# Examine.com

# Insulin Sensitivity & Glucose Uptake

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# Medical Disclaimer & Important Note

This guide is a general health-related information product, intended for healthy adults over the age of 18.

This guide is for educational purposes only. It is not medical advice. Please consult a medical or health professional before you begin any exercise, nutrition, or supplementation program, or if you have questions about your health.

Participating in exercise activities or using products mentioned in this guide may pose risks for people in poor health or with pre-existing physical or mental health conditions.

Do not use any products or participate in any activities if you are in poor health or have a pre-existing mental or physical health condition. If you choose to participate, you do so of your own free will, and you knowingly and voluntarily accept the risks.

While we will mention major known drug interactions, it may be possible for any supplement to interact with medications or other drugs. If you are currently taking medication, consult a health professional prior to using any supplement in this guide.

Specific study results described in this guide should not be considered representative of typical results. Not all supplements provide the exact amount of compounds as listed on the label. Always investigate supplement companies, as well as the supplement itself, before purchasing anything. Herbs, rather than isolated compounds, may also have some variability from one batch to the next that can alter the efficacy.

To read the evidence supporting claims mentioned in this guide, please visit Examine.com.

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# How to use this Guide

The team at Examine.com has been publishing research on nutrition and supplementation since March 2011. In that time, we've learned a great deal about supplements, especially how they can work together to help you with health goals.

This stack guide help you figure out which supplements can help you and which will hinder and/or be a waste of your money for your desired goals.

The following four sections present information on supplements that are relevant to *Cardiovascular & Heart Health*:

1. Base Supplements
2. Proven Options
3. Unproven Options
4. Cautionary and Overhyped Options

**Base Supplements** are recommended for the majority of people with this goal. They are either effective on their own or are required to boost the effects of another supplement. These are the first supplements to consider for your stack. Base Supplements are more researched and have less adverse drug interactions than options.

**Proven Options** are supplements that will provide a lot of benefits, but only in the right context. They cannot be recommended for everyone, but if you read the entry and find that you meet the criteria, feel free to add the supplement to your stack.

**Unproven Options** are another group of potentially beneficial supplements, but they lack evidence for their effects. They cannot be recommended with the same confidence as proven options. They could work or be a waste of your money - there is not enough evidence to know for sure. Keep unproven options in mind, but approach them cautiously when incorporating them into your stack.

**Cautionary and Overhyped Options** are supplements that are claimed to provide benefits but have been shown to be ineffective. If a supplement is deemed too risky to be used, it will also be found in this section. **Do not** add these compounds to your stack; they tend to be a waste of money or potentially harmful to your health.

Once we have explained the various supplements that you need to be aware of, the **Assembling your Supplement Stack** section will outline how different supplements can be combined, based on your objectives.

After that, we follow up with the **Stack Modification FAQ**, in which we cover common questions that may arise when assembling your stack.

Lastly, we include information on **Precautions and Troubleshooting**.

With all this combined, you should be able to identify and assemble a supplement stack best suited for your goals and objectives.

# Zinc

**Why you should take it**
Zinc is an important dietary mineral for general health.

People with insulin resistance can benefit from zinc supplementation, but only if they are deficient in zinc. Supplementation will reduce insulin and glycated hemoglobin (HbA1c) levels in the body while improving insulin sensitivity. HbA1c is a biomarker for diabetes risk, which means high levels of HbA1c are correlated with diabetes, though HbA1c itself does not cause diabetes.

The most reliable way to determine if you have a zinc deficiency is by keeping track of what you eat on a weekly basis, then comparing the zinc contents in your food to the recommended daily allowance of zinc for your age and gender.

People with no insulin resistance and no zinc deficiency do not need to supplement zinc. Zinc is a base supplement only for insulin resistant people with diets low in zinc.

**How to take it**
To supplement zinc, take 25 – 30 mg of elemental zinc. Elemental zinc is the amount of zinc in the supplement you're taking, excluding any compounds included to improve zinc absorption. For example, to take 30 mg of elemental zinc, take 230 mg of zinc gluconate. ***The label displays the elemental zinc content, not the total dosage.***

Zinc should be taken with meals. Taking zinc on an empty stomach may cause nausea. Do not pair zinc with minerals like calcium, magnesium, and iron in combined doses of 800 mg or more. Combining them at low doses is fine, but in high amounts the minerals will compete for absorption and limit the overall effectiveness of supplementation.

If your diet is high in zinc, you do not need to supplement zinc. Foods like meat, fish, beans, nuts, seeds, and eggs are high in zinc.

