restore metabolic choice-making it easier for the liver to process meals, for muscle to use fuel, and for healthy behavior to produce a durable response.

5. Uric Acid: A Parallel Target

Allopurinol and febuxostat are established treatments for appropriate gout and urate indications. Lowering serum urate prevents crystals. That does not make serum-urate lowering a general proxy for reversing intracellular fructose metabolism: a large diabetic-kidney trial of allopurinol was null for its primary kidney benefit, while a large febuxostat-versus-allopurinol trial addressed cardiovascular safety rather than pathway reversal. INT-PERL2020 INT-FAST2020

That does not make uric acid unimportant to the Fructose Model. It shows that three actions are not identical:

1. lowering urate in blood;
1. preventing intracellular uric-acid production during KHK flux;
1. reversing mitochondrial and inflammatory changes already established.

The uric-acid arm may need to be addressed at its source and in the right tissue, alongside restoration of phosphate and nucleotide recovery.

6. Why Luteolin and Tart Cherry Interest Us

Luteolin is especially interesting because it reaches unusually close to the proposed upstream switch. In laboratory work, luteolin directly inhibited KHK. In human kidney cells it reduced fructose-dependent ATP depletion, and intravenous luteolin improved acute kidney injury in mice in a pattern consistent with genetic KHK loss. INT-L2017

That is a real mechanistic signal-not proof that an oral supplement inhibits KHK in people. The effective concentration came from an enzyme and kidney-injury program, luteolin has many biological actions, and oral luteolin is often transformed into conjugates before it circulates. Whether a particular formulation delivers enough active luteolin to the right tissue remains one of the central questions.

Tart cherry approaches the model from the other side. Its polyphenols are studied for urate, oxidative, and inflammatory biology rather than as a demonstrated KHK inhibitor. Small controlled human studies have reported lower serum urate with tart-cherry juice or extract. INT-M2019 INT-J2026 But the evidence is not uniform: a randomized dose study in fifty people with gout found no reduction in serum urate, urinary urate, or short-term flares. INT-S2020

That mixed result does not make tart cherry uninteresting. It tells us that preparation, dose, population, baseline urate, and endpoint matter. In this model, tart cherry is a plausible downstream partner for investigation-not a substitute for prescribed urate-lowering treatment and not a guaranteed way to lower urate.

The combination is therefore compelling as a research idea: luteolin may act nearer the KHK entry point, while tart-cherry compounds may support the urate, redox, and inflammatory side of the pathway. One aims nearer the spark; the other may help with part of the smoke. Both propositions need formulation-specific human testing.

7. SugarShield: Turning the Hypothesis into a Testable Formulation

Commercial disclosure: LIV3 develops and sells SugarShield and therefore has a direct commercial interest in the formulation discussed below. SugarShield itself was not used in the cited ingredient studies. The discussion presents a research hypothesis, not independent evidence of product efficacy. SugarShield is not intended to diagnose, treat, cure, or prevent disease.

SugarShield is LIV3's attempt to translate that two-arm logic into a practical formulation. The current product combines high-purity luteolin and tart-cherry extract in a liposomal blend intended to address luteolin's delivery challenge. INT-SS2026

Why are we excited? Because the formulation follows the map rather than collecting unrelated ingredients. It places a plausible upstream KHK-modulating candidate beside a plausible downstream urate/redox partner. If both ingredients reach useful exposures, the combination could offer a way to test whether reducing pathway entry while easing downstream pressure improves recovery more than either approach alone.

That sentence is the hypothesis. SugarShield itself was not used in the cited KHK or tart-cherry studies. It has not yet been shown in a controlled human trial to inhibit KHK, preserve phosphate or ATP, lower urate, reduce cravings, change body weight, or treat disease. Liposomal delivery is a formulation strategy, not proof of absorption or target engagement for this product.

The appropriate next step is measurement. A credible SugarShield research program would characterize circulating luteolin and metabolites, test KHK pathway engagement, measure F1P and phosphate or nucleotide recovery after a defined challenge, and distinguish urate effects from broader inflammatory or antioxidant effects. Only then should product-level efficacy language advance.

That is the right kind of excitement for a forward-looking whitepaper: the ingredients form a coherent, testable intervention model, and the missing evidence is clear enough to design.

8. Measure Recovery, Not Only Resting Markers

The model's most important intervention question is:

> **Does this treatment increase the ability to meet a challenge and return to full capacity?**

Future studies should measure F1P, phosphate and adenine-nucleotide recovery, intracellular and circulating urate, redox state, mitochondrial function, and response to repeated challenges. They should identify responders by tissue, genetics, disease stage, sex, sleep, activity, and diet.

If KHK is upstream, successful intervention should improve several downstream features together. If it does not, the model must narrow.

The strongest trial design would therefore combine pathway engagement with a recovery outcome. Showing that an inhibitor changes urinary fructose or one fasting biomarker is useful. Showing that it shortens the time required to restore phosphate, nucleotides, redox balance, and organ function after a challenge would test the model itself.

Conclusion

The Fructose Model ends where it began: with recovery.

Reduce rapid repeated loads. Improve the systems that rebuild cellular energy-movement, sleep, oxygenation, vascular health, hydration, nutrition, and established disease care. Test KHK and uric-acid-directed interventions where the pathway can be measured.

The future is not permanent avoidance or one universal blocker. It is a recovery map precise enough to show which lever belongs to which person, tissue, and stage. Luteolin, tart cherry, and SugarShield belong on that map as serious research candidates-promising because the rationale is specific, and credible only if the formulation itself is tested.

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8. The Map Comes Together

A Conclusion and Research Direction

ABSTRACT

The Fructose Model makes one large proposal: many familiar features of metabolic dysfunction may be different expressions of a shared failure to produce, direct, and restore cellular energy.

KHK sits near the center of that map because fructose metabolism can create a low-energy signal while energy is plentiful. It spends ATP and temporarily ties up phosphate. AMP breakdown produces uric acid, adding redox, inflammatory, and mitochondrial pressure. One arm increases the recovery bill; the other can weaken the machinery that must pay it.

No single study proves the whole model. Its force comes from convergence across mechanism, physiology, food structure, history, comparative biology, and the diseases that cluster together. The map is forward-looking. Its value will be decided by whether it predicts who becomes vulnerable, why familiar interventions work or plateau, and how recovery can be measured and restored.

1. One Landscape, Many Diagnoses

Modern medicine divides chronic disease into specialties for good reason. A cardiologist sees vessels and pressure. An endocrinologist sees insulin and hormones. A neurologist sees cognition. An oncologist sees transformed cells. Each view is necessary.

But the boundaries can hide the shared terrain beneath them.

Every organ must turn fuel and oxygen into usable work. Every cell must defend itself, repair damage, communicate, and recover before the next demand. When that capacity narrows, the visible failure depends on the tissue: fatty liver, insulin resistance, vascular stiffness, disrupted appetite, altered reproductive signaling, cognitive vulnerability, or a tissue environment more permissive to cancer.

The Fructose Model does not claim that these conditions are identical or that KHK is their only cause. It proposes that repeated KHK activation may be an unusually powerful amplifier because it can connect substrate excess to an internal signal of scarcity.

2. The Central Loop

The model can be stated simply.

Rapid fructose metabolism draws down ATP and phosphate. Uric-acid-linked signaling adds oxidative and inflammatory work and can impair mitochondrial performance. Recovery slows. A lower-capacity system then handles the next meal, stress, poor night's sleep, infection, or period of inactivity less effectively.

As usable energy becomes harder to access, the body can answer with conservation: hunger, cravings, fat storage, reduced flexibility, and resistance to more incoming substrate. More energy arrives, but the machinery for using it has less margin. The warehouse fills while the delivery system struggles.

This loop does not require dietary fructose to be the only entrance. High glucose, dehydration, salt, alcohol, hypoxia, and other stresses can recruit parts of the same landscape, including endogenous fructose in defined settings. Other toxins, illnesses, nutrient deficits, and inherited vulnerabilities can weaken energy capacity without passing through KHK at all. The unifying claim is not exclusivity. It is convergence.

