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Independent Research & further reading

Guest: Dr Annette Bosworth

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Contents

Ketones

> *"most of the reasons people come to see me could be reversed if they knew how to make ketones on a regular basis (...)*
>
> *when you look at a ketone, it is a product of breaking down fat and using the fat as fuel."*

Ketones are organic compounds defined by a carbonyl group, that is, a carbon atom double bonded to oxygen, attached to two carbon-containing groups. This structure gives ketones characteristic chemical properties, including polarity and the ability to form hydrogen bonds with other molecules, although they do not hydrogen bond with themselves. In biological contexts, the term often refers to ketone bodies, specifically acetoacetate, 3-hydroxybutyrate, and acetone. These molecules are produced in the liver during fat metabolism when glucose availability is low, and they provide an alternative energy source for organs such as the brain and muscles during fasting, prolonged exercise, or carbohydrate restriction. Ketones also have wide-ranging applications in chemistry and pharmaceuticals, since they are stable and reactive intermediates that can be synthesised through several methods and are used in the development of drugs and other materials.

Ketone Production from Fat Breakdown

Ketones are produced when the body breaks down fat, particularly in situations where carbohydrate availability is low. During fasting, prolonged exercise, ketogenic diets, or insulin deficiency, the body increases lipolysis, which is the breakdown of stored triglycerides, that is, the body's main form of stored fat, into free fatty acids. These fatty acids are transported to the liver and converted through β-oxidation, a metabolic process that breaks fatty acids into smaller units, into acetyl-CoA, a central metabolic molecule. When acetyl-CoA exceeds the capacity of the TCA cycle, the tricarboxylic acid cycle that generates cellular energy, it is channelled into ketogenesis, which is the liver's production of ketone bodies. This process produces acetoacetate, β-hydroxybutyrate, and acetone. The resulting metabolic shift enables ketones to serve as an alternative energy source for tissues, including the brain, during periods of reduced carbohydrate intake or impaired insulin signalling.

References 1-9.

The Role of an Internist

> *“So I'm an internist. That means if you go to an internal medicine doctor and we don't know what's wrong, you're gonna die. We take care of tough puzzles, and we do this over long management, chronic disease management.”*

Internists are medical specialists who provide comprehensive care for adults, focusing on the prevention, diagnosis, and management of diseases that affect all organ systems. They play a central role in treating people with multiple or complex chronic conditions and often coordinate care across different specialities to ensure continuity and a holistic approach. Internists work in settings such as hospitals, outpatient clinics, and long-term care facilities, and their practice includes both acute care, such as managing emergencies and hospital admissions, and ongoing outpatient management. Many internists also subspecialise or combine clinical work with research or teaching. Their expertise in diagnostic reasoning and in managing patients with undifferentiated or complicated presentations makes them key members of multidisciplinary healthcare teams.

References 10-15.

Metabolic Effects of Processed Food Consumption

> *“you live in the 21st century where there's lots of processed foods and lots of ways that your body did things without telling you.”*

Consuming high amounts of processed and ultra-processed foods can disrupt metabolic processes and increase the risk of several metabolic diseases. These foods are associated with higher body weight, increased body mass index, and greater waist circumference, and they contribute to a higher prevalence of metabolic syndrome, which includes abdominal obesity, high blood pressure, dyslipidaemia (an abnormal level of lipids in the blood, such as elevated triglycerides or low HDL cholesterol), and insulin resistance (reduced responsiveness of cells to insulin).

Processed foods that are high in added sugars and unhealthy fats can raise fasting glucose, impair insulin sensitivity, lower HDL cholesterol, and increase triglyceride levels, which elevates the risk of type 2 diabetes and cardiovascular disease. Mechanistic research indicates that these foods promote chronic inflammation and oxidative stress, and can disrupt the gut microbiota, all of which further impair metabolic regulation. Their typical nutritional profile, characterised by high energy density and low fibre and micronutrient content, encourages overeating and contributes to metabolic dysfunction.

References 16-24.

Meal Timing and Metabolic Health in Older Adults

> *"when you're 54, you should probably put the calories in the morning, not at night. We know that as you age, the cost of a calorie turns into timing. If you eat that food, one bite of food after six o'clock is worth 10 bites of food before noon."*

Meal timing influences metabolic responses and energy balance in older adults. Eating a larger proportion of daily calories later in the evening is associated with a higher risk of metabolic syndrome, which is a cluster of conditions that includes abdominal obesity, high blood pressure, dyslipidaemia, and insulin resistance. Even when considering total calorie intake and physical activity, late eating is associated with elevated triglyceride levels and greater abdominal fat. Conversely, eating more calories earlier in the day correlates with a lower body mass index, improved nutrient intake, and enhanced insulin sensitivity.

Studies also show that longer eating windows, meaning periods of more than twelve hours between the first and last calorie consumed, are linked with poorer cardiometabolic profiles in older adults. These patterns may relate to age-related changes in circadian rhythms, which regulate daily metabolic cycles. Overall, earlier energy intake and shorter eating windows appear to support better metabolic health in older adults.

References 25-35.

Late-Day Eating and Insulin Regulation

> *“waited all the way till four o'clock to eat (...) This is a really common pattern of people doing what we would say intermittent or time restricted eating. They put that eating window in this, but it's got that balloon at the end of the day (..) what you're stimulating is an excessive production of insulin (...) Your insulin is still churning, especially if the meal was large and there was carbs in it (...) So now you've got these processed foods late at night and you're at the beginning of the disease, right? You're at the beginning of the chronic inflammatory [response]… ”*

Eating most of your daily calories late in the day is associated with poorer insulin sensitivity and less favourable metabolic health than consuming more calories earlier. Studies show that meals eaten in the evening or at night produce higher postprandial glucose and insulin levels, meaning greater rises in blood sugar and the hormone needed to regulate it, than identical meals consumed in the morning. These effects appear in healthy adults, overweight people, and individuals with prediabetes or type 2 diabetes.

Early time-restricted eating, which limits food intake to the morning and early afternoon, tends to improve measures such as fasting insulin and glucose more consistently than late eating windows. Eating late also disrupts circadian rhythms, the body’s internal timing system that regulates metabolic processes, which can alter hormone regulation, reduce energy expenditure, and promote fat storage. While some controlled studies suggest that total calorie reduction plays a role in metabolic improvements, the overall pattern indicates that shifting calorie intake earlier in the day supports healthier metabolic responses.

References 36-44.

Insulin Function and Metabolic Regulation

> *“insulin insulates (...) it puts the fat on. It's got some other roles too (...) and when it's in excess, it will store energy for when you go through a famine (...) it's coming out like a transporter and helping put away the sugar, or deal with the excess sugar (...) But if all the cells are full, their storage is full, it's gonna start to pack it into the liver (...)*
>
> *unfortunately, most people have been making buckets of insulin without knowing it (...) carbs (...) instead of whole foods, instead of a fat forward diet, which would then push that body into making ketones. So you can't make a ketone if you're insulin high (...)”*

The Roles of Insulin

Insulin is a central hormone that regulates metabolism by coordinating how the body handles glucose, fats, and proteins. It lowers blood glucose by promoting its uptake into muscle and adipose tissue and by reducing glucose production in the liver. In fat metabolism, insulin encourages the storage of triglycerides, which are the body’s main form of stored fat, and suppresses lipolysis (the breakdown of fat into free fatty acids). Insulin also supports protein metabolism by stimulating protein synthesis, enhancing amino acid uptake, and limiting protein breakdown, which contributes to tissue growth and repair. Its actions extend to cell growth and differentiation, and it influences brain functions such as memory, mood, and appetite regulation.

