Community notes

Guest: Dr Georgia Ede

Disclaimer 1: The literature presented here, directly (or as closely as possible) looks at statements made by the guest. In order to fully understand each topic mentioned, an extensive literature review (beyond the scope of this document) would be required.

Disclaimer 2: The information provided in this podcast and any associated materials is not intended to replace professional medical advice. For any medical concerns, it is essential to consult a qualified health professional.

Topics covered in this episode

Ketogenic diet and neuroprotection

“So it is as though you are fundamentally changing the brain's operating system in very healthy ways that allow not brain cells, not only to work better, but for but for brain cells to heal. So the longer you stay on a ketogenic diet, the more healing, the more brain healing can take place.”

The neuroprotective effects of the ketogenic diet are attributed to improved mitochondrial function (shown in patients with cerebral ischemia and neurodegenerative diseases) and decreased oxidative stress and inflammation (research using Ketone Bodies *in vitro* and *in vivo*). For a recent review, please see reference 1.

Healthy diet: animal foods

“So what is a brain healthy diet? It needs to nourish, protect and energize, nourish. It must contain and be able to safely deliver all essential nutrients to your cells. So you have to know where those nutrients are. You cannot use whole food principles and not including supplements or specially fortified processed foods, you cannot meet that goal without including some animal foods in your diet. That's just the truth of our biology.”

The nutritional adequacy of diets with or without animal products is a complex subject. Animal-derived foods offer essential nutrients like calcium, iron, zinc, and omega-3 fatty acids. However, with careful planning and supplementation, a vegetarian diet can also support good health. Plant-based diets are linked to improved metabolic health markers, such as enhanced lipid profiles, greater insulin sensitivity, and lower levels of inflammation. However, traditional plant-based diets may carry a higher risk of nutritional deficiencies, especially in vulnerable populations. The interplay between plant and animal foods in enhancing nutrient absorption suggests that a balanced approach, incorporating moderate amounts of animal products, may be advantageous for most people.

Neuroinflammation and depression

“You we the brain doesn't have nerve endings, but many, many people have brain inflammation without being aware of it. That's a main driver of depression and all kinds of other brain conditions.”

Neuroinflammation significantly contributes to the development and persistence of major depressive disorder by affecting key processes such as serotonin regulation, HPA axis function, and hippocampal neurogenesis. Emerging insights into the roles of microglial activation, neurovascular dysfunction, and molecular signaling highlight potential pathways for improved biomarkers and targeted therapies for depression.

Ketogenic diet and antioxidants

“What we really need to be told is what's causing all that oxidative stress in the first place, and remove those things, because the antioxidant strategy really doesn't work.”

An individualized, balanced diet with adequate antioxidant intake remains the best approach for maintaining optimal antioxidant status. Diets rich in fruits and vegetables, which provide a diverse mix of antioxidants working together, are generally more beneficial than supplements that typically offer only one or two isolated compounds. In fact, clinical trials have found no clear benefits from a limited selection of antioxidant supplements and suggest that excessive supplementation with certain antioxidants may even be harmful (13, 14).

Ketogenic diet and insulin and glucose

“if you have excellent metabolic health, and we can talk about what that means, then you may not need to eat a ketogenic diet to properly to really get those glucose and insulin levels under control and thoroughly energize your brain cells. But if you have significant metabolic damage, if you're sedentary, if you're older, if you have pre diabetes or type two diabetes, then you may need to reduce the amount of carbohydrate in your diet, even from Whole Foods. You may even need to go to a ketogenic level.“

Research indicates that ketogenic diets can have complex effects on glucose and insulin regulation, with long-term use of the ketogenic diet potentially impairing insulin sensitivity and glucose tolerance. While short-term benefits, like lower glucose and insulin levels, may be observed, prolonged adherence to a ketogenic diet could lead to adverse metabolic effects, though these can be reversed.