3. Why the Separate Papers Matter

The mechanism paper identifies the switch. Fragile systems show how a local loss of margin can scale across tissues. Endogenous fructose explains why removing obvious sugar may help without closing every entrance. Fat gain connects cellular scarcity signals to whole-body storage.

Nature, fruit, and history explain context. Timing, food structure, dose rate, seasonality, effort, and recovery can change the meaning of the same molecule.

The disease papers then test the map against its hardest cases. Metabolic and cardiovascular dysfunction show how liver, kidney, vessels, fat, and muscle can reinforce one another. Cognition asks whether brain KHK can participate in energy triage. Cancer shows that the pathway can help create a permissive terrain and support selected tumors, while also revealing less-documented metabolic architectures in which the direction reverses. Hormones show how one shared energetic disturbance can produce different endpoints through appetite, liver, gonadal, and feedback branches.

These are not fourteen proofs of one conclusion. They are independent views of the same proposed landscape. Their agreement gives the model its bite; their differences tell us where the map needs more detail.

4. What the Model Changes

This framework does not discard familiar approaches. It helps explain why many of them work.

Reducing refined carbohydrate can lower exogenous and glucose-driven endogenous pressure. Exercise increases demand but, when followed by recovery, builds capacity and improves substrate disposal. Sleep and treatment of sleep apnea protect a major recovery window. Minimally processed food slows delivery and improves satiety. Weight loss, blood-pressure treatment, diabetes care, and urate-lowering therapy address important parts of the downstream burden.

It also suggests why progress can plateau. One intervention may close one entrance while poor sleep, alcohol, hyperglycemia, inflammation, inactivity, vascular insufficiency, or low mitochondrial

reserve keeps another part of the loop active. A plateau is not always failure of will. It may be evidence that the remaining bottleneck has not yet been identified.

5. The Decisive Tests

A useful unified model must risk being wrong.

The next research phase should measure dynamic recovery, not only fasting snapshots. After a defined challenge, how quickly do F1P, phosphate, adenine nucleotides, urate, redox balance, mitochondrial function, and tissue performance return toward baseline? Does KHK inhibition improve several linked domains together? Do the benefits disappear in people or tissues without meaningful pathway activation? Can the model predict responders before treatment?

The same discipline applies to interventions. Pharmaceutical KHK inhibitors, luteolin, tart-cherry compounds, SugarShield, and other candidates must demonstrate their own exposure, target engagement, safety, and outcomes. A sound mechanism earns a test. It does not transfer efficacy from an ingredient, animal, or neighboring formulation.

Conclusion

The Fructose Model is a map of metabolic dysfunction organized around cellular energy, with KHK as a primary causal amplifier and recovery as the missing dimension.

Its promise is practical. If diseases that travel together share an upstream pressure, then reducing that pressure and rebuilding capacity may allow several systems to improve together. If a challenge-response test can reveal the active bottleneck, intervention can become more personal and less dependent on guesswork.

The map is still fuzzy in places. That is not a reason to abandon it. It is a reason to mark the uncertain ground, test the routes that matter most, and redraw the boundaries when evidence requires it.

The series therefore ends with a proposal, not a verdict: chronic metabolic dysfunction may become easier to understand when we stop asking only how much energy the body stores and begin asking how well its cells can use, protect, and restore it.

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Bibliography and Evidence Notes

Centralized bibliography for The Fructose Model whitepaper series - 17 August 2026

This bibliography was rebuilt from the program's canonical evidence library. The frozen public bibliography was used only to identify legacy links; it was not treated as evidence that a citation was correct.

A whitepaper can properly use primary studies, systematic reviews, consensus guidance, and clearly identified hypothesis papers. The source class below tells readers what kind of support each item provides. A source can support a component of the map without proving the whole Fructose Model.

Evidence language. "Primary research" means the source reports an experiment, trial, cohort, or other original analysis. "Review and hypothesis synthesis" means it helps assemble the map but does not substitute for direct proof of a pivotal empirical claim. Product information establishes only what LIV3 currently says the product contains.

Commercial disclosure. LIV3 develops and sells SugarShield and therefore has a commercial interest in the formulation discussed in Paper 7. SugarShield itself was not used in the cited ingredient studies.

Core model

[CORE-J2023] The fructose survival hypothesis for obesity

Richard J. Johnson, Miguel A. Lanaspa, L. Gabriela Sanchez-Lozada, Dean Tolan, Takahiko Nakagawa, Takuji Ishimoto, et al. (2023). *The fructose survival hypothesis for obesity*. Philosophical Transactions of the Royal Society B, 378(1885).

Source class: Review or synthesis

Used in this series for: Integrative survival-pathway synthesis used to frame the unifying hypothesis

Boundary: Orientation and citation discovery

Canonical record: S017

Source link: Open source record

Mechanism and cellular energy

[MECH-P1978] Evidence that the Severity of Depletion of Inorganic Phosphate Determines the Severity of the Disturbance of Adenine Nucleotide Metabolism in the Liver and Renal Cortex of the Fructose-Loaded Rat

R Curtis Morris Jr, Kathleen Nigon, Elizabeth B Reed (1978). *Evidence that the Severity of Depletion of Inorganic Phosphate Determines the Severity of the Disturbance of Adenine Nucleotide Metabolism in the Liver and Renal Cortex of the Fructose-Loaded Rat*. Journal of Clinical Investigation, 61(1), 209-220.

Source class: Primary research

Used in this series for: Direct phosphate-depletion and adenine-nucleotide experiment

Boundary: Severe intraperitoneal fructose loading reduced phosphate ATP and total adenine nucleotides in rat liver and renal cortex; prior phosphate or adenosine loading produced tissue-specific rescue, but the design did not include washout or a later standardized challenge

Canonical record: S074

Source link: Open source record

[MECH-U2012] Uric Acid Induces Hepatic Steatosis by Generation of Mitochondrial Oxidative Stress

Miguel A Lanaspa, Laura G Sanchez-Lozada, Yea-Jin Choi, Christina Cicerchi, Mehmet Kanbay, Carlos A Roncal-Jimenez, et al. (2012). *Uric Acid Induces Hepatic Steatosis by Generation of Mitochondrial Oxidative Stress*. Journal of Biological Chemistry, 287(48), 40732-40744.

Source class: Primary research

Used in this series for: Urate-linked mitochondrial oxidative stress and hepatic fat mechanism

Boundary: HepG2 and mouse evidence linking fructose-derived urate with mitochondrial NOX4 redox effects and triglyceride accumulation; inhibitor off-target and conflict boundaries recorded

Canonical record: S043

Source link: Open source record

[MECH-H2012] Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes

MF Abdelmalek, M Lazo, A Horska, S Bonekamp, EW Lipkin, A Balasubramanyam, et al. (2012). *Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes*. Hepatology, 56(3), 952-960.

Source class: Primary research

Used in this series for: Human association between higher fructose exposure and impaired hepatic ATP recovery

Boundary: Exploratory human 31P-MRS subset for C018; full text reviewed in PMC

Canonical record: S022

Source link: Open source record

[MECH-H2016] Investigating the effects of an oral fructose challenge on hepatic ATP reserves in healthy volunteers: A 31P MRS study

S J Bawden, M C Stephenson, E Ciampi, K Hunter, L Marciani, I A Macdonald, et al. (2016). *Investigating the effects of an oral fructose challenge on hepatic ATP reserves in healthy volunteers: A 31P MRS study*. Clinical Nutrition, 35(3), 645-649.

Source class: Primary research

Used in this series for: Controlled human fructose-challenge study of hepatic ATP reserves

Boundary: Ten healthy men; registered study NCT02217605; publisher and registry records reviewed

Canonical record: S023

Source link: Open source record

Endogenous fructose

[ENDO-L2013] Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome

Miguel A Lanaspa, Takuji Ishimoto, Nanxing Li, Christina Cicerchi, David J Orlicky, Philip Ruzycki, et al. (2013). *Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome*. Nature Communications, 4, 2434.