Insulin works by binding receptors on cell surfaces and activating signalling pathways that regulate metabolism and gene expression. Proper insulin function is essential for maintaining energy balance, and impaired responsiveness to insulin, known as insulin resistance, contributes to conditions such as type 2 diabetes, obesity, cardiovascular disease, and certain cancers.

Excess Insulin and Liver Fat Accumulation

Excess insulin encourages fat storage in both adipose tissue and the liver through several metabolic mechanisms. High insulin levels stimulate de novo lipogenesis, which is the conversion of carbohydrates into fat within the liver, increasing the storage of hepatic triglycerides. Insulin also suppresses lipolysis, the breakdown of stored fat in adipose tissue, leading to greater fat retention in adipocytes. When the storage capacity of adipose tissue is exceeded, surplus fatty acids are redirected to the liver. Chronic hyperinsulinaemia (persistently elevated insulin levels in the blood) increases the expression of fatty acid transporters such as CD36 in the liver, further promoting the uptake and storage of fat. These processes contribute to the accumulation of fat in non-adipose tissues, particularly the liver, and play a central role in the development of nonalcoholic fatty liver disease.

Dietary Carbohydrates and Insulin Levels

Higher dietary carbohydrate intake is associated with higher insulin levels compared with higher fat intake, particularly after eating. Studies show that carbohydrate-rich meals produce greater postprandial insulin responses, meaning larger rises in insulin following a meal, than isocaloric meals higher in fat. Both healthy individuals and those with insulin resistance or diabetes exhibit this pattern. Long-term patterns of high carbohydrate intake, especially from simple or high glycaemic index sources, are linked to higher fasting insulin and greater insulin resistance, while diets higher in unsaturated fats are associated with lower insulin resistance. The type of carbohydrate affects the magnitude of the response, with fibre-rich or low glycaemic index carbohydrates producing smaller increases in insulin.

Insulin Levels and Ketone Production

When insulin levels are high, the body can't make ketones. Insulin directly inhibits ketogenesis in the liver by acting on the enzymes involved in ketone synthesis, and it also reduces lipolysis, which is the breakdown of stored fat into free fatty acids that serve as the main substrate for ketone production. Studies in humans and animals show that raising insulin levels, whether through carbohydrate intake or insulin infusion, rapidly reduces circulating ketone concentrations, while insulin deficiency during fasting or uncontrolled diabetes increases ketone output. Insulin can also suppress ketone production independently of changes in free fatty acid levels, indicating a direct hepatic effect. This regulatory role explains why insulin therapy is essential in treating diabetic ketoacidosis, where halting excessive ketone production is critical.

References 45-67.

Health Consequences of High Insulin (Hyperinsulinemia)

> *"When you have excess insulin, which is this chronic disease maker, it is what makes cancer, it is what makes high blood pressure (...) depression, or brain fog, or Parkinson's (...) autoimmune disorder (...) PCOS (...) All of them are linked to high insulin (...)"*

Hyperinsulinaemia and Cancer Risk

High insulin levels, known as hyperinsulinaemia (persistently elevated insulin concentrations in the blood), are strongly associated with increased risk of developing and progressing various cancers. Insulin can act as a growth factor, stimulating the proliferation and survival of malignant cells, particularly those that overexpress insulin receptors such as the IR-A isoform, which is strongly linked to tumour growth. Elevated insulin also increases levels of insulin-like growth factors, including IGF-1 and IGF-2, which activate signalling pathways such as PI3K–AKT and MAPK that promote cancer development and metastasis.

In addition, high insulin reduces sex hormone-binding globulin, leading to greater availability of oestrogens and androgens that can drive hormone-sensitive cancers such as breast and endometrial cancer. Hyperinsulinaemia is further associated with systemic inflammation and metabolic disturbances that create conditions favourable to tumour growth. Research shows that this increased cancer risk is independent of obesity, and experimental studies indicate that reducing insulin levels can slow cancer initiation and progression. These findings suggest that lowering hyperinsulinaemia may be a useful strategy for cancer prevention and treatment.

Hyperinsulinaemia and Blood Pressure

Hyperinsulinaemia is strongly associated with increased blood pressure and a higher risk of developing hypertension. Elevated insulin promotes sodium retention in the kidneys, which increases plasma volume and raises blood pressure. It also stimulates the sympathetic nervous system, leading to a higher heart rate and increased vascular resistance. Insulin can influence blood vessel structure by promoting the growth of vascular smooth muscle cells and increasing arterial stiffness, both of which contribute to elevated blood pressure. Hyperinsulinaemia also activates the renin–angiotensin–aldosterone system, a hormonal system that regulates blood pressure and fluid balance. Although some studies indicate that factors such as obesity may influence the strength of this association, the overall evidence identifies hyperinsulinaemia as an independent risk factor for hypertension.

Hyperinsulinaemia and Depression

Hyperinsulinaemia is associated with a greater risk of depression, although the relationship is complex and influenced by multiple factors. Epidemiological studies show that people with higher insulin resistance or markers of hyperinsulinaemia have increased odds of experiencing depressive symptoms, including in non-obese populations. Diets and lifestyles that raise insulin levels are also linked with more severe depression and anxiety, although these findings do not establish causation. In individuals with type 2 diabetes, insulin therapy, which can lead to peripheral hyperinsulinaemia, is associated with a higher risk of depression compared with non-insulin treatments.

Mechanistic research suggests that chronic hyperinsulinaemia may contribute to inflammation, oxidative stress, and dysregulation of the hypothalamic–pituitary–adrenal axis, all of which are processes implicated in depression. The association appears bidirectional, as depression itself can worsen insulin resistance and is partly influenced by factors such as obesity, central fat distribution, and lifestyle. Somatic symptoms of depression, such as fatigue and changes in appetite, show the strongest links to insulin resistance.

Hyperinsulinaemia and Brain Fog

Hyperinsulinaemia is associated with cognitive difficulties that align with what is often described as brain fog. Studies link insulin resistance and the resulting rise in insulin levels to lower performance in areas such as memory, attention, and working memory, independent of fluctuations in blood glucose. Chronic hyperinsulinaemia can impair insulin signalling within the brain, disrupt the blood–brain barrier, and increase neuroinflammation and oxidative stress, all of which contribute to neuronal dysfunction. Biomarkers such as elevated proinsulin, which reflects impaired insulin processing, are associated with poorer cognitive scores, even in people without diabetes. Studies in humans and animal models indicate that hyperinsulinaemia and insulin resistance can hinder hippocampal function and diminish synaptic plasticity, both of which are critical for learning and memory.

Hyperinsulinaemia and Parkinson’s Disease

Hyperinsulinaemia is associated with an increased risk of developing Parkinson’s disease and with faster disease progression in those already diagnosed. Large cohort studies show that people with diabetes or prediabetes, conditions marked by hyperinsulinaemia and insulin resistance, have a higher likelihood of developing Parkinson’s Disease, and those with both conditions often experience more severe motor symptoms and greater cognitive decline. Even in individuals without diabetes, markers of insulin resistance, such as the triglyceride to HDL cholesterol ratio, where HDL refers to high-density lipoprotein cholesterol, are linked to higher Parkinson's risk.

