Insulin

The **pancreas** is responsible for regulating blood sugar. It secretes the hormone **insulin** from its' **beta cells** to regulate blood sugar levels after the consumption of food by inhibiting **glucose** production in the liver and increasing glucose uptake, triggering signalling pathways to stimulate cells, such as muscle and fat cells, to absorb glucose. Glucose is shuttled into cells via **GLUT transporters**. Some GLUT transporters are independent of insulin, but GLUT4, the main glucose transporter for skeletal muscle cells, is insulin dependant. Skeletal muscle acts as a sponge for glucose, storing most of the body's **glycogen** reserves.

Insulin sensitivity versus resistance

Insulin sensitivity refers to the amount of insulin the body needs to produce for the cells to be stimulated and absorb a certain amount of glucose. You are insulin sensitive if a small quantity of insulin results in a specific level of glucose uptake but **insulin resistant** (IR) if you require more insulin to absorb the same amount of glucose. Insulin sensitivity can be impaired or reduced by **inflammation** in the liver or body.

IR may be increased with reductions in the ratios of lean mass (muscle): fat, nutritional status, alterations in gut microbiota, physical inactivity, and impairment of insulin secretion by the beta cells in the pancreas, or reduction of **binding insulin receptor sites** and **post receptor defects** seen in aging.

SUMMARY

Insulin is a hormone that regulates blood sugar. Skeletal muscle is the main storage site of glycogen in the body. Insulin sensitivity is beneficial to your health. IR is when your body stops responding as well to insulin and may be harmful to your health.

Related health conditions

The decline in effectiveness of insulin seen with increasing IR is termed **metabolic syndrome**. The condition is concurrent with an increased risk of **cardiovascular disease** (heart disease), **hypertension** (blood pressure), decreased fasting **HDL** (good) **cholesterol** and increased blood **triglycerides**, **pre-diabetes,** and **type 2 diabetes** (elevated blood sugar), decreased **total testosterone** and **erectile dysfunction**.

Many other health conditions have been linked to IR, such as **polycystic ovary syndrome** (PCOS), **non-alcoholic fatty liver disease** (NAFLD), **Alzheimer's** disease, **cognitive decline,** and aging.

SUMMARY

Insulin resistance can lead to higher insulin and blood sugar levels and may result in metabolic syndrome, low HDL (good) cholesterol, high blood triglycerides, and type 2 diabetes. Possible factors causing insulin resistance are overeating and high sugar intake, increased body fat, inflammation, inactivity, and genetics.

GDAs: Traditional use

Glucose disposal aids (GDAs) are substances that aim to effectively lower blood glucose by decreasing liver glucose production and increasing glucose absorption into skeletal muscle cells rather than fat cells, where glucose can fuel recovery and muscle growth. They have commonly been

used during bulking or gaining phases, or following a carbohydrate dense meal, enabling the calorie surplus to aid muscle growth whilst minimising fat gain, or during a fat loss phase when carbohydrate is lower, ensuring the maximum amount of glycogen is stored in muscle tissue. It can reduce fasting blood glucose and glycated haemoglobin (HbA1c).

It could be argued the ultimate GDA is **metformin**, a synthetic compound on the **WHO**'s (World Health Organisation) list of essential medicines, commonly prescribed in the treatment of type 2 diabetes. Metformin activates **AMPK** (adenosine monophosphate-activated protein kinase), an enzyme that works as an intracellular fuel gauge. It enhances muscle insulin sensitivity, signalling the need for the muscle to absorb glucose from the bloodstream whilst preventing liver glucose production, cholesterol and triglyceride synthesis and fat breakdown.

GDA supplements are formulated from a combination of ingredients which act in a similar way to metformin, activating AMPK. Some ingredients aim to slow digestion and delay gastric emptying, reducing the rate glucose enters the blood. Others are included to reduce chronic low-grade inflammation caused by **oxidative stress**, supporting insulin sensitivity.

GDAs may increase muscle pump during training. They aim to improve body composition over time and aid performance.

SUMMARY

GDAs are supplements formulated from several ingredients which lower blood glucose by increasing muscle glucose absorption following a high carbohydrate meal. They enable glucose to fuel recovery and muscle growth whilst minimising fat gain. GDAs aim to improve body composition over time and aid muscle pump and performance.