Source class: Primary research

Used in this series for: High-glucose polyol-pathway fructose and metabolic phenotype in mice

Boundary: Wild-type KHK-A/C-null and aldose-reductase-null mice under fourteen weeks of ten-percent glucose support a hepatic endogenous-fructose contribution to selected metabolic phenotypes; an author-name correction changes Ruzicky to Ruzycki; no recovery or reserve endpoint was measured

Canonical record: S076

Source link: Open source record

[ENDO-S2018] High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism

Miguel A Lanaspa, Masanari Kuwabara, Ana Andres-Hernando, Nanxing Li, Christina Cicerchi, Thomas Jensen, et al. (2018). *High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism*. Proceedings of the National Academy of Sciences of the United States of America, 115(12), 3138-3143.

Source class: Primary research

Used in this series for: High-salt endogenous-fructose pathway in mice

Boundary: Mouse and adipocyte hyperosmolality evidence; salt insulin resistance retained a KHK-independent component; PMID 30224469 corrects only Nanxing Li's author name

Canonical record: S045

Source link: Open source record

[ENDO-A2025] Identification of a common ketohexokinase-dependent link driving alcohol intake and alcohol-associated liver disease in mice

Ana Andres-Hernando, David J Orlicky, Gabriela E Garcia, Esteban C Loetz, Richard Montoya, Vijay Kumar, et al. (2025). *Identification of a common ketohexokinase-dependent link driving alcohol intake and alcohol-associated liver disease in mice*. Nature Metabolism, 7(11), 2250-2267.

Source class: Primary research

Used in this series for: Alcohol-associated polyol-KHK activation in mouse liver and intestine

Boundary: Ethanol increased portal osmolality and liver or intestinal sorbitol fructose and pathway activity in mice; AR and global tissue-specific or pharmacologic KHK perturbations supported causal roles in alcohol preference and ALD; concentration dependence and mouse-to-human translation remain material boundaries; relevant patent and inhibitor-development conflicts disclosed

Canonical record: S-P005-021

Source link: Open source record

[ENDO-B2026] Endogenous fructose production in patients and mice with aldolase B deficiency

Amée M Buziau, Nynke Simons, Dean R Tolan, Florian Caiment, Jean L J M Scheijen, Marjo P van de Waarenburg, et al. (2026). *Endogenous fructose production in patients and mice with aldolase B deficiency*. Molecular Genetics and Metabolism, 149(1-2), 110219.

Source class: Primary research

Used in this series for: Human post-glucose serum-fructose response plus mouse glucose-to-F1P tracing and steatosis-null boundary

Boundary: In fourteen patients with hereditary fructose intolerance and fourteen matched controls serum fructose rose after a seventy-five-gram oral glucose challenge; mouse isotope tracing linked glucose carbon to hepatic F1P and aldose-reductase inhibition lowered hepatic fructose but did not lower intrahepatic lipid over nine days. Human glucose carbon was not isotope traced; tissue source flux magnitude KHK consequences and ordinary-diet clinical importance remain unresolved, and the mouse liver-fat null argues against endogenous fructose as the sole driver of established steatosis in this model

Canonical record: S-P005-045

Source link: Open source record

Nature and adaptation

[NAT-P2017] Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat

Thomas J Park, Jane Reznick, Bethany L Peterson, Gregory Blass, Damir Omerbasic, Nigel C Bennett, et al. (2017). *Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat*. Science, 356(6335), 307-311.

Source class: Primary research

Used in this series for: Fructose-supported anoxia tolerance in naked mole rats

Boundary: Supports anoxia-associated fructose-driven glycolysis in naked mole rats; does not test cancer resistance or human premalignant terrain

Canonical record: S-P005-012

Source link: Open source record

Fruit and food matrix

[FRUIT-G2024] Are all sugars equal? Role of the food source in physiological responses to sugars with an emphasis on fruit and fruit juice

Javier T Gonzalez (2024). *Are all sugars equal? Role of the food source in physiological responses to sugars with an emphasis on fruit and fruit juice*. European Journal of Nutrition, 63(5), 1435-1451.

Source class: Review or synthesis

Used in this series for: Human evidence synthesis on food source matrix and sugar physiology

Boundary: Review concludes that food source and matrix alter physiological responses to sugars and distinguishes evidence for whole fruit fruit juice and sugar-sweetened beverages; it synthesizes heterogeneous evidence and does not prove a fixed rank order for every person dose or endpoint

Canonical record: S-P005-033

Source link: Open source record

[FRUIT-N2024] Consumption of 100% Fruit Juice and Body Weight in Children and Adults: A Systematic Review and Meta-Analysis

Michelle Nguyen, Sarah E Jarvis, Laura Chiavaroli, Sonia Blanco Mejia, Andreea Zurbau, Tauseef A Khan, et al. (2024). *Consumption of 100% Fruit Juice and Body Weight in Children and Adults: A Systematic Review and Meta-Analysis*. JAMA Pediatrics, 178(3), 237-246.

Source class: Systematic review or meta-analysis

Used in this series for: Systematic review and meta-analysis of 100-percent fruit juice and body weight

Boundary: Meta-analysis found small prospective BMI gain per additional daily serving of 100-percent juice in children; adult cohorts differed by energy adjustment and adult randomized trials were null with wide uncertainty; does not establish a simple whole-fruit-to-juice causal gradient for every outcome

Canonical record: S-P005-032

Source link: Open source record

Historical context

[HIST-M1986] Sweetness and Power: The Place of Sugar in Modern History

Sidney W Mintz (1986). *Sweetness and Power: The Place of Sugar in Modern History*. Penguin Books, 320.

Source class: Scholarly historical synthesis

Used in this series for: Scholarly history of sugar commodification colonial production and forced labor

Boundary: Scholarly historical synthesis connecting sugar production colonial systems forced labor industrialization and the transition from luxury to everyday commodity; does not quantify modern individual exposure or establish biomedical causation

Canonical record: S-P005-037

Source link: Open source record

[HIST-USDA2025] Food Availability Per Capita Data System - Food Availability Documentation

Andrzej Blazejczyk, Linda Kantor, United States Department of Agriculture Economic Research Service (2025). *Food Availability Per Capita Data System - Food Availability Documentation*. USDA Economic Research Service.

Source class: Official government data documentation

Used in this series for: Official long-run caloric-sweetener availability documentation and measurement limits

Boundary: Documents annual United States caloric-sweetener availability estimates since 1941 and explicitly warns that availability can overstate ingestion and includes losses or exported ingredients; supports exposure history but not disease causation

Canonical record: S-P005-038

Source link: Open source record

Metabolic dysfunction

[MET-K2020] Deletion of Fructokinase in the Liver or in the Intestine Reveals Differential Effects on Sugar-Induced Metabolic Dysfunction

Ana Andres-Hernando, David J Orlicky, Masanari Kuwabara, Takuji Ishimoto, Takahiko Nakagawa, Richard J Johnson, et al. (2020). *Deletion of Fructokinase in the Liver or in the Intestine Reveals Differential Effects on Sugar-Induced Metabolic Dysfunction*. Cell Metabolism, 32(1), 117-127.e3.

Source class: Primary research

Used in this series for: Liver-versus-intestine KHK deletion and sugar-induced metabolic effects in mice

Boundary: Thirty-week male-mouse experiments separated intestinal from hepatic KHK. Intestinal deletion reduced sugar intake but lost metabolic protection when exposure was matched; liver deletion preserved intake yet protected against weight gain fatty liver adipose inflammation hyperinsulinemia hyperleptinemia and insulin resistance. Developmental deletion small groups extreme liquid sugar male-only design and investigator KHK-inhibitor patents limit transition and translation claims; no reproductive endpoints

Canonical record: S239

Source link: Open source record

[MET-K2021] Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: A randomized phase 2 trial

David J Kazierad, Kristin Chidsey, Veena R Somayaji, Arthur J Bergman, Morris J Birnbaum, Roberto A Calle (2021). *Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: A randomized phase 2 trial*. Med, 2(7), 800-813.e3.

