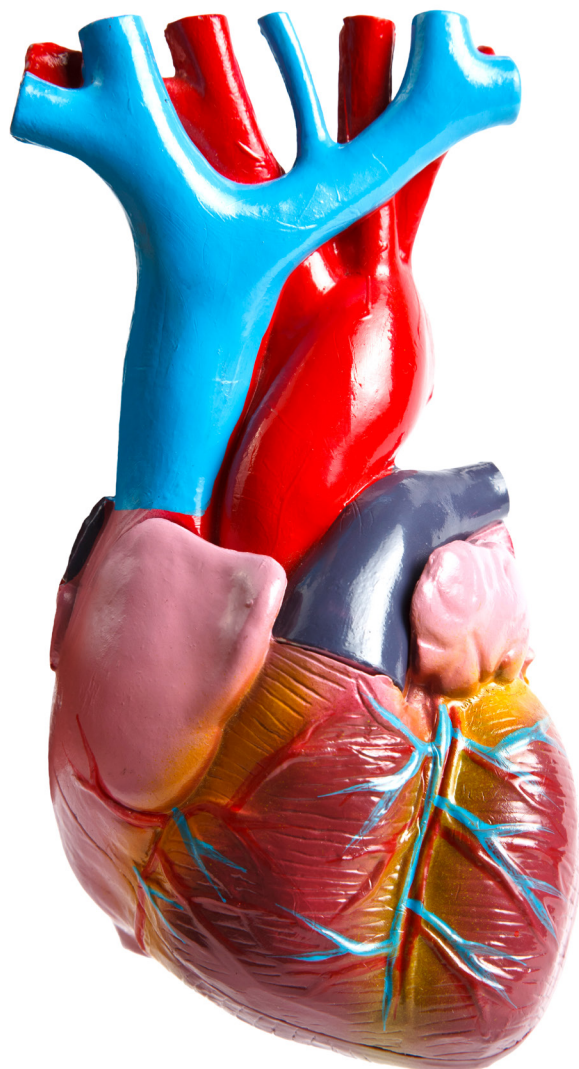# Can magnesium supplementation reduce cardiovascular disease risk factors in people with diabetes?