***Note:*** This dose is commonly recommended for athletic people who have high zinc losses in sweat. If you are either sedentary, don't produce a large amount of sweat, or have a diet moderate to high in meat products this dose could be dangerous for long-term daily usage. If that is the case, then reduce the daily dose to the range of 10-20 mg once daily.

## Myo-inositol

**Why you should take it**
Myo-inositol is a compound with a similar structure to glucose. It can improve insulin signaling because it is an ingredient in the reaction that creates phosphatidylinositol (3,4,5)-trisphosphate (PIP3).

Myo-inositol deficiencies are associated with reduced PIP3 levels. Reduced PIP3 levels prevent insulin from signaling effectively. Supplementation of myo-inositol can benefit people suffering from type II diabetes or polycystic ovarian syndrome (PCOS), since it can improve insulin sensitivity.

**How to take it**
To supplement myo-inositol, assuming a powder supplement, take 4 g. To supplement with a soft gel formulation of myo-inositol, take 1,200 mg.

Myo-inositol should be taken with food, though more research is needed to confirm that this is the best way to take myo-inositol.

***Pregnant women should not supplement myo-inositol.*** Myo-inositol supplementation can induce uterine contractions.

## Creatine

**Why you should take it**
Creatine is a source of fuel for muscle cells. Supplementing creatine will improve exercise performance and may benefit heart health. It also improves glucose uptake during muscle contractions, specifically during exercise.

Improved glucose uptake gives the muscles more energy to work with and staves off fatigue.

Creatine is a base supplement for glucose uptake and insulin sensitivity because it's cheap, safe, and does not interact with pharmaceuticals. People with no insulin resistance will still benefit from creatine supplementation.

**How to take it**
The best way to supplement creatine is to take creatine monohydrate. Other forms of creatine may be more expensive, but studies have not found them to be more effective than creatine monohydrate.

If you are particularly sensitive to creatine's digestive side-effects, which include nausea and cramping, consider supplementing micronized creatine, which may be gentler on the digestive system.

The daily dose for creatine is 5 g a day.

Loading creatine means taking a high dose of creatine for a short period of time before moving down to a smaller maintenance dose, which can be taken indefinitely. This is not necessary for effective supplementation. Though loading may result in benefits appearing slightly faster, results normalize after a few weeks.

Some people are creatine nonresponders, which means creatine is unable to pass from their blood to their muscles.

More research is needed to find a proven way to circumvent creatine nonresponse. Some evidence suggests it helps to take creatine with a meal high in both protein and carbohydrates, close to the time of actual muscle contraction. If you experience creatine nonresponse, consider taking creatine with a meal either before or after a workout.

If you respond to creatine, you don't have to worry about timing supplementation, though you will probably want to take it with a meal to lower the risk of an upset stomach.

# Berberine

**Why it is a proven option**
Berberine is a compound derived from plants like *Berberis aristata*, *Argemone mexicana*, and *Berberis aquifolium*. These plants are claimed to be anti-diabetic due to their berberine content.

Berberine lowers blood glucose levels by activating a protein called 5' AMP-activated protein kinase (AMPK). AMPK is responsible for drawing glucose into cells and signaling the body to convert the fuel to energy. This lowers blood sugar levels without interacting with insulin. Berberine supplementation will not cause low blood sugar levels, also known as hypoglycemia, like excess insulin does.

Berberine cannot be recommended as a base supplement due to its interactions with various enzymes, including CYP3A4, CYP2C9, and CYP2D6. These enzymes metabolize many pharmaceuticals. It is possible that berberine could interact with various oral contraceptives.

**How to take it**
To supplement berberine, take 300 – 500 mg of berberine in three or four divided doses throughout the day, for a total daily dosage of 900 – 2,000 mg. Start at the low end of the range. People with insulin resistance should then slowly increase their berberine dose to 1,500 mg a day, in three divided doses of 500 mg a day.

Berberine should be taken with or shortly after a carbohydrate-containing meal. High doses of berberine can cause stomach distress and diarrhea.

# Cinnamon

**Why it is a proven option**
Cinnamon, from the plant *Cinnamomum cassia*, can reduce blood sugar levels in healthy people when taken with carbohydrates. Cinnamon does not have

this effect in insulin-resistant people, though it does help maintain blood glucose levels between meals, if taken daily.

Though multiple studies suggest cinnamon can reduce glucose and insulin levels, much more research is needed to determine the optimal dosing and timing to achieve this effect.

Cinnamon can be included in this stack to improve the rate at which blood glucose is drawn into the muscles, as long as the user is not insulin resistant.