Mechanistic research indicates that chronic hyperinsulinaemia disrupts insulin signalling in brain regions central to Parkinson's pathology, including the substantia nigra and basal ganglia. These disruptions impair dopamine regulation, reduce mitochondrial function, and increase oxidative stress, processes that contribute to neurodegeneration. Insulin resistance also promotes the abnormal aggregation of α-synuclein, a protein whose accumulation is a hallmark of Parkinson's disease, and enhances neuroinflammatory activity.

Hyperinsulinaemia and Autoimmune Disorders

Hyperinsulinaemia is closely linked to several autoimmune conditions, particularly type 1 diabetes. In type 1 diabetes, insulin itself functions as an autoantigen, meaning it is targeted by the immune system, and insulin autoantibodies often appear early in at-risk individuals. Genetic variations in the insulin gene and in the HLA region increase susceptibility to both insulin autoimmunity and type 1 diabetes, indicating a genetic basis for the association. Hyperinsulinaemia also appears in other autoimmune diseases. In rheumatoid arthritis, higher insulin levels are more common than in the general population and may influence immune activity by promoting T cell senescence and lowering the production of pro-inflammatory cytokines, although chronic inflammation may also contribute to increased insulin secretion. In myasthenia gravis, diabetes accompanied by hyperinsulinaemia can worsen disease severity by amplifying immune responses. In rare cases, insulin autoimmune syndrome develops when autoantibodies bind to insulin, causing unpredictable episodes of low blood glucose. These findings show that hyperinsulinaemia can both reflect and influence autoimmune processes, with effects that depend on the specific disease context.

Hyperinsulinaemia and Polycystic Ovary Syndrome

Hyperinsulinaemia is a central feature of Polycystic Ovary Syndrome and plays a major role in its development and severity. Most women with PCOS have insulin resistance, which leads the body to produce more insulin in an attempt to maintain normal blood glucose levels. Elevated insulin directly increases androgen production by ovarian theca cells and reduces the liver's production of sex hormone-binding globulin, resulting in higher levels of free testosterone. These hormonal changes contribute to key PCOS symptoms, including hirsutism, acne, and irregular ovulation. Hyperinsulinaemia also reinforces androgen excess, creating a cycle that worsens both metabolic and reproductive dysfunction. In addition, PCOS accompanied by high insulin levels is associated with chronic low-grade inflammation and a higher risk of type 2 diabetes, cardiovascular disease, and complications during pregnancy.

References 68-114.

Insulin Levels, Skin Tags, and Acanthosis Nigricans

> *"[with high insulin] skin gets a little thicker, they have skin tags (...) Acanthosis nigricans"*

Elevated insulin levels, known as hyperinsulinaemia, meaning persistently high insulin concentrations in the blood, are strongly associated with both skin tags and Acanthosis nigricans. In Acanthosis nigricans, high insulin stimulates the growth of keratinocytes and fibroblasts, which are skin cells involved in structure and repair, through insulin and IGF-1 receptors, producing the characteristic thickened and darkened skin.

Studies also show that people with multiple skin tags are more likely to have higher insulin levels or insulin resistance, even when factors such as body mass index or diabetes status are taken into account. The number and severity of these skin findings often increase in parallel with rising insulin levels, making them useful clinical indicators of underlying insulin resistance and increased risk of metabolic syndrome and type 2 diabetes.

References 115-124.

Toe Hair Loss and Insulin Levels

> *"And when your body has had that high insulin state for a couple of decades now, it will start to say, we don't send resources to a couple parts of the body anymore. And the follicles in their toe are one of 'em"*

Research indicates loss of hair on the toes is not directly caused by high insulin levels, although insulin resistance is associated with other forms of hair loss. Studies link insulin resistance with androgenetic alopecia on the scalp, where higher fasting insulin and measures of insulin resistance, such as HOMA-IR, are frequently observed. Hair loss on the toes or lower legs, however, is more often a sign of peripheral arterial disease, a condition involving reduced blood flow that can occur as a complication of diabetes and long-standing metabolic dysfunction. Research in people with type 2 diabetes shows that lower-limb hair loss is largely related to impaired circulation rather than insulin levels themselves.

References 125-131.

Markers of Metabolic Fuel Use and Adaptation

> *“a really good quotient for burning glucose versus burning fat, that's a sign of health. That's a really important measurement of health (...)*
>
> *When you wake up in the morning with a few ketones in your blood, that is a sign that you're not making as much trash as I'm worried about.”*

Glucose and Fat Oxidation Ratios as Indicators of Metabolic Health

The ratio of glucose oxidation to fat oxidation, often measured as the respiratory exchange ratio, can be used as an indicator of metabolic health, although its interpretation depends on context. A higher respiratory exchange ratio, meaning greater reliance on glucose for energy, is associated with impaired metabolic health, including higher fasting glucose, insulin resistance, and increased risk of metabolic syndrome and type 2 diabetes. Lower values, which reflect greater fat oxidation, are linked to improved glycaemic control and a healthier metabolic profile, particularly after lifestyle interventions in people at risk of diabetes. Longitudinal studies indicate that elevated fasting respiratory exchange ratio predicts a higher likelihood of developing metabolic syndrome or diabetes over time.

However, the measure has limitations, as some cross-sectional research shows no direct relationship between fasting substrate oxidation and metabolic disease. Metabolic flexibility, which is the capacity to switch efficiently between glucose and fat as fuel sources, is considered a more comprehensive marker of metabolic health. Factors such as diet, physical activity, genetics, and acute metabolic state can influence respiratory exchange ratio, so it is most informative when assessed alongside broader metabolic measures.

Ketones After Overnight Fasting

The presence of ketones in the blood after an overnight fast reflects a normal metabolic shift from using carbohydrates to using fat for energy. As liver glycogen, which is the body's stored form of glucose, becomes depleted overnight, the body increases lipolysis, meaning the breakdown of stored fat, and the liver produces ketone bodies such as beta-hydroxybutyrate and acetoacetate. Low or moderate ketone levels in this context indicate healthy metabolic adaptation to short-term fasting. Typical ketone concentrations in healthy adults are below 0.3 mmol per litre, while consistently higher levels may indicate a metabolic or endocrine disorder, particularly in children.

References 132-137.

The Role of Glycogen

> *"glucose, when you wanna store it, we put it in (...) glycogen, and it's just an efficient way to store glucose (...)*
>
> *it could be up to two weeks, for example, before my glycogen stores are empty, and it's not until my glycogen stores, my glucose stores are empty, that my body can start producing ketones (...) So it's gonna exhaust all of those glycogen stores and then once it's ran out, it's gonna switch into this ketogenic state (...)"*

Glycogen is a highly branched polymer made of glucose units and serves as the main form of carbohydrate storage in animals. Its structure, which includes α-1,4-glycosidic bonds linking most glucose molecules and α-1,6-glycosidic bonds at branch points, allows glucose to be released quickly when energy is required. Glycogen is stored in the form of granules within cells, together with enzymes and regulatory proteins that control its synthesis and breakdown. In the liver, glycogen helps maintain stable blood glucose levels during fasting, while in muscle it provides an immediate energy source during physical activity. Smaller amounts of glycogen are present in the brain, where it supports neuronal activity, learning, and memory and helps protect against energy shortages. Disruptions in glycogen metabolism can lead to conditions such as glycogen storage diseases, diabetes, and certain neurological disorders, underscoring the molecule's importance for metabolic health.