Plastics, pesticides, antibiotics and food additives

“So these are things like plastics and pesticides and antibiotics and and, and food additives and and all kinds of you know, ultra processed foods that we were never designed to handle. These are really stressful on the human body, and they do break down our defenses over time.”

<u>On plastics:</u>

Microplastics and nanoplastics can cause particle toxicity, leading to oxidative stress, inflammatory lesions, and increased uptake or translocation in biological systems.

<u>On pesticides:</u>

Pesticides are widely used chemicals that can induce oxidative stress in living organisms, leading to various health issues.

On food additives:

Some food additives have been linked to health issues like asthma, ADHD, obesity, and cancer, with children being particularly vulnerable. Nanoparticle-containing additives such as titanium dioxide and silicon dioxide may accumulate in organs, causing gastric toxicity and hepatotoxicity, with oxidative stress as a potential mechanism.

Guest's article

"You, you did a study on the ketogenic diet, got the study here, the ketogenic diet for refractory mental illness, a respect, a retrospective analysis of 31 in patients" (27)

Ketogenic diet and epilepsy

"ketogenic diet was originally created in 1921"

This initial study mentioned by the guest on the ketogenic diet on patients with epilepsy was done on three patients only, but started a trend, with 9 papers being published during the 1920s, involving more than 400 patients with epilepsy. They have shown effectiveness in treating intractable epilepsy, particularly in children, with potential benefits for infants, adolescents, and adults.

"For seizures, more than more than 50% of children had more than a 50% and adults as well. It's since been shown more than 50% response rate in children and adults, and 10 to 20% completely free of seizures following a ketogenic diet."

A meta-analysis revealed that children on the ketogenic diet are 5.6 times more likely to achieve a 50% reduction in seizures compared to control groups (34).

Ketogenic diet, inflammation, oxidative stress and insulin resistance

"The ketogenic diet reduces inflammation. It reduces oxidative stress, and it reduces insulin resistance."

On inflammation:

The ketogenic diet has demonstrated notable anti-inflammatory effects, including reductions in pain, fever, and inflammatory markers. These properties, potentially linked to ketone bodies, caloric restriction, fatty acid profiles, and gut microbiota changes, may have applications in managing epilepsy and other neurological disorders.

On oxidative stress:

The ketogenic diet appears to reduce oxidative stress and enhance antioxidant capacity by improving mitochondrial function and modulating redox homeostasis. These effects, observed in both clinical and athletic contexts, highlight the ketogenic diet's potential in managing oxidative stress, though further research is needed to explore its broader applications.

Calorie restriction and mental health

"Had I just restricted their calories, for example, that kept them on whatever diet they were on, would I have seen an improvement as well? That study has not been done to the best of my knowledge."

Calorie-restricted diets have been shown to reduce depression scores in obese individuals, with moderate effect sizes. However, the long-term impact of chronic calorie restriction on mood remains uncertain, as it may negatively affect serotonin function and leptin levels.

Lowering insulin levels

"lower your insulin levels through fasting, intermittent fasting. You can lower your insulin levels through exercise. You can lower your insulin levels through calorie restriction."

On fasting:

Fasting has complex effects on insulin levels and sensitivity. Insulin levels drop during fasting, but their relationship with insulin resistance and weight regulation varies, depending on factors like fasting duration and individual metabolic responses.

On intermittent fasting:

Intermittent fasting can lower blood glucose, insulin levels, and improve insulin resistance in some cases, though studies show mixed results. While intermittent fasting may reduce body fat, BMI,

and cholesterol levels, its long-term effects and impact on insulin sensitivity, particularly with high-fat diets, remain uncertain and require further study.

On exercise:

Exercise has been shown to lower insulin levels by reducing insulin secretion and increasing insulin clearance, benefiting insulin sensitivity in various populations.

Ketogenic diet and appetite

"I've been I had a weight issue growing up. Everyone in my family did, and I've been on lots of different diets in my life. This is the easiest one to stay on. I can't say about any other diet that I've followed for 12 years. And the reason why is this diet really stabilizes appetite hormones."

