

Clinical Nutrition & Supplements when using Glucagon-Like Peptide-1 (GLP-1) Agonists for Weight Loss

Original | Clinical Research White Paper

June 2023 | Saju Joseph MD FACS, Devan A. Patel PharmD, Jill Barat PharmD, Teri A. Standridge B.S.

Introduction to Clinical Nutrition & Supplements when using Glucagon-Like Peptide-1 (GLP-1) Agonists for Weight Loss

Obesity is a growing epidemic in the Western world, especially in the United States. Statistics show that 69 percent of US adults are overweight or obese.¹ An excess of fast-food options, less availability of healthier food choices, and modern sedentary lifestyles are all contributing factors to the obesity epidemic. Lifestyle changes, such as regular exercise and healthier food choices, remain the most effective solution for reversing obesity.

Consuming fewer calories from more nutritious foods and engaging in regular exercise can help individuals both reduce their weight and maintain it. However, weight loss is difficult for most people. Making lifestyle changes requires a significant amount of discipline, time, and effort. Many Americans are unable to stick to a weight loss program long enough to see changes. Furthermore, those that do manage to lose weight, often gain it back.


Doctors and specialists have been searching for an alternative solution to weight loss for years. The weight loss industry is a multi-billion-dollar industry inundated with diet foods and supplements that deliver false promises.² On top of being largely ineffective, some of them may cause more harm than good.

Fenfluramine-phentermine, also known as fen-phen, was a weight loss drug discontinued in 1997 due to its serious negative side effects. Fen-phen combined appetite suppressants with amphetamine to curb hunger and increase metabolism. However, the powerful duo led to dangerous heart valve problems in close to a third of individuals who took the drug.³

Today, there is still no "magic pill" for weight loss that is both safe and effective. But there are medications that supplement weight loss efforts and make losing weight easier for many people. These medications work by focusing on hormone regulation. Two of the most notable hormone-regulating medications include semaglutide and tirzepatide.

Hormone Regulation for Weight Loss

Hormones are natural substances in the body that play a role in numerous bodily functions, including growth, development, and metabolism. When hormone levels become imbalanced, it can affect normal bodily function, like weight management. By controlling hormone function,



doctors and scientists believe medications like semaglutide and tirzepatide can help aid in weight loss. Both drugs work to help regulate the hormones GLP-1 and GIP, two important hormones for blood sugar and weight management. Although, semaglutide is more selective for GLP-1, while tirzepatide targets both GLP-1 and GIP.⁷⁸

What Is A GLP-1 Hormone?

GLP-1 hormone, also known as glucagon-like peptide 1, is a form of incretin hormone found naturally in the body. It helps regulate blood sugar levels by stimulating the release of insulin while at the same time slowing gastric emptying and suppressing appetite. It has been used to successfully aid in weight loss and treat type 2 diabetes for many years.⁴

In addition to these benefits, GLP-1 hormones have been shown to improve beta cell function and help prevent further beta cell damage or destruction. Furthermore, GLP-1 may even be beneficial for cardiovascular health due to its ability to reduce inflammation and platelet aggregation. As such, it is gaining increased attention as an important target for potential therapeutic interventions for metabolic diseases.

What Is A GIP Hormone?

GIP (gastric inhibitory polypeptide) is a hormone secreted in response to food consumption. It helps regulate the absorption of nutrients from meals, as well as signaling satiety and inhibiting gastric acid secretion. Additionally, GIP may contribute to the regulation of blood glucose levels and insulin sensitivity. Studies have suggested that GIP plays an important role in controlling hunger, body weight, and energy balance. However, more research is needed to fully understand the role of GIP in metabolic health.

Semaglutide vs Tirzepatide: What Are They and How Are They Used?

Semaglutide and tirzepatide are two new drugs that are both GLP-1 agonists, meaning they stimulate the release of glucagon-like peptide-1 (GLP-1) from cells in the digestive system. Both medications have been used in the management of type 2 diabetes to improve blood sugar control. However, they have also been shown to be effective in promoting weight loss and weight management.

Semaglutide and tirzepatide aid in diabetes and weight management by promoting insulin secretion, suppressing glucagon secretion, reducing appetite, and slowing gastric emptying. In terms of side effects, both medications may cause nausea, vomiting, diarrhea, and constipation, as well as a risk for hypoglycemia or weight gain. However, due to its higher potency, semaglutide carries an additional risk of pancreatitis compared to tirzepatide.



A Closer Look at Semaglutide (Wegovy®)

Semaglutide is a type of drug known as glucagon-like peptide-1 receptor agonists, or (GLP-1 RAs). It works by mimicking the human hormone GLP-1, which is released in the gut while eating. Semaglutide was developed to improve glycemic control in people with type 2 diabetes. It was approved in 2019 and sold under the brand names Wegovy®, Ozempic®, and Rybelsus®.

Currently, Wegovy® is the only semaglutide drug approved for weight loss in individuals without diabetes who are overweight or have other health problems. Wegovy® is administered by a once-weekly subcutaneous injection. Wegovy® works by binding to and activating receptors on pancreatic beta cells, which are responsible for producing insulin when needed. As a result, it increases glucose-dependent insulin secretion from these cells and reduces glucagon secretion. This helps regulate blood sugar levels and improves overall glycemic control.

In addition, Wegovy® also delays gastric emptying, which reduces hunger, regulates appetite, and increases satiety, further helping to reduce calorie intake for weight loss. A study was conducted on just under 2,000 obese adults to compare the effectiveness of semaglutide (Wegovy®) combined with a diet and exercise program, versus the same lifestyle changes without semaglutide.⁵ After 68 weeks, half of the participants using semaglutide lost 15% of their body weight, while nearly a third lost 20%. Participants who only made lifestyle changes lost approximately 2.4% of their weight.

In clinical trials, semaglutide has been found to be significantly more effective than other glucose-lowering medications in terms of reducing glycated hemoglobin (HbA1c) levels, a measure of long-term blood sugar control.⁶ It has also been associated with greater weight loss compared to other anti-diabetic drugs.⁷

Overall, semaglutide as Wegovy® provides an effective solution for people with or without type 2 diabetes who are looking to both improve their glycemic control and reduce their body weight. As it is available as a once-weekly injection, its convenient dosing schedule can help patients stay on track with their treatment regimen, leading to better long-term health outcomes.

A Closer Look at Tirzepatide (Mounjaro®)

Tirzepatide is a long-acting GLP-1/Glucagon dual agonist that has been shown to be effective in the treatment of type 2 diabetes.⁸ It works by stimulating both insulin and glucagon release from the pancreas, thus helping to regulate blood glucose levels and reduce the risk of cardiovascular complications associated with diabetes.

This means it works by imitating two hormones instead of just one: GLP-1 and GIP. Tirzepatide triggers GLP-1 production, leading to more insulin production when necessary. GIP has been proven to reduce food intake and boost energy expenditure, resulting in weight loss.⁹ When combined with GLP-1 receptor agonism, it may have greater effects on metabolic markers such as body weight, glucose, and lipids.

Tirzepatide was approved under the brand name, Mounjaro®, in May 2022. Mounjaro® is administered via subcutaneous injection once a week, with the dosage being adjusted as necessary to achieve desired blood sugar levels. Mounjaro® has been clinically proven to improve glycemic control, significantly reduce body weight, and lower HbA1c levels when compared with other anti-diabetic medications.

The effectiveness of Mounjaro® was assessed in five clinical trials, where three different doses (5mg, 10mg, and 15mg) were administered either alone or in combination with other diabetes medications.¹⁰ This was compared to a placebo, a GLP-1 receptor agonist (semaglutide), and two long-acting insulin analogs.

Mounjaro® was shown to be effective in lowering HbA1c levels when used as a stand-alone therapy or in combination with long-acting insulin. Compared to the placebo, patients who received the maximum recommended dose of Mounjaro® had a 1.6% reduction in HbA1c levels. When compared to other diabetes medications, Mounjaro® resulted in a greater reduction of HbA1c levels, with a 0.5% greater reduction compared to semaglutide, 0.9% greater reduction compared to insulin degludec, and 1.0% greater reduction compared to insulin glargine.¹¹

Many study participants were obese, with an average body mass index of 32 to 34 kilograms/height in meters squared. Patients who took the maximum recommended dose of Mounjaro® lost an average of 15 pounds more than those who took a placebo without insulin, and 23 pounds more than those who took a placebo along with insulin. The maximum recommended dose of Mounjaro® resulted in an average weight loss of 12 pounds more than semaglutide, 29 pounds more than insulin degludec, and 27 pounds more than insulin glargine. Patients who only received insulin tended to gain weight during the study.¹¹

Due to its dual action on both hormones, tirzepatide helps to create a more normalized, balanced response to glucose levels in the body. This helps to reduce swings in glucose levels that can lead to complications associated with diabetes, such as hypoglycemia and hyperglycemia. Additionally, tirzepatide may help lower cholesterol levels and improve overall heart health.