Effect of magnesium supplementation on type 2 diabetes associated cardiovascular risk factors: a systematic review and meta-analysis. 🔗
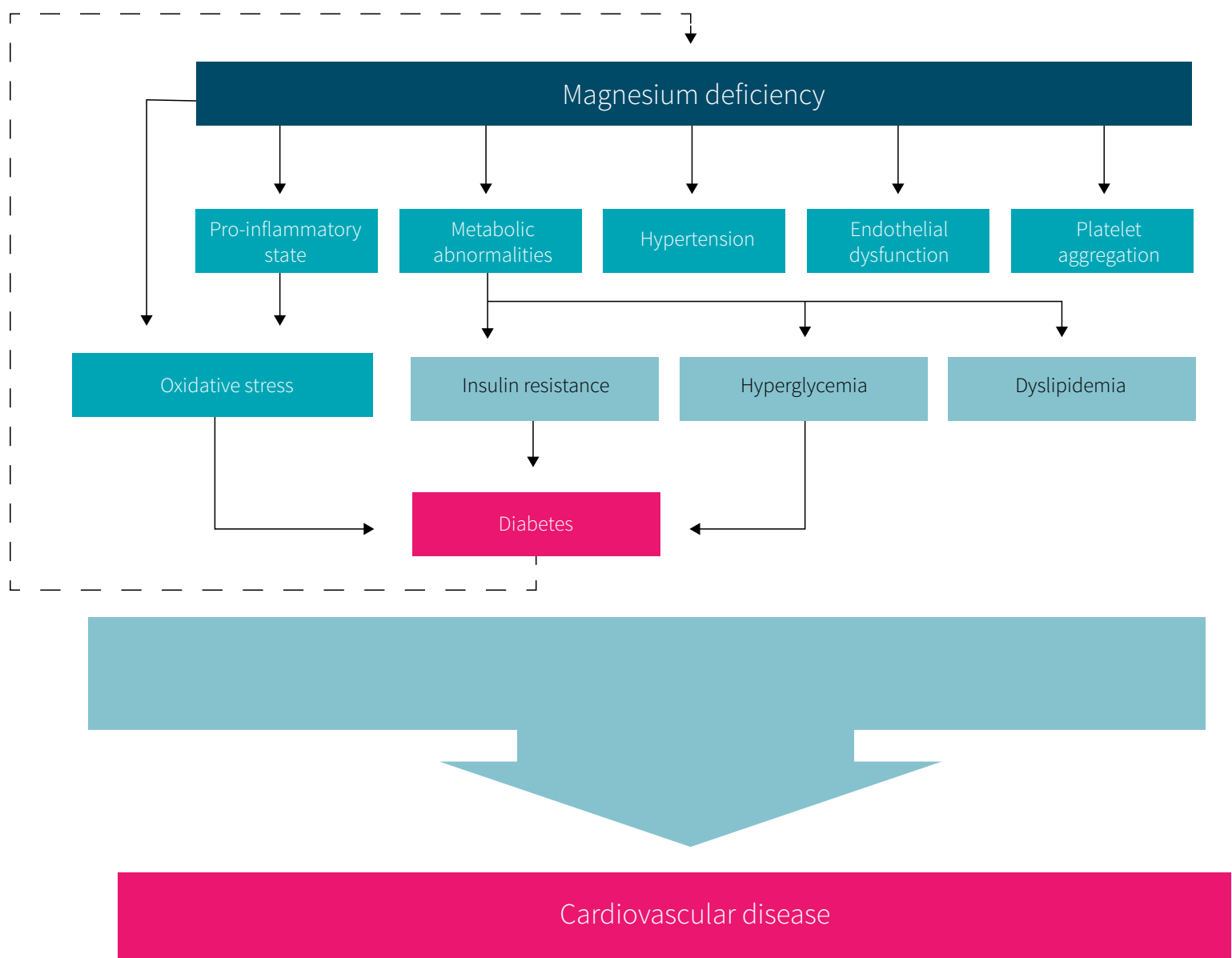
Introduction

Diabetes has rapidly become one the most [prevalent](#) preventable diseases worldwide. It substantially [increases](#) a person's risk of developing cardiovascular disease (CVD), which is the [leading cause](#) of death among people with diabetes.

Magnesium is an essential mineral [involved](#) with the function of over 300 enzymes, including those involved in glucose metabolism and insulin signaling and function. Since magnesium plays a role in so many metabolic processes, it's quite possible that deficiency could impact both type 2 diabetes and CVD. The potential extent of magnesium's effects on CVD and diabetes is laid out in Figure 1.

There's more evidence for magnesium's potential impact in these areas beyond arguments from mechanism, though. Observational studies have found associations between developing type 2 diabetes and having low [serum magnesium](#) or low [dietary intake](#), and [experimental](#) [trials](#) in animals have suggested that consuming magnesium-deficient diets causes insulin resistance. A [meta-analysis](#) of 40 observational studies and over one million people reported that increased dietary magnesium intake was associated with significant reductions in the risk of developing type 2 diabetes, heart failure, and stroke, and a near-significant reduction in developing heart disease. Due to the relationship between diabetes, magnesium intake, and CVD, numerous randomized controlled trials have investigated whether magnesium supplementation can reduce CVD risk factors in people with type 2 diabetes.

Figure 1: Role of magnesium in diabetes and cardiovascular disease

Reference: Bo et al. Curr Opin Lipidol. 2008 Feb.