GlycoMax: An effectively dosed GDA

A simple 5 ingredient panel with every ingredient at or above the clinically studied dosage. The 300 capsules included will provide 60 servings when split into 5 capsules a day.

How should I use it?
Take 1-2 capsules 5-10 minutes before a carbohydrate containing meal. Build up to a level which suits your individual tolerance and needs. A full clinically dosed serving is 5 capsules a day.

GDA's activate AMPK which may reduce muscle protein synthesis, should I take GlycoMax post workout?
The stimulus of working out will effectively activate GLUT4 transporters and mTor pathway involved in muscle protein synthesis. You should not need to take GlycoMax after your workout!

Berberine HCL 1000 mg

Berberine is a yellow-coloured alkaloid, a natural compound found in the bark, twigs, leaves, stems, and roots of various plants such as barberry, goldenseal, Oregon grape, phellodendron (cork tree) and tree turmeric and has a long history of use in traditional Chinese and **Ayurvedic medicine**. The blood sugar lowering effects were noted when it was used to treat diarrhoea in diabetic patients in China.

Berberine activates AMPK in a similar way to metformin and has been shown to be comparably effective at reducing blood sugar in people with type 2 diabetes. However, unlike metformin, berberine does not appear to lower **insulin-like growth factor 1** (**IGF-1**), an **anabolic** hormone related to **growth hormone** (**GH**) which acts in regulating activities such as **cell proliferation**,

differentiation, and **apoptosis**. Altered levels of serum IGF-1 have been linked with diabetes, cardiovascular disease and cancers and the role of IGF-1 has been demonstrated in longevity and aging. Balance in the level of IGF-1 is important for optimum health.

Berberine may improve body fat levels, HDL cholesterol and lower blood triglycerides in people with metabolic syndrome. Remember, insulin is a fat regulating hormone too. Berberine hydrochloride (HCL) is a popular form of berberine used in. The dose 1000 mg a day should be spread across the day, ideally with meals to aid absorption and thus reduce potential gastric symptoms of flatulence or diarrhoea.

DOI: 10.1016/j.metabol.2008.01.013.
10.1016/j.phrs.2019.104588.

Bitter Melon Extract 500 mg

Bitter melon is a sharp flavoured fruit in the gourd family closely related to courgette, cucumber, squash, and pumpkin. It is low in **carbohydrate** and high in vitamins C, A, and folate. It contains many antioxidants too. Bitter melon has been used in traditional medicine to lower blood sugar and treat the symptoms of metabolic syndrome and diabetes.

Bitter melon is thought to better insulin secretion, decrease glucose absorption during digestion, and increases uptake of glucose in muscle and target cells. Clinical trials have shown improvements in several markers of long-term blood glucose control in people with diabetes.

DOI: 10.2174/1573399809666131126152044.

Cinnulin PF® ((Cinnamon bark extract (Cinnamomum burmanni)) 500 mg

Cinnulin PF® is a water-soluble extract of the spice cinnamon which is made from grinding the dried inner bark of Cinnamomum trees. The compound cinnamaldehyde is found in the oily part and is what gives cinnamon its distinctive smell and taste. It is this compound that gives Cinnulin PF® its' high antioxidant and associated anti-inflammatory properties.

Cinnulin PF® is thought to improve insulin sensitivity, decrease glucose absorption during digestion, and increase uptake of glucose in muscle and target cells and has been shown to reduce fasting blood sugar levels, a potent anti-diabetic effect seen with improvements in blood glucose control in people with diabetes. Supplementation with 500 mg/day of Cinnulin PF® for 12-weeks was shown to have significant improvements in certain features of metabolic syndrome; fasting blood sugar, **systolic blood pressure**, and body composition.

DOI: 10.1186/1550-2783-3-2-45.
10.1080/10408398.2021.1896473

Alpha Lipoic Acid (ALA) 300 mg

ALA (alpha lipoic acid) in this case should not be confused with alpha linolenic acid also commonly abbreviated ALA.