Glycogen Depletion and Ketosis

Ketosis does not require complete glycogen depletion, although low glycogen strongly promotes the shift into ketone production. Ketosis arises when carbohydrate availability is reduced and the body increases fatty acid oxidation to generate ketone bodies as an alternative fuel. Depleting liver glycogen, which is the body's main glucose reserve, encourages this process by reducing glucose availability and signalling the need to switch to fat-derived energy. However, research shows that ketosis can still occur when some glycogen remains.

Studies in children and animals report measurable ketone production despite apparent liver glycogen stores, and exogenous ketone supplementation can raise ketone levels even when muscle glycogen is normal. Certain metabolic disorders, such as McArdle disease, also demonstrate that ketosis can occur without typical glycogen use. Nonetheless, low or declining glycogen, as seen during fasting, prolonged exercise, or energy deficit, remains a major physiological trigger for ketosis, and marked glycogen depletion often accompanies states of accelerated ketone production such as diabetic or alcoholic ketoacidosis.

Time Required for Glycogen Depletion

Glycogen depletion varies widely depending on fasting duration, exercise intensity, and individual metabolic factors. During fasting, liver glycogen is typically depleted within 36–48 hours, while muscle glycogen declines more slowly unless physical activity is added. Intense exercise performed at more than 75 percent of maximal aerobic capacity can substantially reduce muscle glycogen within 30–60 minutes, although complete depletion may require longer or repeated bouts. An overnight fast results in notable but incomplete depletion of liver glycogen, and muscle glycogen remains largely preserved in the absence of exercise. Moderate exercise depletes glycogen more gradually over several hours. Overall, significant glycogen loss commonly occurs after 24–48 hours of fasting or 30–90 minutes of high-intensity exercise, though baseline glycogen levels, fitness, and activity patterns contribute to individual differences.

References 138-152.

Measuring Ketone Levels in Blood and Urine

> *"I think blood is the best [for measuring keto levels]. There is a way you can measure 'em in urine [using] ketone strips."*

Ketone levels can be measured in both blood and urine, although the methods differ in accuracy and clinical usefulness. Blood ketone testing measures beta-hydroxybutyrate, which is the predominant ketone in diabetic ketoacidosis, and provides real-time information about metabolic status. This method is considered more accurate and is widely used for diagnosis and monitoring.

Urine ketone testing detects acetoacetate using dipsticks and is convenient and inexpensive, but results can lag behind changes in blood ketones and are affected by factors such as hydration and kidney function. Urine tests may also remain positive after diabetic ketoacidosis has resolved because beta-hydroxybutyrate is converted back to acetoacetate during recovery. For these reasons, blood testing is generally preferred in clinical settings, while urine testing is most useful for screening or routine monitoring.

References 153-159.

Ketone Utilisation: Antioxidant Effects and Improved Mitochondrial Function

"burning ketones is an antioxidant state (...)

Ketogenic diets can boost mitochondrial function (...)"

Ketone bodies for energy can produce antioxidant effects in the body. Ketones such as beta-hydroxybutyrate and acetoacetate can directly neutralise reactive oxygen species, which are chemically reactive molecules that contribute to cellular damage. Ketone metabolism also triggers mild mitochondrial stress, known as mitohormesis, which activates protective pathways including Nrf2, sirtuins, and AMPK. These pathways increase the body's antioxidant defences and support mitochondrial function. Research indicates that ketone use enhances the activity of antioxidant enzymes and helps maintain redox homeostasis, meaning the balance between oxidants and antioxidants within cells. These effects have been observed in several tissues, including the brain and heart, where ketone usage reduces oxidative stress and supports cellular resilience.

Ketogenic Diets and Mitochondrial Function

Ketogenic diets can enhance mitochondrial function, although these effects vary across different tissues and contexts. Ketogenic diets stimulate mitochondrial biogenesis, which is the process of creating new mitochondria, and improve mitochondrial bioenergetics, meaning the efficiency with which mitochondria produce energy. These effects occur through pathways such as the PGC1α–SIRT3–UCP2 axis, a network of proteins that regulates energy metabolism. Human studies indicate that combining a ketogenic diet with exercise can increase the mitochondrial respiratory control ratio and ATP production, both markers of improved mitochondrial efficiency.

Animal studies similarly show enhanced mitochondrial enzyme activity and increased mitochondrial volume in tissues such as muscle and liver, as well as improved mitochondrial function in models of ageing and mitochondrial disease. In the brain, ketogenic diets strengthen mitochondrial defences and support neuroprotection. However, the impact is tissue-specific, and some research reports reduced mitochondrial biogenesis or impaired function in cardiac tissue with long-term or intensive ketogenic diet use. These findings suggest that while ketogenic diets can boost mitochondrial performance, their benefits depend on the tissue involved and the duration and context of use.

References 160-171.

Ketone Transport Across the Blood–Brain Barrier

> *"[ketones] penetrate through that blood-brain barrier to fuel a brain."*

Ketone bodies, including beta-hydroxybutyrate and acetoacetate, can cross the blood–brain barrier through carrier-mediated transport. This process relies mainly on monocarboxylate transporter 1, known as MCT1, a membrane protein that moves ketones into the brain when they are present in sufficient amounts in the bloodstream. The activity and expression of MCT1 increase during fasting, starvation, ketogenic diets, or low blood glucose, allowing the brain to use ketones more readily as an energy source. The transport mechanism is saturable, meaning it operates up to a maximum rate determined by transporter availability and ketone concentration. Human studies show that higher circulating ketone levels lead to greater ketone uptake into the brain, and animal and cell-model research confirms that MCT1 is essential for this process.

References 172-175.

Insulin Resistance in Pregnancy

> *"Any person who's had a baby (...) You have to be insulin resistant to hold that baby for nine months (...) When you're on a runaway train with insulin (...) the increased risk of a low birth weight (...) go up."*

Pregnancy is associated with increased insulin resistance, especially during the second and third trimesters. This change is a normal physiological adaptation that helps ensure sufficient glucose is available for the developing fetus. Insulin sensitivity typically declines by 30–70 percent compared with the non-pregnant state, largely due to the effects of placental hormones such as human placental lactogen, oestrogen, and progesterone, as well as inflammatory cytokines and broader metabolic adjustments.

Although this adaptation is expected, higher degrees of insulin resistance are linked to complications including gestational diabetes, preeclampsia, preterm birth, and fetal overgrowth. Women with higher pre-pregnancy body mass index, excessive weight gain, or genetic risk factors are more likely to experience pronounced insulin resistance, and the effect is also greater in pregnancies complicated by obesity, gestational diabetes, or type 2 diabetes.

Maternal Insulin Levels and Birth Weight

Increased maternal insulin during pregnancy is not associated with lower birth weight. Research shows that higher insulin levels or greater insulin resistance, often measured using indices such as HOMA-IR, are generally linked to higher birth weight or show no meaningful association. Some studies report an increased likelihood of large-for-gestational-age infants in women with higher insulin resistance, particularly in pregnancies affected by obesity or gestational diabetes. In cases where low birth weight does occur alongside elevated insulin resistance, the association is usually explained by factors such as preterm birth or other gestational complications rather than by insulin itself. Overall, current evidence does not support the idea that higher insulin in pregnancy results in lower birth weight.