Ketogenic diets (KDs) can help reduce hunger during weight loss by lowering the hunger hormone ghrelin and increasing hormones that make you feel full, like GLP-1. Although hunger may increase at first, it usually levels off as the body adjusts to ketosis, making KDs a useful tool for controlling appetite while losing weight. Interestingly, subjective perceptions of appetite may not always align with hormonal measures in athletes following a KD.

"Keto flu"

"I've thought about it like it takes a couple of days to get into a state of ketosis, and then once you're in, and I usually get a headache on my way into ketosis, I feel a little bit bad on the way in. And then once I'm in there, it's fine. So when I have something that breaks my Keto, this is what I refer to my girlfriend, or whatever, I've broken my Keto, whatever, I think, Oh, my God, I've got to go through another headache and another five days of, you know, getting back into it."

There is something called "keto flu", and common symptoms include headache, fatigue, nausea, and gastrointestinal discomfort, typically peaking in the first week and resolving within 4 weeks.

"Much of this can be prevented in a couple of different ways. One is with electrolyte supplementation. Supplementing electrolytes to keep your your salt balance even as you're transitioning. And another is by transitioning slowly onto the ketogenic diet, rather than all at once."

On supplementation:

- To mitigate "keto flu" symptoms, some individuals use exogenous ketone supplements, though their efficacy is not well-established.

- In severe cases, strict low-carbohydrate diets can cause life-threatening ketoacidosis and electrolyte disturbances, requiring aggressive treatment. Proper fluid and electrolyte

management is crucial in treating ketoacidosis, with hypotonic fluids generally preferred to avoid hypernatremia and hyperchloremia.

- While electrolyte imbalances may contribute to the symptoms of “keto flu”, they are not the sole cause. Hydration and electrolyte supplementation can delay the onset of exercise-associated muscle cramps, a potential keto flu symptom, but do not prevent them entirely.

- Supplementations studied include medium-chain triglycerides (MCTs), which effectively increased ketone levels, while exogenous ketones raised blood ketones. Beta-hydroxybutyrate supplementation may also help increase ketone levels.

More research is needed to fully understand the effects of supplementation on keto-induction symptoms.

<u>On slower transition:</u>

To mitigate the symptoms of the “keto flu”, a gradual transition to KD may be preferable to rapid initiation.

Fat

“Fat is metabolically the quietest and safest macronutrient you can eat”

Recent research has renewed interest in low-carb and ketogenic diets, showing that high fat intake doesn’t necessarily lead to obesity or chronic diseases. However, the type of fat matters—saturated and trans fats can harm health, while healthy fats like omega-3s are beneficial.

Ketogenic diet and mental health

“This is something that I came to appreciate a number of years ago, as I've been studying this is that there are many people, unfortunately or fortunately, there are many people who discover with mental health issues that they need to be in ketosis long term in order to be well.”

A study found that ketogenic diets (KDs) may improve mental well-being by increasing calmness and contentment while reducing stress, depression, and anxiety. However, KDs can be hard to stick to and may have side effects. More clinical trials are needed to confirm their effectiveness for mental health treatment.

Children and ketosis

"So for example, it's known that in children who are eating a regular diet, many of them wake up the next morning in ketosis. They're metabolically much healthier than we are as we get older, so they're much more metabolically flexible, and so now they didn't go on a ketogenic diet. They were eating a regular diet. They slept overnight, didn't eat anything. The next morning, they were in ketosis. That's not true for all children, but it's true for enough children that we know it's possible most adults."

Children are more prone to developing ketosis during fasting than adults due to their higher carbohydrate use and smaller glycogen stores. Research shows that children reach higher ketone levels on similar ketogenic diets, indicating that adults have a harder time achieving high levels of nutritional ketosis.