Source class: Primary research

Used in this series for: Six-week randomized human KHK-inhibitor trial in NAFLD

Boundary: Six-week NCT03256526 KHK-inhibitor trial in 53 adults with NAFLD; high dose reduced MRI-PDFF but low dose did not; liver fat is not direct DNL or reserve evidence; Pfizer sponsored and authored

Canonical record: S050

Source link: Open source record

[MET-HFI2025] Safety and efficacy of pharmacological inhibition of ketohexokinase in hereditary fructose intolerance

Evi JC Koene, Amee M Buziau, David Cassiman, Timothy M Cox, Judith Bons, Jean LJM Scheijen, et al. (2025). *Safety and efficacy of pharmacological inhibition of ketohexokinase in hereditary fructose intolerance*. Journal of Clinical Investigation, 135(6), e187376.

Source class: Primary research

Used in this series for: Human KHK target engagement and acute F1P-phosphate response in hereditary fructose intolerance

Boundary: Human crossover KHK-inhibitor evidence for hepatic fructose-1-phosphate and Pi response; open PMC full text reviewed

Canonical record: S039

Source link: Open source record

[MET-F2025] LY3522348, A New Ketohexokinase Inhibitor: A First-in-Human Study in Healthy Adults

Tsuyoshi Fukuda, Brian R Thompson, Bram Brouwers, Hui-Rong Qian, Wei Wang, Bridget L Morse, et al. (2025). *LY3522348, A New Ketohexokinase Inhibitor: A First-in-Human Study in Healthy Adults*. Diabetes Therapy, 16(7), 1399-1415.

Source class: Primary research

Used in this series for: First-in-human study of a second KHK inhibitor

Boundary: Sixty-five healthy adults received single LY3522348 doses or up to fourteen to fifteen daily doses with fructose-challenge target engagement. No serious adverse event death or treatment-related discontinuation was reported. Women were not of childbearing potential and reproductive hormones cycles gonadal function fertility and thyroid-specific endpoints were not reported. Eli Lilly funded the study and all authors were current or former employees; most disclosed equity

Canonical record: S245

Source link: Open source record

[MET-EFG1994] Molecular basis of essential fructosuria: molecular cloning and mutational analysis of human ketohexokinase (fructokinase)

David T Bonthron, Nicola Brady, Iain A Donaldson, Beat Steinmann (1994). *Molecular basis of essential fructosuria: molecular cloning and mutational analysis of human ketohexokinase (fructokinase)*. Human Molecular Genetics, 3(9), 1627-1631.

Source class: Primary research

Used in this series for: Family genetic evidence linking biallelic KHK variants to essential fructosuria

Boundary: All three affected siblings in one well-characterized family with essential fructosuria were compound heterozygous for KHK Gly40Arg and Ala43Thr variants absent from fifty-two unrelated controls; the paper establishes genotype-phenotype cosegregation but does not provide cardiometabolic outcomes or participant-linked modern functional assays

Canonical record: S-P001-200

Source link: Open source record

[MET-EF1994] Changes of liver metabolite concentrations in adults with disorders of fructose metabolism after intravenous fructose by 31P magnetic resonance spectroscopy

Peter Boesiger, Reto Buchli, Dieter Meier, Beat Steinmann, Rolf Gitzelmann (1994). *Changes of liver metabolite concentrations in adults with disorders of fructose metabolism after intravenous fructose by 31P magnetic resonance spectroscopy*. Pediatric Research, 36(4), 436-440.

Source class: Primary research

Used in this series for: Single-participant essential-fructosuria hepatic F1P ATP and phosphate challenge boundary

Boundary: After intravenous fructose one adult with essential fructosuria showed no hepatic fructose-1-phosphate ATP or inorganic-phosphate change whereas three controls showed rapid fructose-1-phosphate accumulation and ATP and

phosphate drawdown; single-patient design and no genotype stated in the report prevent participant-level genotype-function linkage

Canonical record: S-P001-201

Source link: Open source record

Cardiovascular disease

[CVD-Z2008] Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells

Sergey Zharikov, Karina Krotova, Hanbo Hu, Chris Baylis, Richard J Johnson, Edward R Block, et al. (2008). *Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells*. American Journal of Physiology-Cell Physiology, 295(5), C1183-C1190.

Source class: Primary research

Used in this series for: Urate arginase and nitric-oxide mechanism in nonhuman vascular systems

Boundary: Urate reduced stimulated nitric-oxide and cGMP production and increased arginase activity in cultured pulmonary-artery endothelial cells and impaired vasodilation in isolated porcine arteries; nonhuman ex-vivo and cell conditions do not establish ordinary circulating urate as a cardiovascular cause in people

Canonical record: S-P005-031

Source link: Open source record

[CVD-K2012] Regulation of uric acid excretion by the kidney

Michael S Lipkowitz (2012). *Regulation of uric acid excretion by the kidney*. Current Rheumatology Reports, 14(2), 179-188.

Source class: Review or synthesis

Used in this series for: Review of human renal urate handling

Boundary: Reviews renal proximal-tubule urate transport and reports that renal excretion accounts for most urate elimination; does not establish fructose as the cause of impaired urate clearance or cardiovascular disease

Canonical record: S-P005-034

Source link: Open source record

[CVD-B2020] Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological genetic and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

Jan Borén, M John Chapman, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, et al. (2020). *Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological genetic and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel*. European Heart Journal, 41(24), 2313-2330.

Source class: Consensus statement

Used in this series for: Consensus background for LDL-containing apoB particle causality in atherosclerosis

Boundary: European Atherosclerosis Society consensus integrates pathophysiologic genetic epidemiologic and therapeutic evidence that LDL-containing apoB particles are causal in atherosclerotic cardiovascular disease; consensus synthesis supports the established particle mechanism but does not implicate fructose or KHK as its exclusive upstream cause

Canonical record: S-P005-043

Source link: Open source record

[CVD-A2013] Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses

Nancy J Aburto, Sara Hanson, Hialy Gutierrez, Lee Hooper, Paul Elliott, Francesco P Cappuccio (2013). *Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses*. BMJ, 346, f1378.

Source class: Systematic review or meta-analysis

Used in this series for: Systematic-review boundary for potassium intake and blood-pressure support

Boundary: Meta-analysis of twenty-two randomized trials found increased potassium intake lowered blood pressure in adults with hypertension but not normotensive adults; cohort synthesis associated higher intake with lower stroke risk while cardiovascular and coronary-disease associations were nonsignificant; conclusions do not apply without caution to impaired renal potassium handling and do not establish KHK mediation

Canonical record: S-P005-044

Source link: Open source record

[CVD-R2010] Mitochondrial reserve capacity in endothelial cells: The impact of nitric oxide and reactive oxygen species

Brian P Dranka, Bradford G Hill, Victor M Darley-Usmar (2010). *Mitochondrial reserve capacity in endothelial cells: The impact of nitric oxide and reactive oxygen species*. Free Radical Biology and Medicine, 48(7), 905-914.

Source class: Primary research

Used in this series for: Endothelial mitochondrial reserve and redox-nitric-oxide interaction

Boundary: Bovine endothelial-cell extracellular-flux study; nonlethal NO or oxidant exposure reduced FCCP-defined reserve with little basal-OCR change; combined stress linked irreversible reserve loss to cell death

Canonical record: S051

Source link: Open source record

Neurodegeneration

[NEURO-H2017] The human brain produces fructose from glucose

Janice J Hwang, Lihong Jiang, Muhammad Hamza, Feng Dai, Renata Belfort-DeAguiar, Gary Cline, et al. (2017). *The human brain produces fructose from glucose*. JCI Insight, 2(4), e90508.