**How to take it**

To supplement cinnamon, take 5 – 6 g of *Cinnamomum verum*, also known as Ceylon cinnamon, or *Cinnamomum cassia*, also known as cassia cinnamon. Cinnamon should be taken throughout the day, with meals containing carbohydrates.

Cinnamon can also be supplemented by brewing a tea or by purchasing cinnamon supplements. Brewing tea makes it difficult to supplement precise dosages. Cinnamon tea contains less coumarin than cinnamon supplements. Coumarin is a liver toxin that can be harmful in high doses. Tea reduces the risk of coumarin poisoning because the toxin is left behind in the dregs.

Cinnamon supplements should be dosed based on their cinnamon content. For example, to supplement 6 g of cinnamon, assuming a 10:1 cinnamon water extract supplement, take 600 mg of the cinnamon supplement.

# Isoleucine

**Why it is an unproven option**
Isoleucine is one of the three branched chain amino acids (BCAAs). Isoleucine supplementation can improve the rate at which blood sugar is taken up by muscle cells. This effect does not involve insulin or 5' AMP-activated protein kinase (AMPK) signaling.

Though there are a lot of studies on BCAAs and glucose levels, this evidence cannot be used to evaluate isoleucine by itself. Further research is needed to determine if high doses of isoleucine can cause low blood sugar, also known as hypoglycemia. Additional studies are also needed to determine what effect insulin resistance has on isoleucine supplementation.

If you are healthy and not insulin resistant, many of the supplements in this guide will not be very effective for you. Isoleucine, however, can provide benefits for active and healthy people, especially those who have a high carbohydrate diet.

**How to take it**
To supplement isoleucine, take 72 mg per kilogram of bodyweight. This is approximately:

- 4.9 g for a 150lb person
- 6.5 g for a 200lb person
- 8.1 g for a 250lb person

This dose is based off of preliminary animal evidence. People eating at least 60 g of protein a day or people supplementing BCAAs will need less leucine than described above. As a rule of thumb, aim for 5 g of leucine a day.

## Corosolic Acid

**Why it is an unproven option**
Corosolic acid is a compound found in anti-diabetic plants like banaba leaf.

Corosolic acid shares a mechanism (not the major one) with Berberine, another anti-diabetic compound found in plants. Corosolic acid can improve insulin signaling after supplementation.

A lot more research is needed to confirm that corosolic acid supplementation is effective at improving insulin signaling. Preliminary evidence suggests it may be as potent as berberine at suppressing a protein called tyrosine-protein phosphatase non-receptor type 1 (PTP1B).

Suppressing PTP1B gives insulin more time to act in the cells and improves its effectiveness.

Though more human evidence is needed before corosolic acid can be recommended specifically for insulin sensitivity, corosolic acid supplementation could be useful for people concerned with insulin sensitivity who also want to encourage muscle growth. Anyone concerned with muscle growth can consider corosolic acid as an alternative to berberine, since berberine's interaction with the 5' AMP-activated protein kinase (AMPK) receptor may interfere with muscle growth.

**How to take it**
To supplement corosolic acid, take 10 mg with a carbohydrate containing meal. Dosing corosolic acid supplements will depend on their corosolic acid content. For example, to supplement corosolic acid through an herbal supplement like banaba leaf, assuming a supplemental corosolic acid content of 3%, take 330 mg of the banaba leaf supplement.

## Salacia

**Why it is an unproven option**
Salacia refers to the herbs, *Salacia reticulate* and *Salacia oblonga*. Salacia supplementation can prevent the absorption of up to 25% of ingested carbohydrates. It is more reliable than other carbohydrate absorption inhibitors because it acts on a variety of carbohydrate-digesting enzymes.

Preventing the absorption of carbohydrates will reduce the increase in blood glucose and insulin that occurs after a meal. Over time, this kind of effect is beneficial for insulin resistant people.

Preliminary evidence suggests salacia is as potent as acarbose, a pharmaceutical that blocks carbohydrate absorption. However, salacia cannot be specifically recommended over acarbose without additional evidence for its effects.

**How to take it**
To supplement salacia, take 240 – 1,000 mg of *Salacia reticulata* or *Salacia oblonga*.

Salacia must be taken immediately before or after a meal containing carbohydrates, since its main mechanism involves reducing carbohydrate absorption. If supplemented by someone on a low carbohydrate diet, salacia will have no effect.

## Chromium

Chromium supplementation is frequently claimed to increase insulin signaling. Chromium only has this effect when supplemented by people with a chromium deficiency. Outside chronic conditions and hospital emergencies, there has never been a reported case of insulin resistance caused by a chromium deficiency.