Comparison Between Wegovy®, Ozempic®, and Mounjaro®

Below is a comparison chart between the 3 most common semaglutide and tirzepatide medications highlighting their differences in results.


	Mounjaro® (tirzepatide)	Wegovy® (semaglutide)	Ozempic® (semaglutide)
<i>Manufacturer</i>	Eli Lilly & Co.	Novo Nordisk	Novo Nordisk
<i>FDA Approved</i>	May 2022	June 2021	December 2017
<i>Delivery</i>	Once weekly injection	Once weekly injection	Once weekly injection
<i>Dose range</i>	2.5 mg - 15.0 mg	0.25 mg - 2.4 mg	0.25 - 2.0 mg
<i>Targets</i>	GLP-1 and GIP	GLP-1	GLP-1
<i>Most common side effects</i>	Nausea, diarrhea, constipation, vomiting	Nausea, diarrhea, vomiting, constipation	Nausea, vomiting, diarrhea, abdominal pain
<i>Avg. weight loss in clinical trials</i>	22.5% of body weight after 72 weeks (15 mg) ³	14.9% of body weight after 68 weeks (2.4 mg) ⁴	6.1% of body weight after 52 weeks (1.0 mg) ⁵

The Role of Nutrition for Weight Loss with Semaglutide and Tirzepatide

Nutrition is an important factor in any weight loss program, and this is especially true when using GLP-1 agonists like semaglutide or tirzepatide. Though both medications aid in weight loss for people who are overweight or obese, they are not a “magic pill”. Implementing lifestyle changes such as reducing calorie intake and engaging in regular physical activity are both necessary to achieve the best results from taking semaglutide or tirzepatide.

Individuals taking either medication with the intent to reduce body weight should consider a holistic approach to their health and fitness routine. Eating a well-balanced diet with plenty of fresh fruits and vegetables, whole grains, lean proteins, and healthy fats can help to support weight loss and promote overall health. The type of food you eat, how much you eat, and when you eat are all contributing factors to your weight loss or weight maintenance program.

Eating right for weight loss while taking semaglutide or tirzepatide means focusing on nutrient-dense, low-calorie foods that are high in protein, fiber, and healthy fats. Paying attention to your macronutrients in each meal as well as timing your meals strategically throughout the day may also be beneficial for weight management. For example, eating frequent small meals



rather than several large meals may help stimulate metabolism and help keep hunger at bay while controlling blood sugar levels and preventing overeating later in the day.

What Is A Good Diet Plan When On Semaglutide and Tirzepatide?

There is no set diet plan to follow while on either weight loss medication, but it is suggested to follow some kind of structured eating plan to maximize weight loss results. Individuals should consult with their doctor to determine what kind of diet program would be most beneficial for them.

Ultimately, weight loss can only be achieved through creating a calorie deficit. You must burn more calories throughout the day than you consume. The ideal diet plan for individuals taking semaglutide or tirzepatide medications should be low in calories to help them achieve a calorie deficit. A low-calorie diet is easier to implement while taking semaglutide or tirzepatide due to their appetite-suppressing benefits. With these medications, overweight or obese individuals feel less hungry, and thus find eating fewer calories less difficult.

Recommended Calorie Intake for Individuals on Semaglutide or Tirzepatide Medications for Weight Loss

Individuals taking semaglutide or tirzepatide injections are required to follow a low-calorie diet for the best results. On average, women should consume 1600-2400 calories per day, while men should consume 2000-3000 to maintain a healthy weight. However, losing 1 pound requires burning 3500 calories. For example, to achieve an 1800 calorie deficit, an individual that burns 3000 calories daily would need to consume 1200 calories per day.

Following a 1200 calorie diet, individuals that burn approximately 3000 calories daily may experience a weight loss of approximately 3.6 pounds per week. Combining this low-calorie diet plan with regular exercise and semaglutide or tirzepatide medication can assist patients in achieving their desired weight.

Diet Tips When On Semaglutide Medications For Weight Loss

Semaglutide and tirzepatide injections promote blood glucose management, which can lead to prolonged feelings of fullness, decreased hunger and cravings, and delayed digestion. To maximize the benefits of this weight loss medicine and achieve your weight reduction objectives, it is important to follow certain dietary advice:

- Eat more complex carbohydrates
- Consume more protein in the form of lean meats or plant proteins
- Eat more vegetables with every meal
- Eat fruits with a low glycemic index in small portions
- Eat small but frequent meals
- Don't focus on scale weight
- Ensure proper intake of calories

Following these guidelines can help overweight or obese individuals lose more weight while on either medication and may help them develop healthier habits for long-term weight loss and weight maintenance.

Foods To Eat When Using Semaglutide and Tirzepatide Medications for Weight Management

Though calorie intake is the most important factor to consider when losing weight with semaglutide or tirzepatide, the foods you get your calories from are also important. Whole foods, or non-processed foods, are the healthiest food choices. These foods are more nutrient-dense while remaining lower in calories. Some of the foods overweight or obese individuals taking either medication should consider are the following:

Non-Starchy Vegetables

Non-starchy vegetables are low in calories while being rich in fiber, vitamins, and minerals. These types of vegetables will provide satiety without significantly elevating blood sugar levels.

Non-starchy vegetable choices include:

- Asparagus
- Broccoli
- Cabbage
- Cauliflower
- Green leafy vegetables
- Mushrooms
- Squash
- Tomatoes

Whole Grains

Whole grains are complex carbohydrates rich in fiber, which provide slower-release energy to avoid significant blood sugar level spikes.



Some examples of whole grains include:

- Brown rice
- Whole wheat bread
- Oatmeal
- Quinoa
- Millet
- Farro
- Buckwheat

Nuts

Nuts are an excellent source of fiber, protein, and unsaturated fats. Unsaturated fats are heart-healthy and help to increase satiety.

Examples of heart-healthy nuts include:

- Walnuts
- Almonds
- Pecans
- Brazil nuts

Legumes

Legumes are a good source of plant protein and are rich in fiber and nutrients like folate, iron, and magnesium. Legumes should be eaten in moderation along with other non-starchy vegetables.

Examples of legumes include:

- Lentils
- Peas
- Chickpeas
- Red beans
- Peanuts

Lean Protein

Lean protein is important for increasing satiety and preserving muscle mass when losing weight.

Sources of lean protein include:

- 
- Chicken
 - Turkey
 - Fish
 - Beef
 - Tofu
 - Tempeh
 - Cottage cheese

Foods To Avoid While Taking Semaglutide and Tirzepatide

Certain foods should be avoided when taking semaglutide or tirzepatide medications. Many of these foods are counteractive to weight loss and may increase side effects from both medications. Below are some of the foods that people taking semaglutide or tirzepatide should try to avoid.

Fried or Processed Foods

Fried foods and certain processed foods contain large quantities of unhealthy fats which are bad for health as well as highly caloric. Fried foods and processed foods like fast food, doughnuts, pizza, potato chips, and processed meats are counteractive to a weight loss regimen and should be avoided when trying to obtain a calorie deficit.

Additionally, these foods are harder to digest. Side effects like nausea and constipation are common when taking semaglutide and tirzepatide medications. Consuming foods that are harder to digest can make these side effects more severe and in turn, lead to more discomfort.

Alcohol

Alcohol is toxic to the liver and can increase the risk of serious health problems, including obesity. Alcohol can also interact negatively with semaglutide and tirzepatide medications, potentially leading to serious side effects. Additionally, many alcoholic beverages are high in sugar and calories and increase cravings for unhealthy foods, which can be detrimental to weight loss efforts.



Sweets and High-Carbs Foods

Desserts and high-carb foods like pastries, breads, ice cream, and cookies, are high glycemic index foods that spike blood sugar levels. These foods are counteractive to weight loss efforts, especially when eaten in large amounts. These foods should be eaten sparingly if at all while taking semaglutide or tirzepatide.

Carbonated Drinks

Certain carbonated drinks like sodas, energy drinks, and beer not only contain excess calories but can also contribute to bloating. Bloating can increase stomach pain caused as a side effect of semaglutide and tirzepatide medications. Therefore, carbonated drinks should be avoided or consumed sparingly.


Exercise Guidance While Taking Semaglutide and Tirzepatide

Exercise plays a key role in weight loss and weight maintenance while taking semaglutide and tirzepatide medications. It helps to boost metabolism, which can speed up the burning of calories and fat deposits in the body. Regular physical activity also helps to keep hunger levels in check, preventing overeating and cravings for unhealthy foods. Exercise also increases muscle mass, and a higher percentage of muscle mass means that your body burns more calories at rest.

In addition to its metabolic benefits, exercise is important for overall health and wellness. Exercise releases mood-enhancing hormones such as endorphins, increases energy levels, improves sleep quality, reduces stress levels, boosts immunity, and strengthens bones and muscles. It's especially important for people with obesity who are at greater risk for heart disease, diabetes, and other serious health issues.