Source class: Primary research

Used in this series for: Controlled human evidence that brain fructose can rise from glucose

Boundary: Eight healthy adults underwent a four-hour hyperglycemic clamp with proton MRS; intracerebral fructose signal rose with brain glucose rather than plasma fructose, but spectral overlap cannot exclude some sorbitol contribution and no KHK flux energetic outcome or recovery was measured

Canonical record: S073

Source link: Open source record

[NEURO-LI2023] Ketohexokinase-dependent metabolism of cerebral endogenous fructose in microglia drives diabetes-associated cognitive dysfunction

Yansong Li, Tao Jiang, Mengyu Du, Shuxuan He, Ning Huang, Bo Cheng, et al. (2023). *Ketohexokinase-dependent metabolism of cerebral endogenous fructose in microglia drives diabetes-associated cognitive dysfunction*. Experimental & Molecular Medicine, 55(11), 2417-2432.

Source class: Primary research

Used in this series for: Hippocampal KHK perturbation in a diabetic mouse cognition model

Boundary: db/db mouse hippocampus and microglia evidence for endogenous fructose KHK NOX4 redox and mitochondrial effects; diabetes model does not isolate hyperglycemia from obesity or leptin-receptor loss

Canonical record: S048

Source link: Open source record

[NEURO-J2020] Cerebral Fructose Metabolism as a Potential Mechanism Driving Alzheimer's Disease

Richard J Johnson, Fernando Gomez-Pinilla, Maria Nagel, Takahiko Nakagawa, Bernardo Rodriguez-Iturbe, Laura G Sanchez-Lozada, et al. (2020). *Cerebral Fructose Metabolism as a Potential Mechanism Driving Alzheimer's Disease*. Frontiers in Aging Neuroscience, 12, 560865.

Source class: Review and hypothesis synthesis

Used in this series for: Johnson cerebral-fructose Alzheimer hypothesis architecture

Boundary: Proposes cerebral fructose or KHK as an initiating energy-lowering pathway linking foraging food intake mitochondrial dysfunction insulin resistance neuroinflammation and Alzheimer pathology; integrative hypothesis rather than direct human KHK perturbation; multiple authors disclosed equity in fructose-metabolism inhibitor development

Canonical record: S-P005-022

Source link: Open source record

[NEURO-J2023] Could Alzheimer's disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism?

Richard J Johnson, Dean R Tolan, Dale Bredesen, Maria Nagel, Laura G Sánchez-Lozada, Mehdi Fini, et al. (2023). *Could Alzheimer's disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism?*. The American Journal of Clinical Nutrition, 117(3), 455-466.

Source class: Review and hypothesis synthesis

Used in this series for: Updated cerebral energy-triage and Alzheimer synthesis

Boundary: Extends the proposed fructose-triggered survival-state model to cerebral glucose hypometabolism mitochondrial dysfunction and neuroinflammation; valuable whitepaper synthesis but does not directly establish human brain KHK-mediated energy triage or treatment benefit

Canonical record: S-P005-023

Source link: Open source record

[NEURO-P2013] Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways

Kathleen A Page, Owen Chan, Jagriti Arora, Renata Belfort-Deaguiar, James Dzuira, Brian Roehmholdt, et al. (2013). *Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways*. JAMA, 309(1), 63-70.

Source class: Primary research

Used in this series for: Acute human fructose-versus-glucose appetite and brain-response crossover

Boundary: Twenty-person acute crossover found greater hypothalamic CBF suppression and satiety after glucose than fructose; corrected whole-brain direct comparisons were null and the design did not manipulate or measure cerebral KHK

Canonical record: S-P005-024

Source link: Open source record

[NEURO-L2015] Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards

Shan Luo, John R Monterosso, Kayan Sarpelleh, Kathleen A Page (2015). *Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards*. Proceedings of the National Academy of Sciences of the United States of America, 112(20), 6509-6514.

Source class: Primary research

Used in this series for: Acute human food-cue and immediate-reward crossover

Boundary: Twenty-four-person acute crossover found greater food-cue reactivity hunger desire and willingness to choose immediate food after fructose than glucose; acute beverage contrast cannot establish chronic cognition Alzheimer risk or KHK mediation

Canonical record: S-P005-025

Source link: Open source record

[NEURO-O2017] Specific regions of the brain are capable of fructose metabolism

Sarah A Oppelt, Wanming Zhang, Dean R Tolan (2017). *Specific regions of the brain are capable of fructose metabolism*. Brain Research, 1657, 312-322.

Source class: Primary research

Used in this series for: Regional mapping of brain fructose-handling capacity

Boundary: Adult-mouse in-situ hybridization localized Khk Aldoc Slc2a5 and Slc2a9 mainly to cerebellum hippocampus cortex and olfactory bulb and dissected regions metabolized labeled fructose; hypothalamus and Kiss1 cells were not resolved and regional enzyme or oxidation assays cannot establish neuron-autonomous KHK flux

Canonical record: S150

Source link: Open source record

[NEURO-X2016] Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia

Jingshu Xu, Paul Begley, Stephanie J Church, Stefano Patassini, Selina McHarg, Nina Kureishy, et al. (2016). *Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia*. Scientific Reports, 6, 27524.

Source class: Primary research

Used in this series for: Postmortem Alzheimer brain glucose sorbitol and fructose pattern

Boundary: Nine Alzheimer cases and nine controls showed higher glucose sorbitol and fructose across sampled postmortem brain regions; small cross-sectional tissue study cannot establish temporal order KHK mediation disease initiation or treatment effect

Canonical record: S-P005-042

Source link: Open source record

Cancer

[CANC-N2020] Fructose contributes to the Warburg effect for cancer growth

Takahiko Nakagawa, Miguel A Lanaspa, Inigo San Millan, Mehdi Fini, Christopher J Rivard, Laura G Sanchez-Lozada, et al. (2020). *Fructose contributes to the Warburg effect for cancer growth*. Cancer and Metabolism, 8(1), 16.

Source class: Review and hypothesis synthesis

Used in this series for: Review and hypothesis linking fructose metabolism to Warburg-like cancer energetics

Boundary: Relevant whitepaper synthesis and discovery source; may support hypothesis framing but not substitute for primary proof of universal mitochondrial suppression mutagenesis hypoxic survival or clinical KHK targeting

Canonical record: S-P005-013

Source link: Open source record

[CANC-F2024] Dietary fructose enhances tumour growth indirectly via interorgan lipid transfer

Ronald Fowle-Grider, Joe L Rowles III, Isabel Shen, Yahui Wang, Michaela Schwaiger-Haber, Alden J Dunham, et al. (2024). *Dietary fructose enhances tumour growth indirectly via interorgan lipid transfer*. Nature, 636(8043), 737-744.

Source class: Primary research

Used in this series for: Liver-KHK-dependent lipid transfer supporting selected mouse tumors

Boundary: Dietary fructose enhanced melanoma breast and cervical tumor growth in mouse models through liver KHK-dependent circulating LPC production; tumor cells did not readily catabolize fructose; pharmacologic KHK inhibition prevented the fructose-mediated growth effect in vivo but no human intervention was tested; archived BioC fetch error retained

Canonical record: S-P005-016

Source link: Open source record

[CANC-G2023] Genetic ablation of ketohexokinase C isoform impairs pancreatic cancer development

Ilaria Guccini, Guanghui Tang, Trang Thuy To, Laura Di Rito, Solange Le Blanc, Oliver Strobel, et al. (2023). *Genetic ablation of ketohexokinase C isoform impairs pancreatic cancer development*. iScience, 26(8), 107368.

Source class: Primary research

Used in this series for: KHK-C ablation in pancreatic-cancer models

Boundary: Pancreatic KhkC ablation delayed KPC-driven PDAC and extended survival even without a high-fructose diet while altering KRAS-MAPK and mTOR-linked signaling; preclinical genetic program with no human therapeutic intervention

Canonical record: S-P005-017

Source link: Open source record

[CANC-S2022] GLUT5-KHK axis-mediated fructose metabolism drives proliferation and chemotherapy resistance of colorectal cancer

Zhiyong Shen, Zhenkang Li, Yuechen Liu, Yongsheng Li, Xiaochuang Feng, Yizhi Zhan, et al. (2022). *GLUT5-KHK axis-mediated fructose metabolism drives proliferation and chemotherapy resistance of colorectal cancer*. Cancer Letters, 534, 215617.