Two previous meta-analyses have investigated the effects of magnesium supplementation on glycemic control in people with type 2 diabetes. However, one of these meta-analyses did not look at magnesium's effect on other CVD risk factors, while the long-term effects of supplementation in the other were uncertain. The study under review sought to fill this gap in the research by performing a meta-analysis of randomized controlled trials investigating the effects of magnesium supplementation on CVD risk factors associated with type 2 diabetes.

People with diabetes have an increased risk of developing cardiovascular disease. Magnesium levels are lower in people with type 2 diabetes and it has been hypothesized that supplementing with magnesium may help lower these cardiovascular risk factors. The study under review is a meta-analysis of randomized controlled trials investigating the effects of magnesium supplementation on CVD risk factors in people with type 2 diabetes.

Who and what was studied?

The present study is a systematic review and meta-analysis examining the effect of magnesium supplementation on CVD risk factors in people with type 2 diabetes. The authors outlined strict search criteria based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Eligible studies had to be randomized controlled trials with a duration of at least one month and involving adults with type 2 diabetes or at a high risk of developing type 2 diabetes (e.g., having prediabetes or obesity).

Ultimately, 28 studies contributing 1,694 participants were included in this meta-analysis. The average age of the study participants ranged from 28-84 years, but most involved middle-aged or elderly adults. The average dose of elemental magnesium was 384 milli-

grams per day (ranging from 31-1006 milligrams per day) and the average treatment duration was 12 weeks (with a range of four to 24 weeks). Various forms of magnesium salts were used, including pidolate, lactate, chloride, citrate, aspartate, oxide, and sulfate.
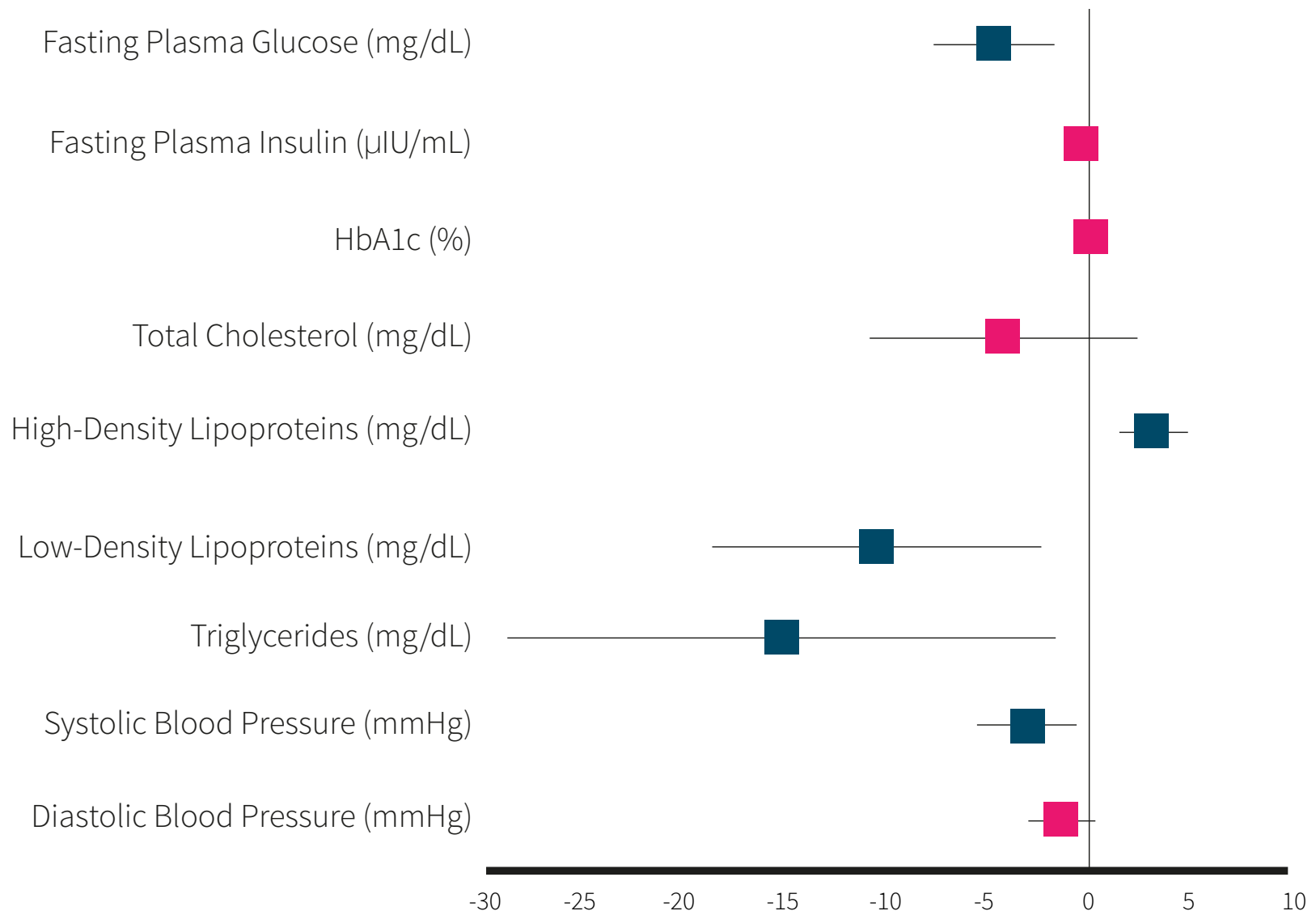
No primary outcomes were specified. Outcomes of interest included fasting plasma glucose (n=27 studies), fasting insulin (n=15), HbA1c (n=14), total cholesterol (n=15), LDL-C (n=12), HDL-C (n=20), triglycerides (n=21), and blood pressure (n=19). Subgroup analyses were performed between people with and without type 2 diabetes, people with normal and low magnesium status, studies lasting less than and longer than three months, and studies using organic and inorganic magnesium salts. Additionally, a meta-regression was performed to assess how the dose of magnesium and duration of supplementation affected the results.