The type of exercise you choose is important for weight loss and maintenance. Aerobic activities such as walking, jogging, biking, and swimming are great for burning calories and increasing cardiovascular fitness, but strength training is also essential. Strength training helps to build lean muscle mass which in turn increases metabolism and the number of calories burned at rest.

Regular physical activity should be part of any weight management plan. It's vital for successful weight loss as well as long-term maintenance of healthy body composition. It is recommended that individuals gradually increase their exercise intensity by adding additional minutes or increasing the intensity of their current routine each week. Furthermore, taking rest days throughout the week is necessary for allowing the body time to recover from exercise while continuing a regular fitness routine.



Overall, having an effective exercise plan while taking GLP-1 agonists may help maximize the benefits of treatment by aiding in weight loss and promoting better health outcomes.

How To Get the Best Results From Semaglutide and Tirzepatide?

Below are a few ways that individuals can maximize the benefits of semaglutide and tirzepatide to achieve the best results. These tips may also help to reduce the severity of negative side effects from both medications.

Eat Smaller Portions More Frequently

Eating smaller portions of food more frequently throughout the day may help stimulate metabolism while possibly preventing overeating. It may also reduce symptoms of nausea, heartburn, or other unpleasant GI problems which are common when taking semaglutide and tirzepatide.

Avoid Foods That May Cause Side Effects

Certain foods that are harder to digest such as processed or greasy foods can increase side effects from semaglutide and tirzepatide medications. These foods should be eaten sparingly or avoided entirely while using either medication.

Drink More Water

Drinking more water to stay hydrated may help reduce nausea associated with taking semaglutide and tirzepatide medications. Additionally drinking up to 64 ounces of water daily can help increase satiety levels and help reduce overeating.

Keep Alcohol To A Minimum

When using semaglutide or tirzepatide, alcohol consumption may cause stomach discomfort and negatively impact blood sugar levels. Combining alcohol with semaglutide can lead to dangerously low blood sugar levels. Additionally, drinking alcohol while taking semaglutide or tirzepatide may increase the chance of developing pancreatitis, although this is an uncommon occurrence.



Increase Physical Movement

Exercising regularly is crucial for good health, whether you take a GLP-1 agonist medication or not. Combining semaglutide or tirzepatide with physical activity can lead to improved outcomes and help maintain long-term weight loss.

Rotate Where Medications are Injected Each Week

Semaglutide and tirzepatide may be administered through injection in three different areas of the body: the thighs, belly, or upper arm. This ensures that the medication is delivered subcutaneously, avoiding any veins. It is recommended to rotate injection sites weekly to allow the skin time to heal.

What Are the Side Effects of Using Semaglutide and Tirzepatide?

Semaglutide and tirzepatide are relatively safe for most people. However, both medications can cause significant negative side effects. The most frequent side effects experienced with both medications include nausea (17-22% in people who received tirzepatide and 18% of people who received semaglutide), diarrhea (13-16% and 12% respectively), vomiting (6-10% and 8% respectively), and decrease in appetite (7-9% and 5% respectively).¹² Most side effects were mild to moderate and experienced only during the dose escalation period for both medications.

Side Effects of Semaglutide

The most common side effects of semaglutide include nausea, diarrhea, dizziness, fatigue, heartburn, burping, vomiting, constipation, acid reflux, and abdominal pain. In rare cases, semaglutide may cause gallbladder problems and has been linked to pancreatitis. Most side effects should lessen the longer semaglutide is taken.

Side Effects of Tirzepatide

The most common side effects of tirzepatide include nausea, vomiting, abdominal pain, diarrhea, headache, dizziness, and fatigue.¹³ Less common side effects include muscle pain, joint pain, back pain, depression or anxiety, and an increased risk of infections.¹⁴ In rare cases, it can cause pancreatitis or gallstone formation.

How Long Do Side Effects of Semaglutide and Tirzepatide Last?

Most side effects of semaglutide and tirzepatide typically resolve within a few weeks as the body adjusts to the medication. Doctors will generally prescribe a dosage of each medication at a low level and gradually increase it to a therapeutic level to reduce the occurrence of adverse effects. Though not everyone may experience side effects, some individuals will feel persistent discomfort from the beginning of use.

If adverse effects persist a few weeks after reaching the therapeutic dose, it is recommended for individuals to discuss this with their prescriber. The healthcare provider may suggest a complementary therapy or temporary reduction in semaglutide or tirzepatide dosage to help alleviate adverse effects.

Can the Side Effects of Semaglutide and Tirzepatide Be Reduced?

To reduce negative side effects associated with GLP-1 agonists, most doctors will prescribe a lower dose and raise the dose over time. This gives the body time to adjust to the new medication and potentially lessen any negative side effects. Unfortunately, some side effects may be impossible to avoid entirely but certain lifestyle habits may help reduce their severity and frequency of occurrence.

Nausea and Vomiting

Nausea and vomiting are two of the most common side effects experienced while taking semaglutide and tirzepatide. In particular, individuals taking semaglutide at a higher dose for obesity experience nausea more commonly than those using the drug at a lower dose for diabetes.¹⁵ However, there are a number of ways to lessen the queasy feeling associated with nausea. Ginger is a natural herb clinically studied for its effectiveness in being a remedy for nausea and upset stomach.¹⁶ Ginger can be consumed in the form of tea, cordials, or even ginger beer to prevent and soothe nausea and vomiting. Additionally, fresh ginger root can be peeled and crushed or steeped into teas or other foods and beverages.

Eating too much at one time can also increase the chance of nausea and vomiting. Individuals taking semaglutide or tirzepatide should consume smaller meals more frequently to reduce hunger and the risk of overeating. Smaller portions of food are easier for the body to digest and can prevent feelings of nausea that may occur after eating too much. Additionally, individuals should avoid eating too close to bedtime and refrain from being overly active after their last meal. Allowing the body to digest food properly before sleep or vigorous activity may help reduce nausea and vomiting.



Diarrhea

Diarrhea causes loose watery stools that can be uncomfortable and even painful. It's a common side effect of GLP-1 agonists and usually persists soon after starting semaglutide or tirzepatide injections. Eating more soluble fiber can help reduce the severity of diarrhea by adding bulk to stool and absorbing extra water. Foods like beans, oats, peas, whole grains, bananas, and potatoes are high in soluble fiber and may help reduce the severity of diarrhea.

Additionally, diarrhea and vomiting can cause an excess of fluid loss. Rehydrating by drinking plenty of water, electrolyte-enhanced beverages, or using oral rehydration sachets can help replace lost minerals and fluids. There are also prescription medications such as Loperamide, which helps to slow down the movement of food as it travels through the gut. Loperamide helps the body absorb more water from stool, making stool firmer and reducing diarrhea.

Acid Reflux, Indigestion, and Heartburn

Although the disorders are separate, acid reflux, indigestion, and heartburn are often referred to interchangeably due to their similar symptoms and similar treatments. Acid reflux can cause a burning sensation in the chest or back of the neck, and individuals may find that their symptoms worsen at night while lying down.

Laying down can increase the possibility of stomach acid flowing into the esophagus. Treatment options for heartburn include elevating the head of your bed and sleeping in a reclined position instead of laying flat. These methods aim at reducing throat and chest irritation by keeping excess acid in the stomach.

Additional strategies to consider include consuming smaller portions or snacking intermittently instead of adhering to set mealtimes in the event that these methods do not alleviate symptoms or you experience indigestion during the day. This approach may result in decreased acid production by the stomach, allowing for reduced consumption.

Constipation

Semaglutide, due to its ability to slow down digestion, can cause feces to become hard, dry, and difficult to pass, resulting in constipation. Constipation can be just as uncomfortable as diarrhea and cause pain and discomfort.

To relieve constipation caused by semaglutide, increasing the intake of insoluble fiber found in fruits and vegetables and drinking more water can help soften and ease the passage of stools. There are also laxatives available in a range of different forms. These may help to stimulate bowel movement and relieve constipation.



Bloating, Gas, and Stomach Cramps

Bloating, gas, and stomach cramps are common side effects of both semaglutide and tirzepatide medications. Excess gas can cause both bloating and cramping, which can be excruciatingly uncomfortable at times. Eating smaller, more frequent meals and eating slower can help reduce these symptoms. Exercise may also be useful for relieving gas as physical movement helps move excess gas through the digestive system.

Supplements for Reducing Side Effects While Taking GLP-1 Agonists for Weight Loss

Supplements are natural vitamins, minerals, and herbs that can be consumed in various forms. Supplements can provide numerous health benefits and may help reduce certain side effects associated with taking GLP-1 agonists (semaglutide and tirzepatide) for weight loss. In addition to possibly reducing the severity or frequency of negative side effects from GLP-1 agonists, supplements may also help to support overall health as well as weight loss.