Diet and neurodivergent disorders

"And what they did was they placed children with ADHD, some quite severe ADHD, even hospital level ADHD, and put them on something called a few foods diet. The scientists called it an oligo antigenic diet, which just means it's kind of a low allergen diet. So they removed all of the common culprits, and they focused mostly on just a few Whole Foods and a few extras. So very specifically describing this diet, most of these diets were chicken, lamb, fruits, vegetables, and sometimes they'd throw in some apple juice and margarine because they couldn't use butter, because dairy is a common allergen, so but these were mostly Whole Foods diets, you know, poultry, red meat, fruits, vegetables, and 62 to 82% response rate to these diets"

Multiple studies have shown that 60-62% of children with ADHD respond positively to a few foods diet, experiencing significant symptom reduction (71, 72, 73).

"As of 2019 major health organizations, including the American Academy of Pediatrics and the National Institute of Health and Care Excellence, do not recommend dietary modifications as standard treatment for ADHD due to insufficient evidence. I and 14 review found elimination diets might offer minor benefits and subs in a subset of children, particularly those with food sensitivities or allergies. However, these benefits are not substantial enough to advocate for widespread dietary changes in ADHD management."

Recent research suggests that diet may influence ADHD, including new studies published after 2019 (71, 72). Healthy eating patterns might help reduce ADHD risk, while diets high in sugar and saturated fat could increase it. The "few-foods" diet, which removes specific foods, has shown promise for improving symptoms in some children. Supplements like omega-3s, zinc, and magnesium have also been studied, but results are mixed.

More research is needed before dietary changes can be firmly recommended for managing ADHD.

ADHD

“people with ADHD are much higher risk for suicidal ideation, they're at much higher risk for substance abuse. They're at much higher risk for accidents. They're at much higher risk for depression, for anxiety, these and twice the, twice the rate of divorce in people with with adults with ADHD”

Adults with ADHD face various challenges, including a higher risk of mood disorders, anxiety, and substance use (74). The condition is also linked to increased aggressive behavior, legal issues, and relationship problems (74).

“children with obesity are twice as likely to have ADHD”

The prevalence of obesity is approximately 40% higher in children with ADHD and 70% higher in adults with ADHD compared to their non-ADHD counterparts (76). Impaired executive functioning and self-regulation difficulties characteristic of ADHD may contribute to abnormal eating behaviors, potentially leading to obesity (78).

“Adults with type two diabetes are twice as likely to have ADHD”

A meta-analysis (79) revealed that individuals with ADHD have more than double the risk of developing type 2 diabetes. While the exact mechanisms underlying this association are not fully understood, psychiatric comorbidities, such as substance use disorder, depression, and anxiety, appear to play a significant role.

Insulin and other hormones

“Insulin is talking to and controlling the behavior and levels and activity of many other hormones in the blood, including stress hormones like adrenaline and cortisol, reproductive hormones like estrogen and testosterone, your blood pressure regulating hormones, your satiety hormones, the hormones that make you feel full after you eat, your hunger hormones”

<u>On cortisol:</u>

The relationship between insulin and cortisol is complex and context-dependent. Insulin can both enhance and suppress cortisol production depending on factors like the levels of ACTH (a hormone that stimulates cortisol release) and the duration of insulin exposure.

<u>On adrenaline:</u>

Insulin and adrenaline interact to regulate blood glucose. Adrenaline inhibits insulin secretion, while insulin can trigger adrenaline release, particularly during low blood sugar. This balance is crucial for countering hypoglycemia, especially in people with type 1 diabetes.

On estrogen and testosterone:

Insulin affects sex hormone levels by promoting androgen production in ovarian cells, and its imbalance can lead to conditions like hyperandrogenism and estrogen deficiency, increasing the risk of heart disease and cancer in women. Estrogen helps regulate energy and glucose metabolism, and its deficiency can contribute to insulin resistance. In men, insulin and estrogen seem to act independently on nutrient intake, with insulin reducing carbohydrate intake and estrogen lowering protein consumption.