Source class: Primary research

Used in this series for: GLUT5-KHK growth and chemotherapy-resistance phenotype in colorectal-cancer models

Boundary: GLUT5-KHK perturbation reduced colorectal-cancer growth and fructose-related chemotherapy resistance in reported preclinical systems; abstract-level audit and no human intervention limit therapeutic translation

Canonical record: S-P005-018

Source link: Open source record

[CANC-T2022] Ketohexokinase-mediated fructose metabolism is lost in hepatocellular carcinoma and can be leveraged for metabolic imaging

Sui Seng Tee, Nathaniel Kim, Quinlan Cullen, Roozbeh Eskandari, Arsen Mamakhanyan, Rami M Srouji, et al. (2022). *Ketohexokinase-mediated fructose metabolism is lost in hepatocellular carcinoma and can be leveraged for metabolic imaging*. Science Advances, 8(14), eabm7985.

Source class: Primary research

Used in this series for: Loss and forced restoration of KHK-C fructolysis in hepatocellular-carcinoma models

Boundary: HCC tissues and models showed reduced fructose-handling proteins and F1P production; forced KHK-C with fructose reduced ATP and selected against cells in reported systems; no clinical therapy or pan-cancer metabolic trap

Canonical record: S-P005-003

Source link: Open source record

[CANC-H2026] Fructose 1-phosphate inhibits mannose phosphate isomerase to suppress hepatocellular carcinogenesis

Yongqiang Wang, Xiangyang Zhang, Ningning Wang, Huimin Jiang, Ningning Liang, Chenxi Du, et al. (2026). *Fructose 1-phosphate inhibits mannose phosphate isomerase to suppress hepatocellular carcinogenesis*. Signal Transduction and Targeted Therapy, 11(1), 195.

Source class: Primary research

Used in this series for: F1P-MPI vulnerability in defined ALDOB-deficient hepatocellular-carcinoma models

Boundary: Human HCC profiling plus cell biochemical and genetically defined mouse studies support an ALDOB-deficient retained-KHK F1P-MPI liability; 10-percent fructose mouse exposure and no human intervention preclude treatment advice or broad protective claims

Canonical record: S-P005-001

Source link: Open source record

[CANC-O2026] The chemotherapy-induced senescence-associated secretome promotes cell detachment and metastatic dissemination through metabolic reprogramming

Aidan R Cole, Raquel Buj, Apoorva Uboveja, Evan Levasseur, Alexander Tom, Hui Wang, et al. (2026). *The chemotherapy-induced senescence-associated secretome promotes cell detachment and metastatic dissemination through metabolic reprogramming*. Nature Aging, 6, 1647-1666.

Source class: Primary research

Used in this series for: KHK-dependent dissemination after chemotherapy-induced senescence in ovarian-cancer models

Boundary: Final Nature Aging version published 2026-07-30; PMID 40832218 and PMCID PMC12363692 identify the bioRxiv preprint and are not attached here; supports defined HGSOC detachment and dissemination requiring KHK and complex I but not clinical dietary advice or polyol-pathway origin of secreted fructose

Canonical record: S-P005-002

Source link: Open source record

[CANC-A2016] Enhanced Fructose Utilization Mediated by SLC2A5 Is a Unique Metabolic Feature of Acute Myeloid Leukemia with Therapeutic Potential

Wen-Lian Chen, Yue-Ying Wang, Aihua Zhao, Li Xia, Guoxiang Xie, Mingming Su, et al. (2016). *Enhanced Fructose Utilization Mediated by SLC2A5 Is a Unique Metabolic Feature of Acute Myeloid Leukemia with Therapeutic Potential*. Cancer Cell, 30(5), 779-791.

Source class: Primary research

Used in this series for: SLC2A5-mediated fructose use in acute-myeloid-leukemia models

Boundary: Supports GLUT5-mediated fructose utilization in defined AML models and outcome associations; does not establish expression or dependence across many tumors

Canonical record: S-P005-007

Source link: Open source record

[CANC-L2018] Fructose fuels lung adenocarcinoma through GLUT5

Yuanyuan Weng, Jin Zhu, Zhenhong Chen, Jingqi Fu, Feng Zhang (2018). *Fructose fuels lung adenocarcinoma through GLUT5*. Cell Death and Disease, 9(5), 557.

Source class: Primary research

Used in this series for: GLUT5-dependent fructose phenotype in lung-adenocarcinoma models

Boundary: Supports GLUT5-dependent fructose-associated proliferation migration invasion and xenograft outcomes in reported lung-adenocarcinoma models; small preclinical program and no human intervention

Canonical record: S-P005-008

Source link: Open source record

[CANC-M2018] Aldolase B-Mediated Fructose Metabolism Drives Metabolic Reprogramming of Colon Cancer Liver Metastasis

Pengcheng Bu, Kai-Yuan Chen, Kun Xiang, Christelle Johnson, Scott B Crown, Nikolai Rakhilin, et al. (2018). *Aldolase B-Mediated Fructose Metabolism Drives Metabolic Reprogramming of Colon Cancer Liver Metastasis*. Cell Metabolism, 27(6), 1249-1262.e4.

Source class: Primary research

Used in this series for: ALDOB-dependent fructose use in colorectal-cancer liver metastasis

Boundary: Supports ALDOB upregulation and fructose use in colorectal-cancer liver metastasis with genetic and dietary perturbation; established metastatic context does not demonstrate premalignant genomic fragility

Canonical record: S-P005-006

Source link: Open source record

[CANC-I2019] High-fructose corn syrup enhances intestinal tumor growth in mice

Marcus D Goncalves, Changyuan Lu, Jordan Tutnauer, Travis E Hartman, Seo-Kyoung Hwang, Charles J Murphy, et al. (2019). *High-fructose corn syrup enhances intestinal tumor growth in mice*. Science, 363(6433), 1345-1349.

Source class: Primary research

Used in this series for: HFCS-associated intestinal-tumor growth in APC-deficient mice

Boundary: HFCS increased tumor size and grade in APC-deficient mice without obesity and supported glycolysis and fatty-acid synthesis; did not test metastasis or establish a general human-cancer effect

Canonical record: S-P005-010

Source link: Open source record

[CANC-WCRF2025] Limit sugar-sweetened drinks: recommendation evidence

World Cancer Research Fund (2025). *Limit sugar-sweetened drinks: recommendation evidence*. World Cancer Research Fund.

Source class: Consensus or public-health guidance

Used in this series for: Consensus prevention guidance for limiting sugar-sweetened beverages

Boundary: WCRF recommends limiting sugar-sweetened drinks chiefly through their contribution to excess energy intake overweight and obesity; it does not state that sugar uniquely feeds tumors or that restriction treats established cancer

Canonical record: S-P005-039

Source link: Open source record

[CANC-NCI2026] Common Cancer Myths and Misconceptions

National Cancer Institute (2026). *Common Cancer Myths and Misconceptions*. National Cancer Institute.

Source class: Consensus or public-health guidance

Used in this series for: Clinical boundary against presenting sugar restriction as tumor starvation or treatment

Boundary: NCI states that no studies show eating sugar makes cancer worse or stopping sugar makes it shrink while recognizing indirect obesity-related pathways; guidance bounds dietary and clinical implications

Canonical record: S-P005-040

Source link: Open source record

Hormonal dysfunction

[HORM-C2008] Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake

Seung Hun Cha, Michael Wolfgang, Yuka Tokutake, Shigeru Chohnan, M Daniel Lane (2008). *Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake*. Proceedings of the National Academy of Sciences of the United States of America, 105(44), 16871-16875.

Source class: Primary research

Used in this series for: Central fructose-versus-glucose feeding signal in mice

Boundary: Acute intracerebroventricular fructose in fasted mice lowered whole-hypothalamus ATP and malonyl-CoA increased AMPK signaling and food intake relative to glucose; high-dose central delivery whole-hypothalamus assays and no KHK perturbation or Kiss1 measurement prevent endogenous or cell-specific inference

Canonical record: S142

Source link: Open source record

[HORM-P2025] Fructose-induced synaptic and neuronal adaptations at neuropeptide Y/agouti-related peptide neurons

Mikayla A Payant, Aditi S Sankhe, Persephone A Miller, Sarah S Vieira, Yasmina Dumiaty, Jenny Phy-Lim, et al. (2025). *Fructose-induced synaptic and neuronal adaptations at neuropeptide Y/agouti-related peptide neurons*. Molecular Metabolism, 99, 102209.