Below are some of the most effective supplements for reducing negative side effects while taking semaglutide and tirzepatide medications.

Vitamin B12 (Methylcobalamin)

Vitamin B12, also known as methylcobalamin, is essential for metabolism and energy production. It helps to break down carbohydrates into glucose, which is then used by cells in the body to make energy. Vitamin B12 also aids in red blood cell formation and helps with proper nerve function. Additionally, it assists in converting fats and proteins into energy and supports the immune system by helping in DNA synthesis.

Vitamin B12 has also been studied for its potential to reduce side effects while taking GLP-1 agonists. In animal studies, B12 was shown to improve glucose tolerance without causing nausea or hypophagia.¹⁷ B12 was also shown to increase fat loss while taking GLP-1 agonists.¹⁸ These findings suggest that those taking GLP-1 agonists for weight loss may benefit from taking a daily vitamin B12 supplement to reduce side effects and improve weight loss outcomes. However, further research is needed to confirm these results.

Overall, Vitamin B12 is an essential nutrient for metabolism and energy production in the body, and its benefits reach far beyond these functions. Supplementing with methylcobalamin may help reduce the side effects of taking GLP-1 agonists for weight loss, as well as fight off fatigue which can be caused by low levels of this vitamin.

L-Methylfolate

L-methylfolate plays an important role in metabolism and energy production. It is a natural form of folate, which is an essential nutrient that helps the body break down nutrients into simple components that can be used for energy or stored for later use. L-methylfolate has been shown to help the body more efficiently absorb and utilize dietary folate as well as other essential vitamins and minerals needed for normal metabolic function.

Studies have also demonstrated the positive effects on cell energy production when taking supplemental L-methylfolate, including increased ATP production and improved mitochondrial efficiency.¹⁹ This means that with regular supplementation, individuals are likely to experience greater energy levels throughout their day without compromising their metabolic health.

Additionally, L-methylfolate can help to reduce homocysteine levels, which are associated with a variety of chronic health conditions.²⁰ Therefore, not only does supplementing with L-methylfolate help provide an energy boost, but it can also potentially reduce the risk of developing certain illnesses and diseases in the future.

5' Pyridoxal Phosphate (Vitamin B6)

5' pyridoxal phosphate (PLP) is an essential cofactor for numerous enzymes involved in metabolism and energy production. It is a key component of many biochemical pathways, especially those related to amino acid metabolism, neurotransmitter synthesis, and fatty acid oxidation. PLP enables metabolic reactions to occur by donating or accepting electrons from one molecule to another. Furthermore, it helps preserve cellular energy levels by transferring its accumulated energy to other molecules.

In short, PLP plays an integral role in maintaining cell function and health by facilitating several metabolic processes. Its ability to transfer energy between molecules means that it can help regulate ATP production, boost enzyme activity, and increase oxygen uptake into cells.²¹ This results in improved mitochondrial performance, enhanced immune response, and improved overall energy production. Additionally, it can protect cells from oxidative damage caused by free radicals, which is important for cellular health.²² Studies show that B6 supplementation may even be useful for reducing nausea and vomiting.²³

In conclusion, PLP provides numerous benefits to metabolism and energy regulation in the body. Its role as an essential cofactor in numerous biochemical pathways ensures that metabolic reactions occur quickly and efficiently, while its ability to transfer energy between molecules helps to preserve cellular energy levels. Furthermore, its antioxidant properties help

protect cells from oxidative stress, thus promoting optimal health and well-being while using GLP-1 agonists for weight loss.

Vitamin B1 (Thiamine)

Thiamine, also known as vitamin B1, is an essential nutrient that plays a critical role in energy metabolism and nervous system function. It is found in a variety of foods, including pork, legumes, whole grains, fortified breakfast cereals, nuts, and seeds.

The benefits of thiamine include its ability to help the body utilize carbohydrates for energy production; support nerve impulse transmission; aid in the production of red blood cells; and regulate appetite, digestion, and metabolism. Additionally, thiamine is also believed to have antioxidant properties that may help protect against cell damage caused by free radicals.

Thiamine is essential for converting carbohydrates into energy, which helps the body to maintain a healthy balance of glucose and insulin levels. Thiamine also plays a crucial role in the metabolism of glucose, meaning more thiamine is needed to metabolize diets high in sugar. Obese individuals who eat diets high in sugar may require more thiamine than others and exhibit a higher rate of thiamine depletion during glucose metabolism.²⁴

A deficiency in thiamine is linked to obesity as well as impairment in insulin synthesis and secretion.²⁵ Furthermore, severe thiamine deficiency is associated with increased endothelial nitric oxide synthase production, reactive oxygen species (ROS) production, and intercellular adhesion molecule-1 (ICAM-1).²⁶

Thiamine B1 also helps protect the nervous system by boosting cognitive function and aiding in nerve transmission. It can even reduce symptoms of stress, anxiety, and depression.²⁷ Furthermore, thiamine B1 supports optimal cardiovascular health by helping to regulate blood pressure and improving circulation throughout the body.²⁸ All these features make it an invaluable nutrient for overall well-being and vitality while undergoing GLP-1 agonist treatment for weight loss.

Chromium Picolinate

Chromium picolinate is a unique form of chromium that has been shown to be 10 times more bioavailable than other forms. Its superior bioavailability means the body can absorb it quickly and easily, enabling it to better support energy levels and digestion. Studies have found that supplementing with chromium picolinate can help regulate blood sugar levels, which can help boost energy and stamina.²⁹⁻³⁰ It's also been shown to improve the body's response to insulin.³¹

In addition, chromium picolinate helps improve the absorption of carbohydrates, fats, and proteins from food into cells for better utilization.³² Furthermore, research suggests that chromium picolinate may help reduce cravings for sugary snacks and reduce calorie intake.³³ In conclusion, chromium picolinate may support and enhance the weight loss effects of GLP-1 agonists in individuals with or without diabetes.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a naturally occurring substance found in the body. It plays an important role in cellular energy production and helps maintain healthy cellular metabolism. CoQ10 has been shown to be beneficial for overall health, including boosting energy levels and helping with bowel movement regularity.

Studies have demonstrated that supplementing with CoQ10 can help increase energy and support cardiovascular health.³⁴ It may also help increase exercise performance and improve muscle function.³⁵ Additionally, other studies suggest that taking CoQ10 may help reduce cholesterol levels, lowering the risk of heart disease.³⁶

In terms of digestive health, CoQ10 may be beneficial for those suffering from constipation and other digestive issues. It has been shown to promote regularity in bowel movements while also supporting overall intestinal health.³⁷ Furthermore, CoQ10 could help protect against inflammation in the digestive tract, which can lead to bloating and discomfort.³⁸

Overall, CoQ10 is an important substance with many potential benefits. By supplementing daily with a quality formula, one may enjoy increased energy levels and better digestive health while taking GLP-1 agonists.

Magnesium Malate

Magnesium malate is a form of magnesium that has many benefits for both body and brain health. Magnesium malate helps to increase energy production in the cells, reduce muscle pain, and improve digestion.³⁹ It can also help to reduce symptoms of anxiety and depression and promote healthy sleep patterns.⁴⁰ As a bonus, it may even be beneficial for those with fibromyalgia or chronic fatigue syndrome as it can help relieve some of their symptoms.⁴¹

Magnesium also acts as a primary ingredient in some laxative medications due to its laxative properties and ability to help relieve constipation.⁴² It can also act as an antacid to reduce symptoms of heartburn and indigestion.⁴³ Additionally, magnesium can help support healthy blood sugar levels, which can be beneficial when trying to lose weight with GLP-1 agonists.⁴⁴

Himalayan Pink Salt (Sodium Chloride)

Himalayan pink salt is a type of edible rock salt mined from the foothills of the Himalayan Mountains. It is believed to be one of the purest salts available and contains more than 80 trace minerals, such as calcium, magnesium, iron, zinc, and potassium. Himalayan pink salt is primarily composed of sodium chloride.

Sodium chloride, commonly known as table salt, is essential for the body to function properly. It helps maintain normal fluid balance and plays a role in nerve conduction and muscle contraction. It is also necessary for acid-base balance, maintaining blood pressure, contracting, and relaxing muscles, and absorbing and transporting nutrients.⁴⁵

Most adults need approximately 2.3g of sodium chloride per day, which can be easily obtained through dietary sources such as processed foods, canned goods, and condiments. When used in conjunction with a Glucagon-Like Peptide-1 (GLP-1) agonist, sodium chloride acts as an electrolyte to help maintain hydration.

By maintaining fluid balance, sodium chloride helps reduce water retention, which can help with weight loss. Additionally, sodium chloride may help improve glucose control in those with Type 2 Diabetes who are using a GLP-1 agonist for weight loss.⁴⁶ Overall, sodium chloride is an important mineral necessary for the body to function properly and can be beneficial for those using a GLP-1 agonist for weight loss.