This meta-analysis of 28 studies investigated the effect of magnesium supplementation for at least one month on fasting glucose and insulin, HbA1c, blood lipids, and blood pressure in adults with type 2 diabetes or at a high risk for developing type 2 diabetes (e.g., having prediabetes or obesity). The average dose of magnesium was 384 milligrams per day and the average treatment duration was 12 weeks.

What were the findings?

The main results are summarized in Figure 2. Overall, magnesium supplementation significantly improved fasting plasma glucose (-4.6 mg/dL), HDL-C (+3.2 mg/dL), LDL-C (-10.7 mg/dL), triglycerides (-15.3 mg/dL), and systolic blood pressure (-3.05 mm Hg), but had no effect on fasting insulin, HbA1c, total cholesterol, or diastolic blood pressure. All outcomes were robust and not overly influenced by any single study, but all demonstrated significant levels of interstudy variability (heterogeneity).

Figure 2: Summary of study findings

Fasting Plasma Glucose (mg/dL)

Fasting Plasma Insulin (μIU/mL)

HbA1c (%)

Total Cholesterol (mg/dL)

High-Density Lipoproteins (mg/dL)

Low-Density Lipoproteins (mg/dL)

Triglycerides (mg/dL)

Systolic Blood Pressure (mmHg)

Diastolic Blood Pressure (mmHg)

-30 -25 -20 -15 -10 -5 0 5 10

Subgroup analyses suggested that people with type 2 diabetes experienced greater improvements in fasting glucose (-6 vs -3 mg/dL), HDL-C (+3.3 vs +2.9 mg/dL), LDL-C (-16 vs -3 mg/dL), and triglycerides (-18 vs -9 mg/dL) than people without diabetes. When the participants were stratified into normal levels of magnesium or low levels of magnesium, the findings held for people with low levels of magnesium; however, only the benefit on HDL-C remained in people with normal levels of magnesium. Studies lasting longer than three months showed greater benefits for fasting glucose and triglycerides compared to studies of a shorter duration, but showed worse outcomes for HDL-C and LDL-C. Inorganic salts resulted in superior benefits to organic salts for fasting glucose and HDL-C.