Fiber

"if you're eating a high carbohydrate diet, fiber can soften your glucose spikes"

High-fiber diets help control blood sugar levels and improve insulin response, especially in people eating high-carb meals. Studies show that fiber can reduce blood glucose and insulin spikes, even in diabetics, sometimes lowering medication needs. The effect works by slowing carbohydrate absorption rather than increasing nutrient loss. Additionally, high-fiber diets can prevent excess fat in the blood by lowering insulin responses compared to low-fiber meals with the same carbohydrate content.

"Another thing people often say about fiber is that it sweeps your colon clean of toxins and kind of and that might otherwise build up and cause problems. But fiber, there's no evidence that fiber is sweeping anything clean, or there's never been a study that demonstrates this. It's really just a belief about what we imagine fiber as being like the broom of the intestines."

Dietary fiber supports intestinal health by influencing the composition and activity of bacterial communities, supplying energy to colonic epithelial cells, aiding in the production of intestinal mucosa, enhancing intestinal motility, and preserving the integrity of the intestinal lining.

"But the biggest myth about fiber is that it's good for digestion, because fiber, by definition, is indigestible by humans."

Dietary fiber is essential for digestive health and overall well-being. It slows down the digestion and absorption of macronutrients through various mechanisms (94). It also helps improve digestive issues like constipation, diarrhea, and irritable bowel syndrome (92). Certain types of fiber, such as guar gum and glucomannan, have shown benefits, especially for children's digestive health, though more research is needed (93). Fiber's effects depend on how it behaves in the digestive system, influencing nutrient absorption and interactions with other compounds (94). While fiber supplements can help, whole fiber-rich foods are preferred due to additional health benefits (95). However, most people consume less than half the recommended amount of fiber, emphasizing the need to eat more high-fiber foods (95).

Insulin and weight loss

“So everybody out there who's trying to lose weight, they need to know one thing, and it works. If you cannot burn fat, if your insulin levels are too high. So if you know what raises insulin, you can look you can turn that insulin knob down.”

The relationship between insulin and weight loss in humans is highly complex. Some studies indicate that insulin can actually help with weight loss. For example, insulin signaling in the brain can lower body weight by interacting with key brain centers (97, 98). Experimental studies (99) found that reducing insulin production in obese mice led to significant weight loss, particularly in belly fat. In humans, a low-insulin-response diet has been linked to greater weight loss.

Diet and stress

“Your diet can also unbalance your stress hormones”

A short-term high-fat diet can disrupt the neuroendocrine stress response, potentially making individuals more vulnerable to stressful events (102). In children, higher cortisol levels and a larger cortisol awakening response are associated with more frequent consumption of sweet foods, while a steeper diurnal cortisol decline correlates with higher consumption of sweet, fatty, and snack foods (102).

“too much cortisol can, over time, damage the brain, including the hippocampus, which is the brain's learning and memory center” (104)

Ketogenic diet and mood and anxiety disorders

“2023 systemic review examine the efficacy of low carbohydrate ketogenic diets and treating mood and anxiety disorders” (105)

“The 2024 pilot study conducted by Stanford Medicine investigated the effects of a ketogenic diet on participants with schizophrenia and bipolar, and participants reported improvements in energy, sleep, mood and quality of life, suggesting that ketogenic diet may stabilize brain functions and serious mental illnesses as well.” (106)

Ketogenic diet’s positive effects

“It's really good for your blood sugar, it's really good for your blood pressure, and you can help you lose some weight. You can do these wonderful things for you. Can lower your inflammation levels.”

On blood pressure:

A systematic review and meta-analysis found no significant impact of ketogenic diets on systolic or diastolic blood pressure (107). Interestingly, a clinical trial on women with obesity and hypertension demonstrated that a very low-calorie ketogenic diet significantly reduced both systolic and diastolic blood pressure (108).

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Ketogenic diet and neuroprotection

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Ketogenic diet, inflammation, oxidative stress and insulin resistance

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