Potassium Citrate

Potassium citrate is a mineral supplement that helps to maintain healthy levels of electrolytes in the body. It is beneficial for people taking glucagon-like peptide-1 (GLP-1) agonists for weight loss because it helps to balance water and electrolytes, and may help reduce side effects such as dehydration, electrolyte imbalances, and muscle cramps. Potassium citrate may also help improve glucose levels and insulin sensitivity.⁴⁷

A deficiency in potassium citrate can cause constipation, muscle cramping, malaise, and fatigue in addition to more serious yet rare conditions such as muscle paralysis or poor respiration. Symptoms of GLP-1 agonist use like diarrhea, vomiting, heavy sweating, or the overuse of laxatives can all contribute to potassium citrate deficiency. Additionally, an increase in dietary potassium citrate may help facilitate greater weight loss in the treatment of metabolic syndrome.⁴⁸

Organic Ginger Root Extract

Ginger root extract is a popular natural supplement associated with numerous health benefits. It has been used in traditional medicine for centuries to treat a variety of ailments and has been clinically studied for its effects in relieving nausea.⁴⁹ In recent years, research has identified several potential benefits linked to ginger root extract when taken as part of a weight loss regimen that includes glucagon-like peptide-1 (GLP-1) agonists. Specifically, ginger root extract may help improve factors associated with metabolic disorder including, hyperglycemia, hyperlipidemia, obesity, and hypertension.⁵⁰ Additionally, it has been known to help improve insulin sensitivity, which can be beneficial for those with Type 2 Diabetes who are using GLP-1 agonists for weight loss.⁵¹

Research has shown that levels of GLP-1 can be influenced by the effect of gingerol on insulin release. The mechanism involves the upregulation and activation of cAMP, PKA, and CREP in pancreatic islets, which are important components of the insulin secretion pathway mediated by GLP-1. Additionally, gingerol can increase the expression of Rab27a GTPase and Slp4-a in pancreatic islets and improve insulin-containing secretory granule exocytosis.

Gingerol increases glycogen storage in muscles by activating GYS1. This is due to an increase in Rab8 and Rab10 GTPases expression, which promotes GLUT4 exocytosis to the membrane. GLP-1 is regulated by the insulinotropic activity of [6]-gingerol and its treatment. This promotes glucose distribution in skeletal muscles by improving GYS1 activity and boosting the presentation of GLUT4s in the cell membrane.⁵²

Bromelain

Bromelain is a protein-digesting enzyme derived from the stem and juice of pineapple. Bromelain has been studied for its potential health benefits, some of which may be beneficial when using glucagon-like peptide-1 (GLP-1) agonists for weight loss. Bromelain is primarily used to reduce inflammation but also has potential as an antimicrobial and anticancer agent. It may also be a natural remedy for easing arthritis symptoms such as joint pain and stiffness.⁵³ Bromelain may benefit the respiratory, digestive, and circulatory systems, as well as potentially the immune system.⁵³

Bromelain is a powerful anti-inflammatory that may help relieve stomach problems associated with inflammation. It may also help to relieve diarrhea by reducing the effects of certain pathogens in the intestines.⁵⁴

Papain Enzyme

Papain enzyme is a protein-digesting enzyme extracted from the latex of unripe papaya fruit. It has been used for centuries as a digestive aid and for its healing properties. A 2013 study showed that papain may be a natural remedy for constipation, bloating, and heartburn.⁵⁵ Other research has suggested that taking papain enzyme as a supplement may offer additional health benefits, including weight loss when combined with other medications such as glucagon-like peptide-1 (GLP-1) agonists.

Studies have shown that the aqueous fruit extract of *C. papaya* has anti-obesity effects in obese rats fed a high-fat diet.⁵⁶ The aqueous extract of its leaves also has anti-hyperglycemic and hypolipidemic activities in diabetic rats.⁵⁷ *C. papaya* is considered to help prevent and treat obesity and its associated metabolic disorders.⁵⁸ Additionally, it is used to treat inflammatory conditions and has anti-inflammatory effects. It is speculated that papain may be effective in reducing obesity-associated inflammation.⁵⁹

Lemon Balm (*Melissa Officinalis*) Whole Leaf Extract


Lemon balm leaf extract, also known as *Melissa officinalis*, is an herbal supplement known for its potential benefits in calming the nerves, supporting cognitive health, and reducing stress. It may also be effective at reducing indigestion and heartburn, according to one 2010 study.⁶⁰ It's also been shown to help reduce nausea in some people.⁶¹

Finally, lemon balm is believed to be helpful for regulating obesity and improving insulin sensitivity.⁶² Both of which can be beneficial for those with Type 2 Diabetes who are trying to lose weight while taking GLP-1 agonists.

Peppermint Leaf Powder (*Mentha Piperita*)

Peppermint leaf powder is a natural supplement derived from peppermint leaves and has been used for centuries to treat symptoms of nausea and indigestion. It contains menthol, which is thought to act on the digestive muscles, resulting in relaxation and improved digestion.⁶³ Studies show that it can even be useful for relieving symptoms of irritable bowel syndrome (IBS).⁶⁴ Additionally, multiple trials involving at least 2000 children found that peppermint relieved the frequency, duration, and severity of abdominal pain.⁶⁵

Peppermint may also be effective for reducing nausea as demonstrated in patients undergoing chemotherapy.⁶⁶



Lastly, peppermint leaf powder may reduce hunger cravings and improve appetite control, making it easier for individuals on GLP-1 agonists to stick to their weight loss regimens.⁶⁷

Organic Licorice Extract (Root)

Licorice extract is an herbal supplement derived from the root of the licorice plant that has a range of potential therapeutic benefits. Historically, it's been used to treat digestive disorders and may be a natural remedy for nausea.

Studies suggest that licorice extract may help alleviate symptoms of nausea, especially when combined with other treatments. For instance, one study found that combining licorice extract with ginger was more effective in treating nausea than either treatment alone.⁶⁸

Licorice also shows promise in treating symptoms of indigestion. In a clinical trial involving 50 adults with indigestion, taking a 75-mg licorice capsule twice daily for 30 days demonstrated significant symptom improvements when compared to a placebo.⁶⁹


Further research suggests that licorice root extract may have beneficial effects on symptoms of gastroesophageal reflux disease (GERD), such as acid reflux and heartburn. In a study conducted over 8 weeks with 58 adults suffering from GERD, the addition of a low dose of glycyrrhetic acid to standard treatment showed significant improvement in symptoms.⁷⁰ Another study involving 58 adults with GERD found that the daily consumption of licorice root proved to be more effective in reducing symptoms over a 2-year period compared to commonly used antacids.⁷¹

Recent research suggests that this herbal remedy may be beneficial for those using glucagon-like peptide-1 (GLP-1) agonists for weight loss, as it might help enhance the effects of these medications. GLP-1 agonists are hormones released by the gut when food is consumed. They help to regulate digestion and absorption of food and can reduce appetite and cravings.

Taking licorice extract in conjunction with GLP-1 agonists may enhance their effects, leading to improved digestion and better weight loss results. Additionally, licorice extract may help improve insulin sensitivity in those with Type 2 Diabetes who are taking GLP-1 agonists for weight loss.⁷²

Phosphatidylcholine

Phosphatidylcholine (PC), also known as lecithin, is a type of phospholipid found in cells throughout the body. It plays an important role in cell structure, as well as numerous other



physiological processes. Phosphatidylcholine is a significant regulator of lipids, lipoproteins, and whole-body energy metabolism. The depletion of PC in tissues can impact energy metabolism and has been associated with the progression of various diseases.

Low levels of PC have been linked to metabolic disorders such as atherosclerosis, insulin resistance, and obesity.⁷³

Phosphatidylcholine may also help aid in reducing fat deposits. A 2014 study found that injecting PC into a lipoma can result in the reduction of its fat cells and size.⁷⁴

Phosphatidylcholine was previously researched for its potential in treating metabolic abnormalities such as hypercholesterolemia and plaque buildup in vessels. Its effectiveness in these areas led to its use in treating localized fat deposits.

Gallstones are solid formations found in the gallbladder, typically composed of undissolved cholesterol or bilirubin. Gallstones are a rare yet possible side effect of using GLP-1 agonists for weight loss. If left unaddressed, they have the potential to obstruct bile ducts and result in significant discomfort or pancreatitis. A 2003 study discovered that PC supplementation decreased cholesterol gallstone formation in mice that were fed a high-cholesterol diet.⁷⁵ It was observed that an increase in PC levels corresponded with a decrease in cholesterol saturation levels.

Lactobacillus Gasseri

Lactobacillus gasseri is a type of probiotic bacteria that has been found to be beneficial for digestion and nausea by suppressing harmful bacteria in the gut.⁷⁶ *Lactobacillus gasseri* has also been found to reduce bloating and abdominal discomfort and improve digestion.⁷⁷ Additionally, it may help to reduce nausea associated with certain medications, such as GLP-1 agonists.