The meta-regression revealed that increasing magnesium dose was associated with greater reductions in all outcomes except for fasting insulin, HbA1c, or systolic blood pressure. Longer supplementation periods were associated with greater reductions in fasting plasma glucose only. Publication bias was present for triglycerides only, but correction for this with the trim and fill method suggested the results were robust.

Magnesium supplementation lowered fasting plasma glucose, LDL-C, triglycerides, systolic blood pressure, and diastolic blood pressure, and raised HDL-C. While these effects were statistically significant, many of them were small improvements and all demonstrated significant heterogeneity. The improvements appeared to be more pronounced in people with type 2 diabetes and when larger doses of magnesium were used. Fasting insulin, HbA1c, and total cholesterol remained largely unaffected in the full and subgroup analyses.

What's the difference between blood and plasma?

Notice that we mentioned "fasting plasma glucose". Why didn't we just say "fasting blood glucose"? We didn't do this because we're trying to be fancy. It is because they are different things and matter to this study. Blood is made up several things which are referred to as blood components, which are things like plasma, red blood cells, white blood cells, and platelets. Plasma refers to the liquid part of the blood that is left after one separates the red blood cells, white blood cells, and platelets from the rest of the blood. Blood glucose levels are what's often read by finger sticks, although some modern glucose meters can report estimates of plasma glucose so that these values can be more easily compared to plasma glucose levels measured by doctors. Plasma glucose reports a roughly 11-12% higher value than whole blood and can differ a lot from whole blood levels at an individual level.

What does this study really tell us?

There are well established mechanisms through which magnesium regulates insulin sensitivity, along with a myriad of other biological processes. People with diabetes often have lower blood levels of magnesium than their healthy counterparts, and it is possible that magnesium deficiency (or insufficiency) might contribute to the elevated risk for cardiovascular disease seen in people with diabetes. The data presented in the current meta-analysis from 28 studies suggests that magnesium supplementation improves several cardiovascular disease risk factors commonly elevated in people with diabetes, including fasting plasma glucose, HDL-C, triglycerides, LDL-C, and systolic blood pressure.

While methodologically sound, there are several limitations to this meta-analysis. First, the study examined risk factors of CVD, not its actual development. Using trials that observed actual CVD development would have made for stronger evidence that magnesium supplementation affects the risk of disease. But it would have also made the meta-analysis impossible to perform since, to our knowledge, no clinical trials examining the effect of magnesium on actual CVD events exist. This is understandable, since clinical trials have to last a pretty long time in order to observe enough cardiovascular events to make them worth doing. And long trials are pretty expensive, which explains the dearth of these types of studies.

Another limitation of this meta-analysis has to do with the clinical trials included in it. Fewer than 40% of the individual studies for nearly all outcomes demonstrated a significant benefit, possibly due to low sample sizes. Also, all outcomes had significant levels of heterogeneity, which suggests that there were large differences in study populations, interventions, and study designs. This raises the question of whether there's some "apples-to-oranges" comparison going on in the meta-analysis, and that the exact numbers obtained for the effects of magnesium should be taken with a grain of salt.

Another reason why the exact effect sizes found here should be interpreted cautiously is because of the possible influence of outliers. The meta-analysis found that magnesium supplementation lowered fasting plasma glucose by about 4.6 mg/dL However, this average effect size was influenced by two big outliers: one study

reported a 30.6 mg/dL lower fasting plasma glucose, while another study reported 41.4 mg/dL lower fasting plasma glucose in the magnesium supplemented group. These data points likely impacted the estimated effect of magnesium on glucose levels, making the drop larger than it otherwise would have been. To put the size of this effect into context, randomized controlled trials examining the effect of SGLT-2 inhibitors, insulin therapy, and metformin (current standard of care therapies) report reductions of between 10 mg/dL and 40 mg/dL. This suggests that the extreme values reported in these two studies may be outliers and led to an overestimate in magnesium's impact on glucose levels.