References 176-185.

Ketogenic Diets: Physical Performance and Recovery

> *“you're deadlifting harder, and you've got a strain in those muscles. One of the key components for repairing that as quickly as possible is to be in a ketogenic state, to take that inflammation way down (...)*
>
> *we looked at this in military people (...) where they are all insulin resistant and we put 'em on a ketogenic diet. And so they're trying to meet their standards and at a month of being in a ketogenic state, they've lost weight, but their power and time didn't didn't do anything too sexy. Then you look at those same soldiers at a year, or I think it was six months, was the next time they did another big check, and by golly, they've lost even more weight, and their power is about 20% more than their counterparts. When they get to 18 months of a ketogenic diet, their power is almost 50% more than what their counterparts were.”*

Ketogenic Diets and Muscle Recovery

Evidence remains limited and mixed on whether ketosis or ketogenic diets improve muscle recovery or reduce exercise-induced inflammation. One small human study reported that a low-carbohydrate ketogenic diet reduced delayed-onset muscle soreness compared with a standard diet, although it did not lower inflammatory markers such as interleukin-6 or tumour necrosis factor-alpha, which are cytokines involved in post-exercise inflammation. Wider reviews say that ketogenic diets may help with inflammation by changing inflammatory mediators and lowering oxidative stress. However, direct evidence in athletes who do resistance or endurance exercise is not consistent. Some animal studies and mechanistic reviews indicate that ketogenic diets or exogenous ketones may support faster fatigue recovery and reduce muscle damage after strenuous exercise, yet these findings have not been robustly confirmed in human trials. Overall, current research does not provide strong support for ketosis as a strategy to enhance muscle repair or reliably reduce exercise-related inflammation.

Ketogenic Diets and Physical Performance

Ketogenic diets are not consistently associated with improved physical performance or power output compared with higher-carbohydrate or mixed diets. Research examining endurance measures such as maximal oxygen uptake, time to exhaustion, and race performance shows little evidence of improvement, and some studies report small declines, particularly in high-intensity or elite athletic settings. Findings for strength and power are similarly mixed, with most studies showing no meaningful change and some reporting reduced peak or average power during short, intense activities such as sprints.

Although ketogenic diets often lead to greater fat loss and reductions in total body mass, these changes do not reliably translate into performance benefits and may involve some loss of lean mass. Performance decrements tend to be more evident in trained athletes, while recreational athletes often show neutral outcomes. Longer adaptation periods may attenuate some negative effects, but evidence remains inconsistent. Overall, current research does not support ketogenic diets as a means of enhancing physical performance or power output, despite their usefulness for fat loss in certain sports contexts.

References 186-193.

Down Syndrome, Insulin Resistance, and Early Onset Alzheimer's Disease

> *"[people with Down syndrome] have advanced insulin resistance and advanced Alzheimer's earlier in life. So it's a great place to study Alzheimer's because they have a more rapid onset of it."*

Down Syndrome and Insulin Resistance

Down syndrome is associated with insulin resistance, particularly in the brain, although the relationship with systemic insulin resistance is more variable. Studies show that individuals with Down syndrome display early markers of brain insulin resistance, including reduced insulin receptor activity and impaired insulin signalling, even before Alzheimer's disease develops. These brain-specific alterations are observed in human tissue and in mouse models and appear independent of peripheral metabolic disorders. The picture is more complex for whole-body insulin resistance.

Adolescents with Down syndrome often show higher rates of insulin resistance, especially when obesity, female sex, or puberty is present. In adults, some studies report increased rates of obesity but do not consistently find higher insulin resistance or metabolic syndrome once age and

Sex differences are taken into account, while other reviews suggest that there is an elevated risk of metabolic syndrome and type 2 diabetes due to premature ageing, inflammation, and characteristic fat distribution patterns. Proposed mechanisms include chronic inflammation, oxidative stress, mitochondrial dysfunction, and genetic factors unique to Down syndrome. Overall, evidence indicates a clear link between Down syndrome and brain insulin resistance, with systemic insulin resistance more likely in those who are obese or older.

Down Syndrome and Early-Onset Alzheimer's Disease

Down syndrome is strongly associated with early-onset Alzheimer's disease. Nearly all adults with Down syndrome develop the characteristic pathology of Alzheimer's, including amyloid-β plaques and tau-related changes, by around age forty, and a large majority are diagnosed with dementia between the ages of forty and fifty-five. This markedly earlier onset compared with the general population is primarily due to the presence of an extra copy of chromosome 21, which carries the gene for amyloid precursor protein; its overexpression leads to early and excessive amyloid-β accumulation.

Other genes on chromosome 21, such as DYRK1A and SOD1, may further contribute to disease development through mechanisms involving tau phosphorylation, oxidative stress, and neuroinflammation. Clinical progression in Down syndrome–associated Alzheimer's resembles that of other forms of early-onset Alzheimer's disease, though with a more predictable and accelerated timeline. Early symptoms may include executive and behavioural changes before memory impairment becomes evident.

References 194-198.

Ketones and Brain Health

> *"I was looking at some of the supporting studies around this, around the impact that can have on the brain. And studies show that in dementia, especially in Alzheimer's, the brain struggles to use glucose efficiently. Ketones provide an alternative cleaner fuel source (...) and keto improves insulin sensitivity, potentially reducing this risk (...)*
>
> *if you're looking at performance (...) let's begin with the sharpest brains and the most focused, the most disciplined, the less impulsivity. All of those things improve when that brain is being fueled*

with ketones (...) Ketones may protect neurons from damage and promote the growth of new neural connections. Small studies show temporary improvements in memory and cognition in people with mild cognitive impairment or early Alzheimer's (...)"

Ketones as an Alternative Energy Source in Alzheimer's Disease

Evidence shows that people with Alzheimer's disease have reduced brain glucose utilisation, a condition known as glucose hypometabolism, which occurs when the brain takes up and uses less glucose than normal. This reduction is linked to decreased activity of glucose transporters such as GLUT1 and GLUT3, as well as impairments in glycolytic enzymes that help process glucose for energy. Imaging studies consistently show that brain areas that are affected take up less glucose. Despite this deficit, the brain's ability to use ketone bodies, specifically beta-hydroxybutyrate and acetoacetate, remains preserved. When glucose levels are limited, ketone bodies can traverse the blood-brain barrier and serve as an alternative energy source. Research indicates that increasing ketone availability through ketogenic diets, medium-chain triglyceride supplementation, or fasting can support brain energy metabolism and may offer modest cognitive benefits in Alzheimer's disease and mild cognitive impairment.

Ketogenic Diets, Insulin Sensitivity, and Alzheimer's Risk

Insulin resistance is a recognised risk factor for Alzheimer's disease. Research indicates that ketogenic diets can improve insulin sensitivity, the body's ability to respond effectively to insulin, and can support metabolic health by lowering blood glucose and reducing markers of metabolic syndrome, which is a cluster of conditions that increase the risk of cardiovascular and metabolic disease. Studies in animals and humans show that ketogenic interventions, including medium-chain triglyceride supplementation, can enhance cognitive function and improve daily living measures in people with Alzheimer's disease, while also improving cardiovascular and metabolic indicators such as glycaemic control, which refers to the regulation of blood sugar levels. Some trials suggest that these benefits may vary depending on genetic factors such as APOE4 status, and long-term effects remain uncertain. Nonetheless, current evidence supports the view that improving insulin sensitivity through ketogenic approaches may help reduce Alzheimer's risk, although definitive proof in humans is still limited.