Are Supplements Safe To Take With GLP-1 Agonists?

In general, most supplements are considered safe when taken in recommended doses along with GLP-1 agonists. However, certain supplements may interact with the medication and should be avoided or taken in reduced doses. Supplements, foods, and beverages that contain caffeine, such as coffee, black tea, and green tea, may increase blood glucose levels when taken in large amounts and should be consumed in moderation if taken at all.

In addition, certain supplements may contain substances that can interfere with how GLP-1 agonists work in the body, so it is important to speak with a healthcare professional before taking any supplement if you are taking a GLP-1 agonist medication.



Who Should Consider Taking Supplements?

Supplements can be consumed by any adult individual experiencing side effects while taking GLP-1 agonists for weight loss. They can also be consumed by individuals who want to potentially increase the benefits and effects of GLP-1 agonist medications. Supplements are safe for most people and may be an inexpensive way to support their weight loss journey while taking GLP-1 agonists.

Conclusion

Semaglutide and tirzepatide are two of the most common GLP-1 agonist medications used in the treatment of metabolic disorders. These medications work alongside a weight loss management regimen that includes a low-calorie diet and regular physical activity. Results from both medications are significant but are not without pitfalls. Semaglutide and tirzepatide can cause negative side effects, particularly in the first few weeks of treatment.

Natural dietary supplements including vitamins, minerals, and herbs might provide numerous health benefits. They may also act as natural remedies for many negative side effects related to taking GLP-1 agonists. Additionally, dietary supplements, when taken as directed, might promote overall health and support weight loss efforts along with GLP-1 agonists.

References:

1. Adult Obesity | Obesity Prevention Source | Harvard T.H. Chan School of Public Health. (n.d.). Harvard T.H. Chan School of Public Health. Retrieved June 15, 2023, from <https://www.hsph.harvard.edu/obesity-prevention-source/obesity-trends-original/obesity-rates-worldwide/>
2. The \$76 Billion Diet Industry Asks: What to Do About Ozempic? (2023, April 10). The Wall Street Journal. Retrieved June 15, 2023, from <https://www.wsj.com/articles/ozempic-wegovy-mounjaro-weight-loss-industry-89419ecb>
3. Why Diet Drug Phen/Fen Damaged The Heart. (2000, December 15). ScienceDaily. Retrieved June 15, 2023, from <https://www.sciencedaily.com/releases/2000/12/001214081821.htm>
4. Nauck MA. Glucagon-like peptide 1 (GLP-1): a potent gut hormone with a possible therapeutic perspective. *Acta Diabetol.* 1998 Oct;35(3):117-29. doi: 10.1007/s005920050116. PMID: 9840447.
5. Wegovy® STEP 1 Clinical Trial Results | Wegovy® (semaglutide) Injection 2.4 mg. (n.d.). novoMEDLINK. Retrieved June 15, 2023, from <https://www.novomedlink.com/obesity/products/treatments/wegovy/efficacy-safety/clinical-trial-1-results.html>
6. Singh G, Krauthamer M, Bjalme-Evans M. Wegovy® (semaglutide): a new weight loss drug for chronic weight management. *J Investig Med.* 2022 Jan;70(1):5-13. doi: 10.1136/jim-2021-001952. Epub 2021 Oct 27. PMID: 34706925; PMCID: PMC8717485.
7. Ahrén B, Atkin SL, Charpentier G, Warren ML, Wilding JPH, Birch S, Holst AG, Leiter LA. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab.* 2018 Sep;20(9):2210-2219. doi: 10.1111/dom.13353. Epub 2018 Jun 12. PMID: 29766634; PMCID: PMC6099440.
8. Chavda VP, Ajabiya J, Teli D, Bojarska J, Apostolopoulos V. Tirzepatide, a New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Mini-Review. *Molecules.* 2022 Jul

5;27(13):4315. doi: 10.3390/molecules27134315. PMID: 35807558; PMCID: PMC9268041.

9.Zhang Q, Delessa CT, Augustin R, Bakhti M, Colldén G, Drucker DJ, Feuchtinger A, Caceres CG, Grandl G, Harger A, Herzig S, Hofmann S, Holleman CL, Jastroch M, Keipert S, Kleinert M, Knerr PJ, Kulaj K, Legutko B, Lickert H, Liu X, Luippold G, Lutter D, Malogajski E, Medina MT, Mowery SA, Blutke A, Perez-Tilve D, Salinno C, Seherer L, DiMarchi RD, Tschöp MH, Stemmer K, Finan B, Wolfrum C, Müller TD. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. *Cell Metab.* 2021 Apr 6;33(4):833-844.e5. doi: 10.1016/j.cmet.2021.01.015. Epub 2021 Feb 10. PMID: 33571454; PMCID: PMC8035082.

10.A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight - Full Text View. (n.d.). ClinicalTrials.gov. Retrieved June 15, 2023, from <https://www.clinicaltrials.gov/ct2/show/NCT04184622>.

11.FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes. (2022, May 13). FDA. Retrieved June 15, 2023, from <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes>.

12.Frias M.D., J. P. (2021, August 5). Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *The new england journal of medicine*. <https://www.nejm.org/doi/full/10.1056/NEJMoa2107519#:~:text=Nausea%20was%20reported%20in%2017,to%209%25%20and%205%25>.

13.Safety summary with warnings. Retrieved June 19, 2023, from <https://www.mounjaro.com/>

14.Tirzepatide (Subcutaneous Route) Side Effects. (2023, May 1). Mayo Clinic. Retrieved June 15, 2023, from <https://www.mayoclinic.org/drugs-supplements/tirzepatide-subcutaneous-route/side-effects/drg-20534045>

15.Hutchinson, P. (n.d.). Once-Weekly Semaglutide in Adults with Overweight or Obesity | NEJM. *New England Journal of Medicine*. Retrieved June 15, 2023, from

https://www.nejm.org/doi/10.1056/NEJMoa2032183?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed

16. Allué, J. (n.d.). The Effectiveness of Ginger in the Prevention of Nausea and Vomiting during Pregnancy and Chemotherapy. NCBI. Retrieved June 15, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818021/>

17. Mietlicki-Baase EG, Liberini CG, Workinger JL, Bonaccorso RL, Borner T, Reiner DJ, Koch-Laskowski K, McGrath LE, Lhamo R, Stein LM, De Jonghe BC, Holz GG, Roth CL, Doyle RP, Hayes MR. A vitamin B12 conjugate of exendin-4 improves glucose tolerance without associated nausea or hypophagia in rodents. *Diabetes Obes Metab*. 2018 May;20(5):1223-1234. doi: 10.1111/dom.13222. Epub 2018 Feb 20. PMID: 29327400; PMCID: PMC5899935.

18. Borner T, Shaulson ED, Tinsley IC, Stein LM, Horn CC, Hayes MR, Doyle RP, De Jonghe BC. A second-generation glucagon-like peptide-1 receptor agonist mitigates vomiting and anorexia while retaining glucoregulatory potency in lean diabetic and emetic mammalian models. *Diabetes Obes Metab*. 2020 Oct;22(10):1729-1741. doi: 10.1111/dom.14089. Epub 2020 Jun 25. PMID: 32410372; PMCID: PMC7927944.

19. Zheng Y, Cantley LC. Toward a better understanding of folate metabolism in health and disease. *J Exp Med*. 2019 Feb 4;216(2):253-266. doi: 10.1084/jem.20181965. Epub 2018 Dec 26. PMID: 30587505; PMCID: PMC6363433.

20. Hoepner CT, McIntyre RS, Papakostas GI. Impact of Supplementation and Nutritional Interventions on Pathogenic Processes of Mood Disorders: A Review of the Evidence. *Nutrients*. 2021 Feb 26;13(3):767. doi: 10.3390/nu13030767. PMID: 33652997; PMCID: PMC7996954.

21. Parra M, Stahl S, Hellmann H. Vitamin B₆ and Its Role in Cell Metabolism and Physiology. *Cells*. 2018 Jul 22;7(7):84. doi: 10.3390/cells7070084. PMID: 30037155; PMCID: PMC6071262.

22. Hsu CC, Cheng CH, Hsu CL, Lee WJ, Huang SC, Huang YC. Role of vitamin B6 status on antioxidant defenses, glutathione, and related enzyme activities in mice with homocysteine-induced oxidative stress. *Food Nutr Res*. 2015 Apr 29;59:25702. doi: 10.3402/fnr.v59.25702. PMID: 25933612; PMCID: PMC4417078.