However, if we do take the effects found in this study at face value, what kind of impact would these changes make on disease risk? An 18 mg/dL drop in fasting plasma glucose reduces the risk by about 23% and each 88 mg/dL increase in plasma triglycerides increases the relative risk of cardiovascular disease by 14% for men and 37% for women. Compare this to the approximate 5 mg/dL drop in glucose and the 15.3 mg/dL fall in triglycerides, and there's probably some lowering of CVD risk, but it'd be pretty small. That's not too surprising, given that the effects of magnesium on glucose, triglycerides, and cholesterol are smaller than the effect of current standard of care therapeutics. Metformin has been shown to lower blood glucose up to 50 mg/dL and HbA1c by about 1% (and recall that magnesium didn't affect A1c). Statin therapy has been shown lower LDL-C by about 20 mg/dL (versus the ~10 mg/dL drop seen with magnesium), and fenofibrate therapy have been shown to lower triglycerides by about 130 mg/dL (versus the mild ~15 mg/dL drop magnesium yielded). Thus, if magnesium does impact CVD risk, the overall risk reduction would be small, and doesn't come anywhere close to current pharmaceutical therapies. So, magnesium supplementation may be a good adjunct to standard treatments, but it certainly won't be able to replace them.

The findings of the current study are most applicable to people with type 2 diabetes, particularly those who have low levels of serum magnesium. As suggested by the subgroup analysis, the effects of magnesium supplementation may not improve these markers in people with normal levels of magnesium or who don't have type 2 diabetes.

In people with type 2 diabetes and a magnesium deficiency, supplementing with magnesium may beneficially impact fasting plasma glucose, LDL-C, HDL-C, and systolic blood pressure. However, the impact on glucose levels may be overstated due to extreme values reported in two of the studies. Additionally, the effects are relatively small compared to standard pharmaceutical therapy; magnesium supplementation should not be considered a replacement for standard care.

The big picture

Diabetes substantially increases the risk for developing CVD through metabolic and hemodynamic changes associated with the development of type 2 diabetes. Elevated fasting plasma glucose, fasting plasma insulin, blood lipids, and blood pressure are the main risk factors that predict the development of CVD in people with diabetes. Magnesium, which intrinsically linked to metabolism and often deficient in people with type 2 diabetes, has been hypothesized to play a role as a therapeutic intervention to reduce many of these risk factors. The current study showed that magnesium supplementation appears to have small, beneficial effects on glucose, lipids, and systolic blood pressure in people with type 2 diabetes.

What the current study didn't show is by what mechanisms magnesium may affect these parameters. Mechanistically speaking, magnesium may influence

glucose levels in at least two ways: by affecting insulin signalling and by influencing insulin production. Magnesium can also affect lipid metabolism, and has been shown to directly suppress postprandial hyperlipidemia. It is also a direct cofactor for the enzyme lipoprotein lipase, suggesting a deficiency may also directly affect cholesterol metabolism. Magnesium conveys direct antihypertensive properties by lowering vascular resistance, and magnesium can be used in addition to antihypertensive medications such as angiotensin II receptor blockers.

Beyond reducing cardiovascular risk factors, magnesium may have additional benefits on mental health. Higher rates of depression are observed in people with type 2 diabetes and low levels of magnesium have been linked to diabetes-associated depression. In a study of elderly people with type 2 diabetes, magnesium supplementation was found to be as effective as pharmaceutical antidepressants for improving symptoms of depression. For more on magnesium's effect on depression, check out ERD 29, volume 1 where we cover that aspect of magnesium's effects in a little more detail.