Source class: Primary research

Used in this series for: Sex-dependent NPY-AgRP circuit remodeling after high-fructose feeding in mice

Boundary: Male and female mice received chow or sixty-percent-calorie fructose or dextrose diets for up to eight weeks with one- or four-week withdrawal arms; fructose uniquely remodeled NPY-AgRP synaptic input with sex-dependent persistence while ninety-minute slice fructose was null; no KHK perturbation ATP measure Kiss1 endpoint or reproductive outcome

Canonical record: S160

Source link: Open source record

[HORM-S2008] Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding

Alexandra Shapiro, Wei Mu, Carlos Roncal, Kit-Yan Cheng, Richard J Johnson, Philip J Scarpace (2008). *Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding*. American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 295(5), R1370-R1375.

Source class: Primary research

Used in this series for: Leptin resistance preceding weight gain in a high-fructose male-rat model

Boundary: Male rats fed a sixty-percent-fructose versus fructose-free diet for six months lost the anorexic response to peripheral leptin and had lower basal whole-hypothalamus pSTAT3 despite similar weight adiposity leptin insulin and glucose; triglycerides rose and could impair leptin transport, and no identified AgRP cell KHK ATP Kiss1 or reproductive endpoint was measured

Canonical record: S180

Source link: Open source record

[HORM-T2004] Dietary fructose reduces circulating insulin and leptin attenuates postprandial suppression of ghrelin and increases triglycerides in women

Karen L Teff, Sharon S Elliott, Matthias Tschöp, Timothy J Kieffer, Daniel Rader, Mark Heiman, et al. (2004). *Dietary fructose reduces circulating insulin and leptin attenuates postprandial suppression of ghrelin and increases triglycerides in women*. The Journal of Clinical Endocrinology and Metabolism, 89(6), 2963-2972.

Source class: Primary research

Used in this series for: One-day human fructose-versus-glucose leptin ghrelin and insulin response

Boundary: Twelve normal-weight women completed two one-day isocaloric high-fructose-versus-high-glucose feeding conditions; fructose lowered insulin and leptin responses attenuated meal-related ghrelin suppression and raised triglycerides; extreme thirty-percent-energy monosaccharide exposure one-day duration female-only sample and lack of KHK measurement limit translation

Canonical record: S-P005-026

Source link: Open source record

[HORM-P2017] AgRP to Kiss1 neuron signaling links nutritional state and fertility

Stephanie L Padilla, Jian Qiu, Casey C Nestor, Chunguang Zhang, Arik W Smith, Benjamin B Whiddon, et al. (2017). *AgRP to Kiss1 neuron signaling links nutritional state and fertility*. Proceedings of the National Academy of Sciences of the United States of America, 114(9), 2413-2418.

Source class: Primary research

Used in this series for: AgRP-to-Kiss1 nutritional-state and fertility circuit in female mice

Boundary: AgRP neurons formed direct inhibitory synapses onto arcuate and AVPV Kiss1 neurons and sustained AgRP activation delayed estrous cycles and fertility in female mice; a pair-fed activated group was included because activation increased body weight but the accessible report does not provide a clean adult weight-independent mediation estimate; no fructose endogenous fructose KHK or male reproductive test

Canonical record: S141

Source link: Open source record

[HORM-B2022] Rescue of obesity-induced infertility in female mice by silencing AgRP neurons

Xueyan Bai, Lei Fu, Naiqian Jin, Xiaoyan Liu, Lili Chen, Yinghua Shan, et al. (2022). *Rescue of obesity-induced infertility in female mice by silencing AgRP neurons*. Biochemical and Biophysical Research Communications, 623, 32-38.

Source class: Primary research

Used in this series for: AgRP-neuron intervention in obesity-associated female infertility in mice

Boundary: Female mice received a sixty-percent-kilocalorie high-fat diet for ten weeks and chemogenetic AgRP-neuron inhibition restored reported sex-hormone ovulation and fecundity outcomes; a separate thirty-woman comparison found higher serum AgRP with overweight or obesity; no fructose KHK ATP Kiss1 or neuronal AgRP measurement in women and feeding or body-weight mediation of the rescue remains incompletely audited

Canonical record: S171

Source link: Open source record

[HORM-A2024] The evolutionary conserved miR-137/325 tandem mediates obesity-induced hypogonadism and metabolic comorbidities by repressing hypothalamic kisspeptin

María S Avendaño, Cecilia Perdices-Lopez, Yolanda Guerrero-Ruiz, Francisco Ruiz-Pino, Ana B Rodriguez-Sanchez, María J Sanchez-Tapia, et al. (2024). *The evolutionary conserved miR-137/325 tandem mediates obesity-induced hypogonadism and metabolic comorbidities by repressing hypothalamic kisspeptin*. Metabolism, 157, 155932.

Source class: Primary research

Used in this series for: Obesity-associated hypothalamic kisspeptin repression and rescue in male rodents

Boundary: Male rodent and cell evidence identifies miR-137/325 repression of Kiss1 and target-site-blocker rescue during continued obesogenic feeding; the model combines early overfeeding with 45-percent-fat feeding and does not test fructose KHK endogenous brain fructose females or human clinical efficacy

Canonical record: S131

Source link: Open source record

[HORM-S2013] Melatonin and diet-induced metabolic syndrome in rats: impact on the hypophysial-testicular axis

Pablo A Scacchi Bernasconi, Nancy P Cardoso, Roxana Reynoso, Pablo Scacchi, Daniel P Cardinali (2013). *Melatonin and diet-induced metabolic syndrome in rats: impact on the hypophysial-testicular axis*. Hormone Molecular Biology and Clinical Investigation, 16(2), 101-112.

Source class: Primary research

Used in this series for: Fructose-associated low testosterone with higher LH in male rats

Boundary: Rats drinking ten-percent fructose solution for ten weeks had higher LH and lower testosterone without FSH or most reproductive-organ-weight changes; the authors interpreted the pattern as compatible with primary testicular inhibition rather than central LH suppression; melatonin did not restore testosterone

Canonical record: S167

Source link: Open source record

[HORM-PMOS2026] Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process

Helena J Teede, Mahnaz Bahri Khomami, Rachel Morman, Joop S E Laven, Anju E Joham, Michael F Costello, et al. (2026). *Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process*. Lancet, 407(10545), 2329-2339.

Source class: Consensus statement

Used in this series for: Global consensus process adopting the PMOS name

Boundary: A global process involving 56 organisations iterative surveys with 14360 responses modified Delphi methods nominal group workshops and implementation analyses selected Polyendocrine Metabolic Ovarian Syndrome PMOS as the consensus new name for PCOS. The paper explicitly frames PMOS as capturing endocrine metabolic and ovarian dysfunction and describes a managed global transition. It establishes terminology and consensus rationale; it does not establish any specific fructose KHK mechanism.

Canonical record: S267

Source link: Open source record00717-8)

[HORM-S2007] Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene

David M Selva, Kevin N Hogeveen, Sheila M Innis, Geoffrey L Hammond (2007). *Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene*. Journal of Clinical Investigation, 117(12), 3979-3987.

Source class: Primary research

Used in this series for: Monosaccharide-driven hepatic lipogenesis and SHBG expression

Boundary: Human-SHBG transgenic mice and HepG2 cells support reversible carbohydrate-associated SHBG suppression through lipogenesis HNF-4alpha and promoter regulation; tiny animal groups human transgene and tumor-derived cells limit translation and the study does not isolate KHK or test humans

Canonical record: S130

Source link: Open source record

[HORM-T2012] Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome

Flavia Tosi, Carlo Negri, Fabrizia Perrone, Romolo Dorizzi, Roberto Castello, Enzo Bonora, et al. (2012). *Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome*. Journal of Clinical Endocrinology and Metabolism, 97(5), 1712-1719.