Alpha Lipoic Acid (ALA) is beneficial in blood sugar control, weight management and is a potent antioxidant. ALA activates AMPK in a similar way to metformin and may improve body fat levels, HDL cholesterol and lower blood triglycerides in people with metabolic syndrome by improving insulin sensitivity and muscle blood glucose absorption. ALA may regulate oxidative stress and reduce low grade inflammation by inhibiting the release of **proinflammatory cytokines.**

ALA may activate SIRT1 by and restore AKT/mTOR/S6K in stimulated skeletal muscle cells. mTOR and SIRT1 pathways increase health-spans and are fundamental in protein synthesis, growth, differentiation, and survival in skeletal muscle in old age. In this way, the possible suppression of protein synthesis by activation of the AMPK pathway may be attenuated.

DOI: 10.1186/s12986-018-0302-y.

Chromium Picolinate 250 mg

Chromium Picolinate is a trivalent form of chromium, considered an essential mineral, as it needs to be obtained **exogenously** from foods. Dietary chromium is poorly absorbed, and many people are deficient.

Evidence suggests chromium enhances AMPK activity and amplifies insulin signalling at the insulin binding sites, stimulating blood glucose transport by increasing the number of GLUT4 transporters. These combined actions lead to increased blood glucose absorption in skeletal muscle cells. People with prediabetes and type 2 diabetes have lower levels of chromium in their blood compared with people without the conditions. Chromium may reduce insulin resistance in metabolic syndrome, particularly in overweight individuals.

Chromium may regulate oxidative stress and reduce low grade inflammation by inhibiting the release of proinflammatory cytokines during **hyperglycaemic** (high blood sugar) conditions.

Chromium picolinate has been shown to improve blood glucose control in people with diabetes and improve blood lipid status. It is the most efficacious form of chromium supplementation.

DOI: 10.1016/j.jnutbio.2011.11.001.

Are there reasons to use GlycoMax or a GDA outside of reducing blood glucose?

You might be thinking I'm not prediabetic or diabetic, I don't have issues regulating my blood sugar. Are there other benefits to using GlycoMax or a GDA?

Yes, there are. Many in fact. GDAs can influence our health in numerous ways.

There is an impressive body of literature emerging about the theories of aging. Aging, now recognised as a disease can be treated and reversed by lifestyle changes. We can implement bio hacks, ways to manipulate our epigenome to stimulate our longevity genes. By engaging the pathways of AMPK, boosting NAD levels, and activating the sirtuins, we can optimise our healthspan, the period we are able to live an independent, healthy, active life.

A key element of improving healthspan and longevity is marked with enhanced insulin sensitivity and AMPK activation. Something our modern lifestyles have little respect for. Whether we appreciate it or not, our biological clocks and internal workings are often advanced many years beyond our chronological age.

Accelerated aging is associated with diabetes and increasing insulin resistance with age. Along with blood glucose homeostasis in muscle and fat cells, insulin influences neurobiological processes. It is still unclear how much of an effect insulin has in relation to cognitive function and aging in the brain, but evidence shows insulin plays a part in learning and memory, attention, and mood.

``Inflammaging', is a condition characterised by chronic, low-grade inflammation, different to the inflammation needed to stimulate growth, repair, and tissue turnover. A persistent blood inflammatory response is associated with the development of age-related diseases, and insulin

resistance, associated with inflammaging, is something we can influence. Preserving insulin sensitivity may reduce the risk of hypertension, coronary artery disease, stroke, cancer, and type 2 diabetes.

Reduced insulin sensitivity:

- receptor sites
- post-receptor sites
- decreased pancreatic beta cell response to glucose
- impaired GLUT4 glucose response
- inability to supress liver glucose production following a carbohydrate rich meal

Another mechanism is the reduced stimulation of whole-body glucose oxidation in mitochondria and the reduced production of ATP seen with cellular aging. The links between inflammaging (accumulation of cellular debris, senescent cells, immunosenescence, altered gut microbiome and deregulation of the coagulation system), metabolic health, brain health, and their effect on aging are remarkable.

IR exposes skeletal muscle to high levels of blood lipids and can result in increased intramyocellular triglyceride storage. The closeness of these lipid storage sites to muscle mitochondria can affect the efficiency of mitochondrial function and the ability to switch between fat and glucose oxidation, acting to further the development of IR.

Changes in body composition and the reduced ratio of muscle: fat mass, seen with increased levels of obesity, may be suggestive of increasing IR, however, it is visceral fat accumulation that appears to be the main contributor. The higher levels of visceral adipocytes (fat cells) chronically activate inflammatory pathways and lead to mitochondrial dysfunction and oxidative damage. The persistent inflammatory response can lead to further tissue catabolism from impaired insulin signalling due to inflammation of the hypothalamus.