Ketone Bodies and Cognitive Performance

Ketone bodies may improve certain aspects of cognitive performance, particularly in older adults and individuals with mild cognitive impairment or Alzheimer's disease. Studies show that ketogenic diets or medium-chain triglyceride supplementation, both of which raise circulating ketone levels, can enhance memory, executive function, and overall cognitive performance in these groups, and higher blood ketone concentrations are often linked with greater benefit. In healthy adults, acute increases in ketone levels, whether through medium-chain triglycerides or exogenous beta-hydroxybutyrate, have produced modest improvements in working memory, attention, and executive function, especially in older adults with lower baseline performance.

However, findings in broader populations are mixed, with some large studies reporting associations between higher ketone levels and poorer working memory, which suggests a more complex relationship. Proposed mechanisms include improved brain energy metabolism, reduced inflammation, and enhanced synaptic plasticity. Overall, ketone bodies appear to support cognitive function most consistently in people with impaired glucose metabolism or neurodegenerative conditions, while effects in young, healthy adults remain limited and variable.

Neuroprotective and Neurogenic Effects of Ketones

Ketone bodies, including beta-hydroxybutyrate and acetoacetate, have neuroprotective properties. They provide an alternative energy source for neurons when glucose is limited, support mitochondrial function, and reduce oxidative stress, which refers to the accumulation of harmful reactive oxygen species. Ketones also stop apoptosis, which is the planned death of cells, and help lower neuroinflammation, which is inflammation in the nervous system. These effects contribute to improved synaptic plasticity and have been demonstrated in models of neurological conditions such as Alzheimer's disease, Parkinson's disease, epilepsy, and traumatic brain injury.

Research further indicates that ketogenic diets and ketone bodies can upregulate brain-derived neurotrophic factor, a molecule that supports the growth and survival of neurons, and may promote neurogenesis in the hippocampus, which is the formation of new neurons in a key brain region involved in memory. While human evidence remains limited, preclinical studies consistently show that ketones can support both neuroprotection and processes associated with neurogenesis.

References 199-217.

The Dawn Phenomenon: Early-morning Rise in Blood Sugar

> *“you make glucose first thing in the morning. How much glucose? Depends on how insulin resistant you are (...) Glucose has been stored for this purpose. It's gonna wake you up.”*

The dawn phenomenon is a natural early morning rise in blood glucose that occurs between roughly 4 a.m. and 8 a.m. It happens in both healthy individuals and people with diabetes, but it is much more pronounced in diabetes. The rise in blood sugar is caused by higher levels of hormones overnight, like growth hormone, cortisol, and catecholamines, which make the body less responsive to insulin and cause the liver to release more glucose. In people without diabetes, the pancreas responds by secreting additional insulin to counterbalance this glucose rise. In those with type 1 or type 2 diabetes, limited insulin production or impaired insulin responsiveness means the early morning glucose increase is not adequately controlled. The dawn phenomenon can worsen fasting and post-breakfast blood glucose levels and has been shown to contribute to higher long-term glycaemic measures such as HbA1c. Management approaches typically involve adjusting insulin timing or type, using insulin pumps, or adding medications that help reduce early morning glucose excursions.

References 218-222.

Low-Carbohydrate Diets and Menstrual Cycle Regularity

> *“women in my life that they've told me that their menstrual cycles become more synced up when they are in a lower carbohydrate diet”*

Low-carbohydrate diets can affect menstrual cycle regularity, but the direction of the effect depends on the population and context. In women with polycystic ovary syndrome, these diets often improve menstrual function. Clinical trials and systematic reviews show that low-carbohydrate and ketogenic diets can restore regular cycles, support ovulation, and improve hormonal balance, in some cases leading to the return of regular menstruation in all participants after several months. These improvements are attributed to increased insulin sensitivity and reductions in androgen levels, both central features of PCOS.

Outside of PCOS, the evidence is less consistent. Very low-carbohydrate or energy-restricted diets can disrupt menstrual cycles, causing irregular periods or amenorrhoea, particularly when accompanied by significant weight loss, low body fat, or high levels of physical or psychological stress. Some survey data indicate elevated rates of endocrine symptoms in women adhering to low-carbohydrate diets, although these results are likely affected by the diet's severity and quality. Overall, low-carbohydrate diets tend to benefit menstrual regularity in PCOS, while extreme or poorly balanced carbohydrate restriction may have the opposite effect in women without underlying metabolic disturbances.

References 223-229.

Exogenous Ketone Supplementation

> *“I really push my patients to have ketones around (...) exogenous ketones”*

Exogenous ketones are supplements designed to raise blood ketone levels without requiring fasting or a ketogenic diet. They typically contain beta-hydroxybutyrate or acetoacetate, which are the main ketone bodies used by the body for energy. These supplements are available in several forms, including ketone salts, ketone esters, and ketogenic compounds such as medium-chain triglycerides or 1,3-butanediol. Once consumed, they are absorbed and metabolised, producing a temporary rise in circulating ketone levels and creating a state sometimes referred to as nutritional ketosis. The elevated ketones can serve as an alternative fuel for the brain, heart, and muscles, particularly when glucose availability is low.

Exogenous ketones may also influence inflammation, oxidative stress, and gene expression, and in some cases can lower blood glucose. They are being investigated for potential applications in athletic performance, metabolic and neurological conditions, and as adjunctive therapies in disorders such as epilepsy or diabetes. Although generally well-tolerated, their long-term safety and optimal dosing remain areas for further research.

References 230-235.

Sardines: Nutrition, Microbiome Effects, and Metabolic Health

> *“she eats sardines for a hundred days (...) she has the best gut microbiome (...)*
>
> *Fiber is for farting. We haven't been fiber eaters forever. And when you look at many of my carnivore patients (...) their symptoms of irritable bowel, of chronic diarrhoea, of bloody ulcers reverse. Why? Because that gut biome got a lot stronger and a lot healthier (...)*
>
> *[eating only sardines] you still get a vitamin C (...) magnesium (...) lots of that (...) magnesium I still think is one supplement we all need (...) I think the whole world's low on magnesium (...) our food is low on it (...)*
>
> *how well you use sodium is dependent on how well you've eaten in the last week. So when you increase the sodium, those receptors get better. When you decrease the sodium those receptors showed down (...)*
>
> *mercury and the other sort of metals (...) little fish, little problems (...) we tested that for her too. A hundred days no problem (...)*
>
> *[If] I'm eating sardines, four or five cans a week, I probably don't need vitamin D.”*

Dr. Anette’s patient completed the “100-sardine-a-day” diet under medical supervision with regular monitoring of all health parameters. Any prolonged, unusual, or single-food diet should only be done under the guidance of a qualified healthcare professional.