Source class: Primary research

Used in this series for: Hyperinsulinemia and stimulated ovarian steroid output in women with PCOS

Boundary: Hyperinsulinemia amplified GnRH-agonist-stimulated ovarian steroid secretion in women with PCOS; this supports a peripheral insulin-LH ovarian route but does not establish dietary fructose endogenous fructose KHK or kisspeptin causality

Canonical record: S134

Source link: Open source record

[HORM-C2024] Fructose intake from sugar-sweetened beverages is associated with a greater risk of hyperandrogenism in women: UK Biobank cohort study

Huadong Chen, Amée M Buziau, Miguel E Rentería, Pomme I H G Simons, Martijn C G J Brouwers (2024). *Fructose intake from sugar-sweetened beverages is associated with a greater risk of hyperandrogenism in women: UK Biobank cohort study*. European Journal of Endocrinology, 190(1), 104-112.

Source class: Primary research

Used in this series for: Sex-divergent androgen associations with estimated SSB fructose exposure

Boundary: UK Biobank dietary and KHK-variant analyses associate SSB fructose with lower SHBG in both sexes lower total testosterone in men and higher free testosterone plus slightly higher biochemical-hyperandrogenism risk in women; BMI may mediate most dietary association and neither component proves neuronal or endogenous-fructose causality

Canonical record: S129

Source link: Open source record

[HORM-N2025] Effects of glucose and fructose supplementation on serum sex hormone-binding globulin and testosterone levels: Post-hoc analysis of a double-blind randomized controlled trial

Huadong Chen, Pomme I H G Simons, Nynke Simons, Marjo P H van de Waarenburg, J A P Bons, E M C van der Ploeg, et al. (2025). *Effects of glucose and fructose supplementation on serum sex hormone-binding globulin and testosterone levels: Post-hoc analysis of a double-blind randomized controlled trial*. Clinical Nutrition ESPEN, 69, 384-388.

Source class: Primary research

Used in this series for: Six-week randomized fructose-versus-glucose sex-hormone null

Boundary: In 36 adults with BMI at least 28 and high fatty-liver index a six-week fructose-restricted diet supplemented with fructose versus glucose produced no significant differential SHBG total-testosterone or free-testosterone effect; small post-hoc mixed-sex analysis and replacement-level exposure do not address PCOS central signaling or high-dose SSB exposure

Canonical record: S159

Source link: Open source record

Interventions

[INT-PERL2020] Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes

Alessandro Doria, Andrzej T Galecki, Cathie Spino, Rodica Pop-Busui, David Z Cherney, Ildiko Lingvay, et al. (2020). *Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes*. New England Journal of Medicine, 382(26), 2493-2503.

Source class: Primary research

Used in this series for: Allopurinol kidney-outcome null despite serum-urate reduction

Boundary: In adults with type-1 diabetes and early-to-moderate diabetic kidney disease allopurinol substantially lowered serum urate but did not produce the prespecified clinically meaningful kidney-function benefit; disease-specific trial and xanthine-oxidase inhibition do not test intracellular urate signaling or KHK inhibition

Canonical record: S-P005-035

Source link: Open source record

[INT-FAST2020] Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre prospective randomised open-label non-inferiority trial

Isla S Mackenzie, Ian Ford, George Nuki, Jesper Hallas, Christopher J Hawkey, John Webster, et al. (2020). *Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre prospective randomised open-label non-inferiority trial*. Lancet, 396(10264), 1745-1757.

Source class: Primary research

Used in this series for: Febuxostat-versus-allopurinol cardiovascular safety trial

Boundary: Among older patients with gout and cardiovascular risk febuxostat was noninferior to optimized allopurinol for the primary cardiovascular endpoint; the comparator design does not show that urate lowering prevents cardiovascular disease or tests the fructose-KHK pathway

Canonical record: S-P005-036

Source link: Open source record32234-0)

[INT-L2017] Protective role of fructokinase blockade in the pathogenesis of acute kidney injury in mice

Ana Andres-Hernando, Nanxing Li, Christina Cicerchi, Shinichiro Inaba, Wei Chen, Carlos Roncal-Jimenez, et al. (2017). *Protective role of fructokinase blockade in the pathogenesis of acute kidney injury in mice*. Nature Communications, 8, 14181.

Source class: Primary research

Used in this series for: Luteolin KHK inhibition in vitro kidney-cell ATP preservation and intravenous mouse AKI results

Boundary: Luteolin inhibited fructokinase in vitro with IC50 11.2 micromolar in human proximal-tubule cells and intravenous dosing improved ischemic AKI outcomes in mice alongside global KHK-knockout protection; kidney ischemia context dosing

route off-target actions inventor conflicts and no human endocrine metabolic PCOS testosterone oral or product study prevent therapeutic extrapolation

Canonical record: S146

Source link: Open source record

[INT-M2019] Consumption of 100% Tart Cherry Juice Reduces Serum Urate in Overweight and Obese Adults

Keith R Martin, Katie M Coles (2019). *Consumption of 100% Tart Cherry Juice Reduces Serum Urate in Overweight and Obese Adults*. Current Developments in Nutrition, 3(5), nzz011.

Source class: Primary research

Used in this series for: Small controlled tart-cherry-juice urate signal

Boundary: Twenty-six overweight or obese adults completed four weeks each of 240 milliliters daily tart-cherry juice and calorie or carbohydrate-matched placebo; serum urate fell in the cherry arm while inflammatory outcomes were mostly nonsignificant trends; small industry-supported juice study does not establish extract efficacy KHK modulation gout treatment or product efficacy

Canonical record: S-P005-027

Source link: Open source record

[INT-S2020] Lack of effect of tart cherry concentrate dose on serum urate in people with gout

Lisa K Stamp, Peter Chapman, Christopher Frampton, Stephen B Duffull, Jill Drake, Yuqing Zhang, et al. (2020). *Lack of effect of tart cherry concentrate dose on serum urate in people with gout*. Rheumatology, 59(9), 2374-2380.

Source class: Primary research

Used in this series for: Randomized tart-cherry-concentrate urate null in gout

Boundary: Fifty people with gout were randomized across placebo and four twice-daily concentrate doses for twenty-eight days; no dose effect appeared for serum-urate exposure urinary urate or short-term flares; directly limits dependable urate-lowering claims while not testing standardized dry extract redox endpoints KHK or SugarShield

Canonical record: S-P005-028

Source link: Open source record

[INT-J2026] Effects of Tart Cherry Extract Supplementation on Plasma Urate and C-Reactive Protein Levels in Healthy Adults: a Randomized Controlled Trial

Ralf Jäger, Martin Purpura, Sebastian T Balcombe, Ashok Godavarthi, Suda A Reddy, Ecaterina Vasenina, et al. (2026). *Effects of Tart Cherry Extract Supplementation on Plasma Urate and C-Reactive Protein Levels in Healthy Adults: a Randomized Controlled Trial*. Journal of Dietary Supplements, 23(1), 42-57.

Source class: Primary research

Used in this series for: Very small standardized tart-cherry-extract urate and CRP signal

Boundary: Ten healthy adults completed two four-week phases of five-hundred-milligram standardized tart-cherry extract or placebo; acute measures were null while day-twenty-eight plasma urate and CRP were lower; extremely small study abstract audit and formulation specificity require replication and do not establish KHK or SugarShield efficacy

Canonical record: S-P005-029

Source link: Open source record

[INT-SS2026] SugarShield product page

LIV3 Health (2026). *SugarShield product page*. LIV3 Health.

Source class: Product information - not scientific evidence

Used in this series for: Official product composition and commercial disclosure only

Boundary: Official page states a 450-milligram proprietary liposomal blend containing 98-percent luteolin from Sophora japonica and 30-to-1 Prunus cerasus tart-cherry extract; it states SugarShield was not used in the cited studies and is not intended to diagnose treat or prevent disease; composition may change and snapshot is not efficacy evidence

Canonical record: S-P005-030

Source link: Open source record