Inflammaging and the role of mitochondrial dysfunction play an important role in age related insulin resistance. Currently it may be treatable through changes in lifestyle. It may also be reduced through aspirin and statins. Perhaps supplementation of natural herbs and plant ingredients would be beneficial too?

Doi: 10.3389/fendo.2015.00013.

Berberine

Berberine activates the AMPK/ SIRT1/ PGC- 1α pathway in skeletal muscle. That sounds complicated, and it is, but we've already learnt about the activation of AMPK in regulating blood glucose. Remember it's that enzyme that works as an intracellular fuel gauge, signalling the need for the muscle to absorb glucose from the bloodstream whilst preventing liver glucose production, cholesterol and triglyceride synthesis and fat breakdown. SIRT1 stands for sirtuin 1, a protein member of the silent information regulator family that targets the cell cycle, apoptosis, oxidative stress, cell viability and senescence associated with aging. It acts to extend healthspan by reducing cardiovascular disease and metabolic abnormalities from hypothalamic inflammation. SIRT1 levels may be downregulated with an increase in oxidative stress and inflammation associated with Alzheimer's Disease. It also helps control whole body cholesterol and lipid levels. SIRT1 could be considered the master metabolic regulator. PGC- 1α (proliferator-activated receptor γ coactivator 1-α) is a transcription cofactor. It co-ordinates the activation of gene expression from DNA to RNA where it is transcribed. Basically, it stimulates mitochondrial biogenesis and the remodelling of muscle tissue to become more oxidative in the regulation of both carbohydrate and fat metabolism.

It is via these pathways, berberine has been found to improve cognitive function, mitigating learning and memory defects. It ameliorates morphological changes in muscle tissue (fibre number and alignment), stimulates mitochondrial biogenesis signalling and ATP production, and reduces oxidative stress.

Outside of the role of improving IR, berberine is an important anti-aging therapeutic agent by the activation of AMPK/ SIRT1/ PGC- 1α pathway in skeletal muscle.

Many preclinical studies have shown that berberine plays a therapeutic role in many central nervous system disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia, depression, schizophrenia, epilepsy, and anxiety. The reduction of reactive oxygen species (ROS) by improvements of mitochondrial number and function, along with activation of SIRT1 may have this positive effect. Berberine may favourably alter levels of dopamine, serotonin and norepinephrine levels and regulate nitric oxide pathways to improve mood disorders. These are thought to be influenced by the gut-brain axis as well as direct interactions via signalling pathways in the brain.

There may be a role for the effect of berberine in women with polycystic ovary syndrome (PCOS), a common hormonal disorder of reproductive age women. PCOS features excess insulin secretion, increased levels of male hormones and chronic low-grade inflammation.

Currently, metformin is used to treat PCOS but berberine has been found to better improve body composition by improving lipid profile, lowering visceral adiposity and waist-to-hip ratio. Increased insulin sensitivity in theca cells showed an improvement in the ovulation rate per cycle which may be linked to the improvement in hormone status following the reduction of visceral fat.

GDAs can influence our health in numerous ways:

- anti-aging therapeutic agent by activation of AMPK/ SIRT1/ PGC- 1α pathway in skeletal muscle
- improved mood
- reduced cardiovascular disease
- reduced hypertension
- reduced metabolic abnormalities from hypothalamic inflammation
- improved blood triglycerides
- raised HDL cholesterol
- reduction of cancer
- improved cognitive function, mitigating learning and memory defects
- mitochondrial biogenesis
- reduced age-related morphological changes in muscle tissue
- increased ATP production
- reduced chronic low-grade inflammation and oxidative stress (ROS)
- improve body composition, lower visceral adiposity, increased insulin sensitivity and improvement in the ovulation rate per cycle due to reduction of the level of male hormones
- improvements in non-alcoholic fatty liver disease

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10.1152/advan.00052.2006.
10.1007/s12603-018-1015-7.
10.1007/s00404-020-05450-4.
10.7759/cureus.21781.
10.3892/etm.2021.10543.
10.3389/fphar.2022.845591.