- 23.Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. *Obstet Gynecol.* 1991 Jul;78(1):33-6. PMID: 2047064.
- 24.Kerns JC, Arundel C, Chawla LS. Thiamin deficiency in people with obesity. *Adv Nutr.* 2015 Mar 13;6(2):147-53. doi: 10.3945/an.114.007526. PMID: 25770253; PMCID: PMC4352173.
- 25.Mee L, Nabokina SM, Sekar VT, Subramanian VS, Maedler K, Said HM. Pancreatic beta cells and islets take up thiamin by a regulated carrier-mediated process: studies using mice and human pancreatic preparations. *Am J Physiol Gastrointest Liver Physiol.* 2009 Jul;297(1):G197-206. doi: 10.1152/ajpgi.00092.2009. Epub 2009 May 7. PMID: 19423748; PMCID: PMC2711754.
- 26.Page GL, Laight D, Cummings MH. Thiamine deficiency in diabetes mellitus and the impact of thiamine replacement on glucose metabolism and vascular disease. *Int J Clin Pract.* 2011 Jun;65(6):684-90. doi: 10.1111/j.1742-1241.2011.02680.x. PMID: 21564442.
- 27.Li H, Xu H, Wen W, Wu L, Xu M, Luo J. Thiamine Deficiency Causes Long-Lasting Neurobehavioral Deficits in Mice. *Brain Sci.* 2020 Aug 17;10(8):565. doi: 10.3390/brainsci10080565. PMID: 32824629; PMCID: PMC7464042.
- 28.Dinicolantonio JJ, Lavie CJ, Niazi AK, O'Keefe JH, Hu T. Effects of thiamine on cardiac function in patients with systolic heart failure: systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials. *Ochsner J.* 2013 Winter;13(4):495-9. PMID: 24357996; PMCID: PMC3865826.
- 29.Suksomboon N, Poolsup N, Yuwanakorn A. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. *J Clin Pharm Ther.* 2014 Jun;39(3):292-306. doi: 10.1111/jcpt.12147. Epub 2014 Mar 17. PMID: 24635480.
- 30.Pei D, Hsieh CH, Hung YJ, Li JC, Lee CH, Kuo SW. The influence of chromium chloride-containing milk to glycemic control of patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Metabolism.* 2006 Jul;55(7):923-7. doi: 10.1016/j.metabol.2006.02.021. PMID: 16784965.
- 31.Cefalu WT, Rood J, Pinsonat P, Qin J, Sereda O, Levitan L, Anderson RA, Zhang XH, Martin JM, Martin CK, Wang ZQ, Newcomer B. Characterization of the metabolic

and physiologic response to chromium supplementation in subjects with type 2 diabetes mellitus. *Metabolism*. 2010 May;59(5):755-62. doi: 10.1016/j.metabol.2009.09.023. Epub 2009 Dec 22. PMID: 20022616; PMCID: PMC4020630.

32. Chromium | The Nutrition Source | Harvard T.H. Chan School of Public Health. (n.d.). Harvard T.H. Chan School of Public Health. Retrieved June 15, 2023, from <https://www.hsph.harvard.edu/nutritionsource/chromium/>

33. Anton SD, Morrison CD, Cefalu WT, Martin CK, Coulon S, Geiselman P, Han H, White CL, Williamson DA. Effects of chromium picolinate on food intake and satiety. *Diabetes Technol Ther*. 2008 Oct;10(5):405-12. doi: 10.1089/dia.2007.0292. PMID: 18715218; PMCID: PMC2753428.

34. Zozina VI, Covantev S, Goroshko OA, Krasnykh LM, Kukes VG. Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem. *Curr Cardiol Rev*. 2018;14(3):164-174. doi: 10.2174/1573403X14666180416115428. PMID: 29663894; PMCID: PMC6131403.

35. Drobic F, Lizarraga MA, Caballero-García A, Cordova A. Coenzyme Q10 Supplementation and Its Impact on Exercise and Sport Performance in Humans: A Recovery or a Performance-Enhancing Molecule? *Nutrients*. 2022 Apr 26;14(9):1811. doi: 10.3390/nu14091811. PMID: 35565783; PMCID: PMC9104583.

36. Jorat MV, Tabrizi R, Mirhosseini N, Lankarani KB, Akbari M, Heydari ST, Mottaghi R, Asemi Z. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis*. 2018 Oct 9;17(1):230. doi: 10.1186/s12944-018-0876-4. PMID: 30296936; PMCID: PMC6176512.

37. Zhao X, Feng X, Ye N, Wei P, Zhang Z, Lu W. Protective effects and mechanism of coenzyme Q10 and vitamin C on doxorubicin-induced gastric mucosal injury and effects of intestinal flora. *Korean J Physiol Pharmacol*. 2021 Jul 1;25(4):261-272. doi: 10.4196/kjpp.2021.25.4.261. PMID: 34187945; PMCID: PMC8255120.

38. Farsi F, Ebrahimi-Daryani N, Barati M, Janani L, Karimi MY, Akbari A, Irandoost P, Mesri Alamdari N, Agah S, Vafa M. Effects of coenzyme Q10 on health-related quality of life, clinical disease activity and blood pressure in patients with mild to moderate

ulcerative colitis: a randomized clinical trial. *Med J Islam Repub Iran*. 2021 Jan 6;35:3. doi: 10.47176/mjiri.35.3. PMID: 33996654; PMCID: PMC8111632.

39. Magnesium - Health Professional Fact Sheet. (2022, June 2). NIH Office of Dietary Supplements. Retrieved June 15, 2023, from <https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#en1>

40. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses*. 2006;67(2):362-70. doi: 10.1016/j.mehy.2006.01.047. Epub 2006 Mar 20. PMID: 16542786.

41. Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? *Rheumatol Int*. 2013 Jan;33(1):167-72. doi: 10.1007/s00296-011-2334-8. Epub 2012 Jan 22. PMID: 22271372.

42. Mori H, Tack J, Suzuki H. Magnesium Oxide in Constipation. *Nutrients*. 2021 Jan 28;13(2):421. doi: 10.3390/nu13020421. PMID: 33525523; PMCID: PMC7911806.

43. Guerrero MP, Volpe SL, Mao JJ. Therapeutic uses of magnesium. *Am Fam Physician*. 2009 Jul 15;80(2):157-62. PMID: 19621856.

44. Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. *Diabetes Care*. 2011 Sep;34(9):2116-22. doi: 10.2337/dc11-0518. PMID: 21868780; PMCID: PMC3161260.

45. Marcin, J. (n.d.). What Is Sodium Chloride and How Is It Used? Healthline. Retrieved June 15, 2023, from <https://www.healthline.com/health/sodium-chloride>

46. Ames RP. The effect of sodium supplementation on glucose tolerance and insulin concentrations in patients with hypertension and diabetes mellitus. *Am J Hypertens*. 2001 Jul;14(7 Pt 1):653-9. doi: 10.1016/s0895-7061(01)01310-3. PMID: 11465650.

47. Chatterjee R, Biggs ML, de Boer IH, et al. Potassium and glucose measures in older adults: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci*. 2015;70(2):255-261. doi:10.1093/gerona/glu071

48. Tal B, Sack J, Yaron M, Shefer G, Buch A, Ben Haim L, Marcus Y, Shenkerman G, Sofer Y, Shefer L, Margalioth M, Stern N. Increment in Dietary Potassium Predicts Weight Loss in the Treatment of the Metabolic Syndrome. *Nutrients*. 2019 Jun 2;11(6):1256. doi: 10.3390/nu11061256. PMID: 31159504; PMCID: PMC6627830.
49. Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. *Food Sci Nutr*. 2018 Nov 5;7(1):96-108. doi: 10.1002/fsn3.807. PMID: 30680163; PMCID: PMC6341159.
50. Salaramoli S, Mehri S, Yarmohammadi F, Hashemy SI, Hosseinzadeh H. The effects of ginger and its constituents in the prevention of metabolic syndrome: A review. *Iran J Basic Med Sci*. 2022 Jun;25(6):664-674. doi: 10.22038/IJBMS.2022.59627.13231. PMID: 35949312; PMCID: PMC9320212.
51. Li Y, Tran VH, Kota BP, Nammi S, Duke CC, Roufogalis BD. Preventative effect of *Zingiber officinale* on insulin resistance in a high-fat high-carbohydrate diet-fed rat model and its mechanism of action. *Basic Clin Pharmacol Toxicol*. 2014;115:209–215.
52. Samad MB, Mohsin M, Razu BA, Hossain MT, Mahzabeen S, Unnoor N, et al. [6]-Gingerol, from *Zingiber officinale*, potentiates GLP-1 mediated glucose-stimulated insulin secretion pathway in pancreatic beta-cells and increases RAB8/RAB10-regulated membrane presentation of GLUT4 transporters in skeletal muscle to improve hyperglycemia in *Lepr(db/db)* type 2 diabetic mice. *BMC Complement Altern Med*. 2017;17:395
53. Chakraborty AJ, Mitra S, Tallei TE, Tareq AM, Nainu F, Cicia D, Dhama K, Emran TB, Simal-Gandara J, Capasso R. Bromelain a Potential Bioactive Compound: A Comprehensive Overview from a Pharmacological Perspective. *Life (Basel)*. 2021 Apr 6;11(4):317. doi: 10.3390/life11040317. PMID: 33917319; PMCID: PMC8067380.
54. Properties and Therapeutic Application of Bromelain: A Review. (2012, December 10). Hindawi. Retrieved June 15, 2023, from <https://www.hindawi.com/journals/btri/2012/976203/>
55. Muss C, Mosgoeller W, Endler T. Papaya preparation (Caricol®) in digestive disorders. *Neuro Endocrinol Lett*. 2013;34(1):38-46. PMID: 23524622.