Sardine Consumption and the Gut Microbiome

Eating sardines may offer modest benefits for the gut microbiome, although effects vary by individual and dietary context. Clinical trials show that sardine intake does not substantially increase overall microbiota diversity, but it can shift the balance of specific bacterial groups. An eight-week study reported a reduction in Bacteroidetes, a change that may be favourable in situations where this group is elevated, while leaving genus-level diversity and inflammatory markers unchanged. In people with type 2 diabetes, a six-month sardine-enriched diet altered the composition of the gut microbiota by lowering the Firmicutes to Bacteroidetes ratio and increasing Bacteroides–Prevotella, shifts often associated with improved metabolic profiles.

Broader observational research indicates that diets containing oily fish such as sardines are linked to higher levels of short-chain fatty acid-producing bacteria, including Roseburia and Faecalibacterium prausnitzii, which contribute to anti-inflammatory activity in the gut. Omega-3 fatty acids appear to be a key contributor to these effects. Overall, sardine consumption can modestly support a healthier gut microbiome, though findings are not uniform and further long-term studies are needed.

Dietary Fibre and Gut Health

Dietary fibre is essential for gut health and maintains a healthy gut microbiome. Fibre provides the main energy source for many beneficial intestinal bacteria, particularly those that produce short-chain fatty acids such as butyrate, which help to maintain the gut barrier, regulate immune function, and reduce inflammation. Soluble fibres are readily fermented and support the growth of bacteria such as Bifidobacterium and Lactobacillus, while insoluble fibres contribute to stools' bulk and transit. Human studies and meta-analyses consistently show that increasing fibre intake enhances microbial diversity and boosts short-chain fatty acid production, even if the increase is modest.

In contrast, low-fibre or fibre-free diets lead to reduced microbial diversity, greater gut permeability, and a higher risk of dysbiosis and chronic conditions, including obesity, diabetes, and inflammatory bowel disease. Research also suggests that deprivation of fibre can quickly trigger negative effects that may not fully reverse with later reintroduction. Overall, adequate dietary fibre is a key factor in supporting a resilient, diverse, and metabolically healthy gut microbiome.

Carnivore Diets and Gut Microbiome Health

Carnivore diets, which exclude dietary fibre, produce rapid and marked changes in gut microbiome composition. Research shows that diets based entirely on animal products increase bile-tolerant bacteria such as *Alistipes*, *Bilophila*, and *Bacteroides*, while reducing fibre-metabolising species including *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*. These bacteria are key producers of short-chain fatty acids, particularly butyrate, which is important for maintaining gut barrier integrity and regulating inflammation. A reduction in short-chain fatty acid-producing microbes is generally associated with lower microbial diversity and poorer gut health.

Some evidence also links high animal-fat diets to increased levels of *Bilophila wadsworthia*, a bacterium implicated in inflammatory bowel disease, suggesting potential for increased gut inflammation. Although one case study reported no major loss of microbial diversity in a long-term carnivore dieter, such findings cannot be generalised. Broader research on low-fibre, animal-based diets shows associations with increased gut permeability, reduced anti-inflammatory metabolites, and elevated risk of gastrointestinal and metabolic disorders. Direct evidence on gastrointestinal symptoms in strict carnivore-diet users is limited, but the reduction in beneficial bacteria and short-chain fatty acid production indicates possible negative consequences for long-term gut health.

Vitamin C and Magnesium Content in Sardines

Sardines are a meaningful source of magnesium but contain little to no vitamin C.

Nutrient analyses consistently show that sardines provide substantial amounts of magnesium, typically between 30 and 67 milligrams per 100 grams depending on species and preparation. Magnesium levels are highest when the whole fish is consumed, including bones and skin.

By contrast, sardines do not supply vitamin C in nutritionally relevant amounts. Standard compositional studies list vitamins such as B12, D, A, and folate, but vitamin C is either absent or present only in trace quantities. This reflects the general pattern that most animal-based foods, including fish, are not significant sources of vitamin C.

Prevalence of Magnesium Deficiency

Magnesium deficiency is widespread globally, with studies estimating that 30 to 50 percent of adults do not meet recommended magnesium intake levels. Surveys from North America, Europe, Asia, and South America show similarly high rates of inadequate intake, often exceeding 40 percent and, in some regions, rising above 60 percent. Subclinical magnesium deficiency, which may not be detected by standard blood tests, is also common and is estimated to affect 10 to 30 percent of the population. Deficiency is particularly prevalent among pregnant women, older adults, and individuals with chronic conditions such as type 2 diabetes, cardiovascular disease, or post-stroke complications. Factors contributing to widespread deficiency include low intake of magnesium-rich foods, nutrient losses from food processing, reduced soil mineral content, and increased physiological needs or losses associated with illness and medication use.

Dietary Sodium Intake and Sodium Handling

Research suggests that sodium handling is strongly influenced by recent sodium intake, although longer-term patterns and individual characteristics also play a role. Dietary sodium intake has a direct influence on the body’s sodium handling systems, including the regulation of sodium transporters and receptors involved in maintaining fluid and electrolyte balance. Research shows that changes in sodium intake alter the activity of key renal sodium transporters, such as the sodium–chloride cotransporter (NCC) and the epithelial sodium channel (ENaC), which adjust the amount of sodium reabsorbed by the kidneys. Higher sodium intake generally reduces the activity of these transporters to promote sodium excretion, while low sodium intake enhances their function to increase reabsorption. Sodium intake also affects receptor systems that regulate sodium balance: for example, high dietary sodium can suppress adenosine A1 receptors in the kidney, which facilitates natriuresis (increased excretion of sodium in the urine), while low sodium increases their activity.

Short-term changes in diet produce rapid physiological adjustments, with controlled studies showing that urinary sodium excretion, muscle sodium content, and sweat sodium concentration increase within days of higher intake and decrease when intake is restricted. The kidneys respond by adjusting glomerular filtration rate and fractional sodium excretion to align with recent consumption, a pattern observed in both healthy individuals and those with hypertension. Blood pressure also shifts in a roughly linear manner with changes in sodium intake over the course of weeks, with greater effects in people who have higher baseline intake or salt sensitivity. Although recent intake is the primary driver, habitual sodium consumption can influence the speed and scale of these adaptations, and factors including genetics, obesity, sex, and chronic health conditions such as chronic kidney disease or hypertension further modify how the body regulates sodium.

Mercury Levels in Sardines

Research indicates that mercury concentrations in sardines are generally low and fall well below international safety limits, although notable regional differences exist. Most studies report average mercury levels between 0.04 and 0.19 mg per kg in sardines from the Mediterranean, Atlantic, and Brazilian markets, reflecting the lower bioaccumulation typical of small pelagic fish. However, higher concentrations have been documented in certain regions with greater environmental contamination, including reports of levels approaching 0.94 mg per kg in salted sardines from parts of Indonesia and Egypt. Some samples from Egypt have shown undetectable mercury, illustrating the variability linked to local pollution control.

Health risk assessments consistently find that sardine consumption poses a low risk for most populations, with estimated intakes and hazard quotients below established safety thresholds. Nevertheless, in areas where mercury levels exceed permissible limits, monitoring and adherence to local advisories are recommended. Variation in mercury content can arise from fish size, age, seasonal factors, and regional pollution, and common processing methods such as salting, canning, or grilling do not substantially reduce mercury levels.