Magnesium works at a molecular level to directly regulate glucose and lipid metabolism as well as blood pressure. Supplementation conveys a small benefit in these areas in people with diabetes. Additionally, magnesium may have antidepressant effects in people with diabetes.
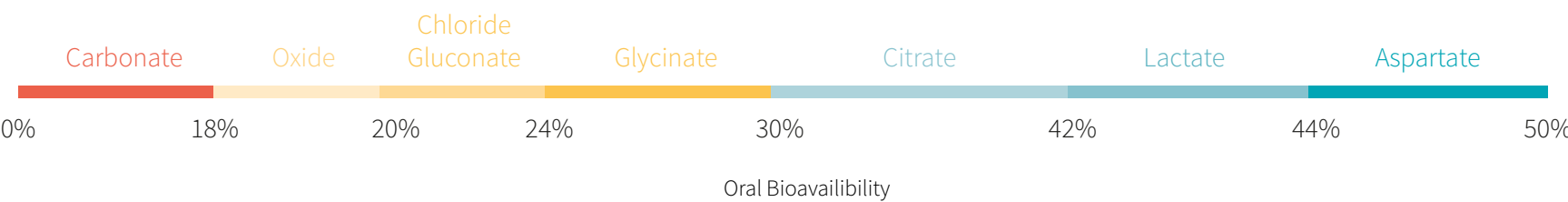

Frequently asked questions

What are other supplements with promising evidence for reducing CVD risk factors in type 2 diabetes?

There is some promising evidence for the use of cinnamon for reducing CVD risk factors in type 2 diabetes. One meta-analysis showed that supplementing with cinnamon had an almost identical effect as the one found in the present study, in that it reduced fasting plasma glucose, low-density lipoproteins, and triglycerides while also increasing high-density lipoproteins. The second meta-analysis only examined blood glucose but also showed that cinnamon lowered blood glucose. However, cinnamon's efficacy is not a closed case. As we mentioned in ERD issue 36, volume 2's *Blood Sugar and Spice*, a 2012 Cochrane review found no firm evidence that cinnamon helped with glycemic control, and noted that the overall quality of evidence is poor. While cinnamon does hold some promise, higher quality evidence is still needed to make a definitive call on its efficacy.

What are the different forms of magnesium and which ones are more bioavailable?

The three most common forms of magnesium found in magnesium supplements are magnesium oxide, magnesium citrate, and amino acid bound magnesium (e.g., L-aspartate). Magnesium oxide has bioavailability ranging from 5-10% while magnesium citrate displays 25-30% bioavailability. Magnesium bound to amino acids show slightly less bioavailability than magnesium citrate. The bioavailability of different magnesium salts is shown in Figure 3.

Figure 3: Oral bioavailability of various magnesium salts in humans

Carbonate	Oxide	Chloride / Gluconate	Glycinate	Citrate	Lactate	Aspartate
0%	18%	20%	24%	30%	42%	44% — 50%

Oral Bioavailibility

Reference: Ranade et al. Am J Ther. 2007 Sep-Oct.

What should I know?

Magnesium plays an important part of maintaining normal homeostatic metabolism. Magnesium deficiency is present in many people with type 2 diabetes and likely contributes to the altered metabolic milieu present in this disease that increases the risk for CVD. This raises the question of whether magnesium supplementation could alter CVD risk factors in this population.

This study was a meta-analysis of 29 randomized controlled trials. It found that supplementing with magnesium likely conveys a small benefit on serum glucose, blood lipids, and blood pressure in people with type 2 diabetes and a magnesium deficiency. Effects outside of this population were weaker to nonexistent. Magnesium supplementation, while helpful, did not have nearly as large an effect on CVD risk markers as pharmaceuticals, suggesting that supplementation's impact on CVD risk would be small. Thus, magnesium supplementation could be helpful to add on top of standard therapies in people with type 2 diabetes whose magnesium levels are low, but it should not serve as a replacement for standard care. ◆

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