56. Athesh K., Karthiga D., Brindha P. Anti-obesity effect of aqueous fruit extract of *Carica papaya* L. in rats fed on high fat cafeteria diet. *Int. J. Pharm. Pharm. Sci.* 2012;4:327–330
57. Maniyar Y., Bhisavathimath P. Antihyperglycemic and hypolipidemic activities of aqueous extract of *Carica papaya* Linn. leaves in alloxan-induced diabetic rats. *J. Ayurveda Integr. Med.* 2012;3:70–74. doi: 10.4103/0975-9476.96519
58. Santana L.F., Inada A.C., Espirito Santo B., Filiu W.F.O., Pott A., Alves F.M., Guimaraes R.C.A., Freitas K.C., Hiane P.A. Nutraceutical Potential of *Carica papaya* in Metabolic Syndrome. *Nutrients.* 2019;11:1608. doi: 10.3390/nu11071608.
59. Adedapo A., Orherhe V. Anti-nociceptive and anti-inflammatory studies of the aqueous leaf extract of *Carica papaya* in laboratory animals. *Asian J. Exp. Biol. Sci.* 2013;4:89–96.
60. Gasbarrini G, Zaccone V, Covino M, Gallo A. Effectiveness of a "cold dessert", with or without the addition of a mixture of digestive herbs, in subjects with "functional dyspepsia". *J Biol Regul Homeost Agents.* 2010 Jan-Mar;24(1):93-8. PMID: 20385075.
61. Ulbricht, Catherine & Brendler, Thomas & Gruenwald, Joerg & Kligler, Benjamin & Keifer, David & Abrams, Tracee & Woods, Jen & Boon, Heather & Kirkwood, Catherine & Hackman, Dana & Basch, Ethan & Lafferty, Heather. (2005). Lemon balm (*Melissa officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *Journal of herbal pharmacotherapy.* 5. 71-114.
62. Lee D, Shin Y, Roh JS, Ahn J, Jeong S, Shin SS, Yoon M. Lemon Balm Extract ALS-L1023 Regulates Obesity and Improves Insulin Sensitivity via Activation of Hepatic PPAR α in High-Fat Diet-Fed Obese C57BL/6J Mice. *Int J Mol Sci.* 2020 Jun 15;21(12):4256. doi: 10.3390/ijms21124256. PMID: 32549364; PMCID: PMC7352304.
63. Silva H. A Descriptive Overview of the Medical Uses Given to *Mentha* Aromatic Herbs throughout History. *Biology (Basel).* 2020 Dec 21;9(12):484. doi: 10.3390/biology9120484. PMID: 33371310; PMCID: PMC7767097.
64. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol.* 2014 Jul;48(6):505-12. doi: 10.1097/MCG.0b013e3182a88357. PMID: 24100754.

65. Anheyer D, Frawley J, Koch AK, Lauche R, Langhorst J, Dobos G, Cramer H. Herbal Medicines for Gastrointestinal Disorders in Children and Adolescents: A Systematic Review. *Pediatrics*. 2017 Jun;139(6):e20170062. doi: 10.1542/peds.2017-0062. Epub 2017 May 4. PMID: 28562281.
66. Efe Ertürk N, Taşcı S. The Effects of Peppermint Oil on Nausea, Vomiting and Retching in Cancer Patients Undergoing Chemotherapy: An Open Label Quasi-Randomized Controlled Pilot Study. *Complement Ther Med*. 2021 Jan;56:102587. doi: 10.1016/j.ctim.2020.102587. Epub 2020 Oct 9. PMID: 33197662.
67. Papathanasopoulos A, Rotondo A, Janssen P, Boesmans W, Farré R, Vanden Berghe P, Tack J. Effect of acute peppermint oil administration on gastric sensorimotor function and nutrient tolerance in health. *Neurogastroenterol Motil*. 2013 Apr;25(4):e263-71. doi: 10.1111/nmo.12102. Epub 2013 Mar 12. PMID: 23489975.
68. Volqvartz T, Vestergaard AL, Aagaard SK, Andreasen MF, Lesnikova I, Uldbjerg N, Larsen A, Bor P. Use of alternative medicine, ginger and licorice among Danish pregnant women - a prospective cohort study. *BMC Complement Altern Med*. 2019 Jan 5;19(1):5. doi: 10.1186/s12906-018-2419-y. PMID: 30611269; PMCID: PMC6320632.
69. Raveendra KR, Jayachandra, Srinivasa V, Sushma KR, Allan JJ, Goudar KS, Shivaprasad HN, Venkateshwarlu K, Geetharani P, Sushma G, Agarwal A. An Extract of *Glycyrrhiza glabra* (GutGard) Alleviates Symptoms of Functional Dyspepsia: A Randomized, Double-Blind, Placebo-Controlled Study. *Evid Based Complement Alternat Med*. 2012;2012:216970. doi: 10.1155/2012/216970. Epub 2011 Jun 16. PMID: 21747893; PMCID: PMC3123991.
70. Di Pierro F, Gatti M, Rapacioli G, Ivaldi L. Outcomes in patients with nonerosive reflux disease treated with a proton pump inhibitor and alginic acid ± glycyrrhetic acid and anthocyanosides. *Clin Exp Gastroenterol*. 2013;6:27-33. doi: 10.2147/CEG.S42512. Epub 2013 Mar 27. PMID: 23569394; PMCID: PMC3615700.
71. Setright, R. (2017). Prevention of symptoms of gastric irritation (GERD) using two herbal formulas: An observational study. *Journal of the Australian Traditional-Medicine Society*, 23(2), 68–71. <https://search.informit.org/doi/10.3316/informit.950298610899394>

72. Alizadeh M, Namazi N, Mirtaheri E, Sargheini N, Kheirouri S. Changes of Insulin Resistance and Adipokines Following Supplementation with Glycyrrhiza Glabra L. Extract in Combination with a Low-Calorie Diet in Overweight and Obese Subjects: a Randomized Double Blind Clinical Trial. *Adv Pharm Bull.* 2018 Mar;8(1):123-130. doi: 10.15171/apb.2018.015. Epub 2018 Mar 18. PMID: 29670847; PMCID: PMC5896387.
73. Van der Veen JN, Kennelly JP, Wan S, Vance JE, Vance DE, Jacobs RL. The critical role of phosphatidylcholine and phosphatidylethanolamine metabolism in health and disease. *Biochim Biophys Acta Biomembr.* 2017 Sep;1859(9 Pt B):1558-1572. doi: 10.1016/j.bbamem.2017.04.006. Epub 2017 Apr 11. PMID: 28411170.
74. Amber KT, Ovadia S, Camacho I. Injection therapy for the management of superficial subcutaneous lipomas. *J Clin Aesthet Dermatol.* 2014 Jun;7(6):46-8. PMID: 25013540; PMCID: PMC4086534.
75. Phosphatidylcholine-enriched diet prevents gallstone formation in mice susceptible to cholelithiasis. (2003, July 1). *Journal of Lipid Research.* Retrieved June 15, 2023, from [https://www.jlr.org/article/S0022-2275\(20\)31947-7/fulltext](https://www.jlr.org/article/S0022-2275(20)31947-7/fulltext)
76. Pan M, Hidalgo-Cantabrana C, Goh YJ, Sanozky-Dawes R, Barrangou R. Comparative analysis of *Lactobacillus gasseri* and *Lactobacillus crispatus* isolated from human urogenital and gastrointestinal tracts. *Front Microbiol.* 2020;10:3146. doi:10.3389/fmicb.2019.03146
77. Shahram Agah, Abolfazl Akbari, Javad Heshmati, Mahdi Sepidarkish, Mojgan Morvaridzadeh, Payman Adibi, Mohsen Mazidi, Farnaz Farsi, Richard Ofori-Asenso, Nicholas J. Talley, Christine Feinle-Bisset, Systematic review with meta-analysis: Effects of probiotic supplementation on symptoms in functional dyspepsia, *Journal of Functional Foods*, Volume 68, 2020, 103902, ISSN 1756-4646, <https://doi.org/10.1016/j.jff.2020.103902>. (<https://www.sciencedirect.com/science/article/pii/S1756464620301262>)
78. Nauck, M.A., D'Alessio, D.A. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regarding glycaemic control and body weight reduction. *Cardiovasc Diabetol* 21, 169 (2022). <https://doi.org/10.1186/s12933-022-01604-7>