Vitamin D Content in Sardines

Research shows that sardines are a rich natural source of vitamin D, although levels vary with processing method, season, and region. Fresh sardines usually have between 3.8 and 9.1 microgrammes of vitamin D3 per 100 grammes. In the winter and fall, the levels are usually higher. Some studies say that the numbers are even higher when they are based on dry weight. Dried sardines provide particularly high amounts, with around 48.9 micrograms per 100 grams, meaning that a 30-gram serving can supply more than three times the recommended daily allowance. Canned sardines also contribute substantially to dietary vitamin D, with concentrations ranging from 3.3 to 10.8 micrograms per 100 grams in oil and 6.8 to 9.2 micrograms per 100 grams in tomato paste or soy oil. Cooking influences vitamin D retention; oven-cooked and grilled preparations maintain most of their vitamin D content, while frying can reduce levels by up to one-third. Regular consumption of dried or canned sardines can meet or exceed daily vitamin D requirements for many adults, offering an important dietary source of this nutrient, particularly in regions with low sunlight exposure.

References 236-267.

How Vitamin D Regulates Cellular Function

> *"[vitamin D] it's a hormone, right? A hormone that goes and talks to every one of the cells in your body and it tells that cell to be its best version of itself. That hormone goes to the nucleus and it makes that skin cell do something different. It makes your brain cell do something different. It makes your heart cell do something different. You read all the benefits about vitamin D and you think it does everything. Like how can it do all of these things? And the reason why is it is not just a vitamin, it's a hormone that changes how the cell functions. Unfortunately, it's made of fat. So if you have high insulin, it gets stuck parked in your fat cells and it didn't get to the cell."*

Research indicates that vitamin D's active form functions as a hormone that directly alters gene expression and cellular behaviour across many tissues. The active form, 1,25-dihydroxyvitamin D3, binds to the vitamin D receptor, which is a nuclear transcription factor, meaning it is a protein in the cell nucleus that regulates how genes are switched on or off. Once activated, this receptor forms a complex with another regulatory protein, the retinoid X receptor, and attaches to specific DNA sequences known as vitamin D response elements. This allows vitamin D to modulate the transcription of hundreds of genes through processes such as chromatin remodelling, which alters how tightly DNA is packaged, and the recruitment of co-regulatory proteins that help control gene activation or repression.

The vitamin D receptor is found in many tissues, including the intestine, kidney, bone, immune system, skin, muscle, cardiovascular system, and brain, and the specific genes affected vary by cell type due to differences in epigenetic regulation. Most of vitamin D’s effects operate through these genomic pathways, although some rapid, non-genomic actions also occur via membrane-associated mechanisms. Overall, vitamin D acts as a steroid hormone that influences cellular activity in multiple organ systems.

Effects of Hyperinsulinaemia on Vitamin D Availability

Research indicates that hyperinsulinaemia, which refers to chronically elevated insulin levels, can reduce circulating vitamin D by increasing its sequestration in adipose tissue and lowering its bioavailability to target cells. Higher insulin levels promote adipogenesis, increasing the storage of lipophilic, or fat-soluble, vitamin D within adipocytes. This effect is especially pronounced in obesity and insulin-resistant states, where adipose tissue functions as a reservoir that traps vitamin D and contributes to lower serum 25-hydroxyvitamin D concentrations.

Insulin resistance also impairs catecholamine-induced lipolysis, the process by which stored fats are broken down, thereby reducing the release of vitamin D from adipose tissue into the bloodstream. In addition, hyperinsulinaemia appears to diminish the activity of enzymes involved in converting vitamin D into its active form, such as CYP27B1, and may contribute to magnesium deficiency, which further interferes with vitamin D activation and transport. These mechanisms collectively lead to lower circulating and bioavailable vitamin D, limiting its ability to reach target tissues. Clinical studies consistently show reduced vitamin D status in individuals with hyperinsulinaemia, obesity, or type 2 diabetes, supporting this mechanistic relationship.

References 268-274.

Methylene Blue

> *“[methylene blue] is a die, but it's also a bridge for how to help mitochondria move fuel along (...) it actually was used for malaria treatment or anti malaria for soldiers (...) it's supposed to supercharge your brain.”*

Methylene blue (MB) is a redox-active compound that can enter mitochondria and participate in electron transport. MB can accept electrons from NADH and donate them directly to cytochrome c, effectively bypassing damaged or inhibited complexes I and III of the electron transport chain. This alternative pathway can help maintain ATP production and mitochondrial membrane potential when the normal electron flow is compromised, such as in neurodegenerative diseases or toxin exposure. MB also stimulates substrate-level phosphorylation, providing ATP even when oxidative phosphorylation is impaired. Additionally, MB can increase mitochondrial biogenesis and reduce oxidative stress by modulating redox signalling and antioxidant gene expression.

Methylene blue (MB) was the first synthetic antimalarial drug, used widely in the late 19th and early 20th centuries. With the rise of drug-resistant malaria and the need for new treatment strategies, MB has regained attention for its potent antimalarial and transmission-blocking properties, especially as a partner in combination therapies.

Methylene Blue and the Brain: Neuroprotective Mechanisms and Therapeutic Potential

Low-dose MB has demonstrated robust neuroprotective effects in animal models of stroke, traumatic brain injury, Alzheimer’s, and Parkinson’s diseases, as well as in models of anaesthesia-induced cognitive impairment. It preserves blood-brain barrier integrity, reduces neuronal apoptosis, and improves learning and memory performance. In humans, MB has been shown to enhance memory retrieval and modulate functional brain connectivity, supporting its cognitive benefits.

MB reduces amyloid-beta and tau pathology, improves mitochondrial function, and decreases neuroinflammation in Alzheimer’s disease models. Clinical and preclinical studies report improved cognitive outcomes and reduced neurodegeneration, with novel delivery methods (e.g., intranasal hydrogels, exosome carriers) enhancing brain targeting.

References 275-296.

Creatine and Jet Lag

> *"what [creatine] does for brain function, especially if there's any ADHD (...) it's got other great findings (...)*
>
> *There's really good studies on [creatine use for jet lag]. Like your reset of sleep is going to be augmented if you take like 20 grams of it after the flight,"*

Interest in the relationship between creatine and ADHD has grown due to creatine's role in brain energy metabolism and its potential cognitive benefits. While creatine supplementation is well-studied for muscle health and some cognitive domains, direct research on its effects in ADHD populations is limited. Animal studies show that deleting the creatine transporter gene in dopaminergic neurons leads to persistent hyperactivity, suggesting a mechanistic link between brain creatine deficits and ADHD-like behaviours. Adults with ADHD have been found to have lower creatine concentrations in the basal ganglia and prefrontal cortex, regions implicated in attention and executive function. Lower creatine in these areas is associated with more severe inattention symptoms.

No studies directly examine creatine as a preventive measure for jet lag. However, since jet lag involves sleep disruption and cognitive fatigue, creatine's benefits in sleep-deprived states may be relevant. The evidence suggests creatine could help travellers maintain cognitive performance and reduce mental fatigue, but it does not address circadian rhythm adjustments or sleep quality, which are central to jet lag.

Creatine supplementation during sleep deprivation helps maintain brain energy homeostasis by increasing phosphocreatine and balancing ATP consumption, particularly in brain regions most affected by sleep loss. It also appears to reduce hemispheric metabolic imbalances induced by sleep deprivation.

While several studies support cognitive benefits of acute high-dose creatine during sleep deprivation, effects are most pronounced for tasks requiring executive function or repeated effort.

Some reviews note mixed results for other cognitive domains and call for more research on optimal dosing and long-term safety.

References 297-306.

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