Though chromium may have a mild effect on blood glucose levels when supplemented by people with type II diabetes, this effect is very small and does not provide benefits for other aspects of insulin resistance, like levels of fasted insulin.

Since true chromium deficiencies are very rare, chromium should not be part of any supplement stack.

# Assembling Your Supplement Stack

The following outlines how to incorporate this supplement stack into your daily nutrition habits.

## Incorporating Base Supplements

The base supplements in the Insulin Sensitivity & Glucose Uptake Stack are unlike other base supplements in the Examine.com stack guides because each one has prerequisites for supplementation.

**Zinc** (20 - 30 mg) and **myo-inositol** (4 g) should be taken by people with insulin resistance, while **creatine** (5 g) should only be used by people that exercise.

Insulin resistant people undergoing an exercise program should consider all three base supplements for the Insulin Sensitivity & Glucose Uptake stack.

## Incorporating Supplement Options

**For people diagnosed with insulin resistance that do not take any medication**

> Take the base **zinc** (25 - 30 mg) and **myo-inositol** (4 g) daily, with a meal. Add **berberine** (300 mg), taken three times daily with a meal. After a week of supplementation, increase the berberine dose to 500 mg at each of the three meals. The two base supplements (zinc and myo-inositol) can be taken at mealtime alongside berberine.
>
> **Salacia** (240 - 1,000 mg) can be added to this stack by people with a high dietary carbohydrate intake.

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**For people that may be resistant to insulin, but have not been diagnosed**

> Take the base **zinc** (25 - 30 mg) and **myo-inositol** (4 g) daily with a meal. Add **berberine** (300 mg), taken three times a day with meals for

a total daily dose of 900 mg. Pair this stack with preventative measures like dietary changes and exercise.

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**For athletes that want to increase muscular glucose uptake during exercise**

Take the base creatine (5 g), once a day. Add **isoleucine** (5 g) or a **branched-chain amino acid (BCAA)** supplement, taken before workouts. Do not add isoleucine if you do not consume carbohydrates before workouts, as isoleucine for the purpose of helping with glucose disposal works in the presence of dietary carbohydrates.

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**For athletes that want to increase muscular glucose uptake during meals**

Take **cinnamon** (6 g or an equivalent extract) once a day, with meals containing carbohydrates. Add **isoleucine** (5 g) if the meal is low in dietary protein.

**Corosolic acid** (10 mg) or **berberine** (300 mg) can be supplemented alongside cinnamon. The effects of these supplements may overlap, so only one should be added to the stack.

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**Other Options**

**Creatine** (5 g) is an option for anybody who is physically active. It is taken once a day, with a meal.

# How do I add supplements to my stack that are not covered in this guide?

Before adding a new supplement to your stack, supplement your current stack for a few weeks to determine if you need to make a new addition. If you want to make multiple changes to your stack, pick one supplement to add at a time. Identify the stack change that you think will be the most effective, and do your research:

1. Use Examine.com to determine if that supplement would have a negative interaction with your current stack. Talk to your doctor about including a new supplement in your stack.

2. Introduce the new supplement at half of the regular dose.

3. After a week with the new supplement, slowly increase the dose to the recommended dose if you are not experiencing the effects you want.

Stacks are intended to be synergistic, which means taking two supplements together may provide more effects than the supplements by themselves. New supplements should be added carefully, since even low doses can be powerful if other supplements in your stack improve their effects.

# Can I modify the recommended doses?

If a supplement has an established advised dosage range, stay within that range. If a supplement has a recommended dose, and not a range, stay within 10% of that dose. Halving or doubling an advised dose could be ineffective or even dangerous.

The safest way to add dietary supplements to your life is one at a time. If you are considering purchasing several supplements, purchase only one and add the others after a week or two of supplementation. This will limit the risk of new supplements, and it will also make it easier to figure out what supplements are providing you with your newfound benefits.

## Can any of these supplements cause low blood sugar?

None of the above supplements, used safely, can cause low blood sugar, also known as hypoglycemia. It is possible for high doses of multiple supplements to have a synergistic effect resulting in hypoglycemia though. Cinnamon is most likely to cause hypoglycemia when taken alongside other supplements because it causes insulin secretion.

When adding cinnamon to stacks, make sure it is consumed alongside some dietary carbohydrates.

# Precautions & Troubleshooting

The safest way to add dietary supplements to your life is one at a time. If you are considering purchasing several supplements, purchase only one and add the others after a week or two of supplementation. This will limit the risk of new supplements, and it will also make it easier to figure out what supplements are providing you with your newfound benefits.