The Role for Vitamin and Mineral Supplements in Diabetes Management
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11:30 a.m. – 12:15 p.m.

The American Diabetes Association Standards of Medical Care currently do not support the widespread use of vitamin and mineral supplements for diabetes management because of the lack of sufficient evidence. Cumulative evidence, however, suggests that supplementation with some vitamins and minerals has the potential to improve glycemic control, and macro- and microvascular complications in at least in some patients. This presentation will review key nutrients that may play a role in diabetes management including chromium, magnesium, vanadium, biotin, vitamins C, D, E and B12, and the scientific evidence supporting (or not supporting) their use either in supplemental doses or as part of a healthful diet and lifestyle pattern.

References:


30. Thompson KH, Orvig C. Vanadium in diabetes: 100 years from Phase 0 to Phase I. J Inorg Biochem 2006; 100: 1925-35.

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Disclosures

no financial conflicts of interest

The American Diabetes Association Standards of Medical Care currently do not support the widespread use of vitamin and mineral supplements for diabetes management because of the lack of sufficient evidence.

- There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies.
- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety.
- There is insufficient evidence to support the routine use of micronutrients such as chromium, magnesium, and vitamin D to improve glycemic control in people with diabetes.
- There is insufficient evidence to support the use of cinnamon or other herbs/supplements for the treatment of diabetes.
- It is reasonable for individualized meal planning to include optimization of food choices to meet recommended daily allowance/dietary reference intake for all micronutrients.

But let's look further....

Vitamin & Mineral
- Chromium
- Magnesium
- Vitamins E & C
- Vanadium
- Vitamin D
- Vitamin B12
- Multivitamin

- Glycemic Control
- Fasting Plasma Glucose (FPG)
- HbA1c
- Insulin Resistance
- Diabetes Complications
- Lipoproteins, Blood pressure
- Neuropathy, Retinopathy, Nephropathy
- & more

Emphasis on clinical trials and patient outcomes

Randomized Controlled Trials
Prospective Cohort
Retrospective Cohort
Case-Control
Cross-sectional
Ecological

Source: Institute of Medicine, DRI for Calcium and Vitamin D, National Academies Press, 2011
Chromium

**FUNCTION:**
- Carbohydrate & fat metabolism
- Deemed "glucose tolerance factor" in late 1950's

**SOURCES:**
- CrCl3 widely distributed in foods (most foods have <1-2 µg/serving). Rich sources include broccoli, bran, egg yolk, grape juice, some wines, brewers yeast
- Chromium content in Food Tables influenced by geochemical factors and analysis errors
- Intestinal absorption: 0.4 - 2.5% (dampened by simple sugars)

**AI:** Adults 19-50 yr = 35 µg men and 25 µg women (>50 yr ↓ 5 µg)

**PURPORTED FUNCTION IN DIABETES:**
- Deficiency results in insulin resistance & diabetes
  - ↑ insulin receptors,
  - ↑ insulin binding at action site,
  - ↑ receptor signaling (via chromodulin),
  - ↓ protein-tyrosine phosphatase 1B

**STUDIES:**
- Over 200 human studies → 28 RCT

**DOSING:** 150 -1000 µg/day as CrCl3, Cr Picolinate (salt), Cr-yeast or Brewers Yeast (1.28 to 42 µg day) for 3 to 24 weeks.

**RESULTS:**
- Improvement in HbA1c (↓ 0.55 - 0.88%) better with CrPic (↓ 0.6 %, CI=1-0.06-0.193).
- Doses <200 µg/d for <3 wk needed; better response in those with HbA1c >8% (14 studies)
- Reduction in FPG with CrPic (↓ 23.4 mg/dL, CI=1.97–0.30) and Brewers Yeast (24 studies)
- Improvement in TG (↓ 50 mg/dL) and HDL (↑ 4.6 mg/dL) with CrPic; No impact on Total- and LDL-Cholesterol (15 studies)

**SIDE EFFECTS:**
- RCTs show risk of adverse advents is no different than placebo
- Long-term safety not known
- Patients with renal or liver disease more susceptible to adverse effects
- Cr supplementation can interact with some medications (supplementation may alter effect of β-blockers, insulin, corticosteroids; gastric neutralizers may reduce absorption)

**CLINICAL IMPLICATIONS:**
- 200-1000 µg/day CrPic or Brewers Yeast improves HbA1c and FPG
- Effect on HbA1c (0.55 to 0.6 %) similar to alpha-glucosidase inhibitors & DPP-4 inhibitors
- Supplementation for >3 weeks not effective (e.g., half-life of RBC)
- Some evidence CrPic may be adjunct therapy for certain subgroups (patients with HbA1c >8% who are not on specific medications)

Biotin

**FUNCTION:**
- Coenzyme in bicarbonate-dependent reactions

**SOURCES:**
- Widely distributed in natural foods but Food Composition Tables rarely list biotin

**PURPORTED FUNCTION IN DIABETES:**
- Modulates glucokinase activity → suppresses hepatic glucose output & gluconeogenesis (limits phosphoenolpyruvate carboxykinase)
- Acts synergistically with chromium to enhance glucose uptake (pre-clinical)
Biotin plus Chromium

**STUDIES:**
- Pilot study* and several RCT** of Biotin plus Chromium Picolinate

**DOsing:** 2 mg biotin/day plus 600 µg CrPic/day for 28-90 days

**RESULTS:**
- Combined supplementation improved HbA1c (↓0.53%) and FPG (↓9.5 mg/dL) in patients with T2DM (n=226) poorly control DM on antidiabetic therapy vs placebo (n=121)**, and improved glucose response following OGTT (9.7% ↓ ACI (n=43))
- Improvement in serum lipids in patients with high cholesterol (↑ total cholesterol ↑0.9 mg/dl and LDL ↑22 mg/dL) with some influence on TG
- Studies have not looked at combined supplementation vs biotin and chromium alone

**SIDE EFFECTS:**
- Magnesium
  - Benefits to maintaining magnesium status through diet high in minimally-processed foods with selective supplementation to maintain normal status.
  - Magnesium supplementation is well tolerated and is attracting interest in diabetes.
  - Suggestive benefit of magnesium supplementation on improving glucose parameters and
  - Hypermagnesemia possible in those with renal insufficiency or taking Mg-containing Meds
  - Low pharmacological doses known to cause nausea, abdominal cramps, diarrhea
  - Pharmacological doses can cause metabolic hypokalemia, paralytic ileus
  - Hypermagnesemia possible in those with renal insufficiency or taking Mg-containing Meds

**FUNCTION:**
- Cofactor in over 300 metabolic reactions
- Intracellular calcium & potassium homostasis
- Mg cofactor in phosphorylation & dephosphorylation reactions in glycolysis (Hexokinase)
- Mg deficiency strongly related to insulin resistance
- Protein kinase in insulin signaling cascade and insulin secretion Mg-dependent
- Mg status and/or intake commonly decreased in patients with diabetes

**SOURCES:**
- Green leafy vegetables, legumes, whole-grains, nuts & seeds; milk, meat (med)

**DRI:** Adults 19-70 yr = 360 - 450 mg/day

**PURPORTED FUNCTION IN DIABETES:**
- Mg cofactor in glucose metabolism (Insulin resistance and signaling) Mg-dependent
- Mg status and intake commonly decreased in patients with diabetes
- Reduction in systolic (↓20.4 mmHg) and diastolic (↓8.7 mmHg) blood pressure with 4 mo supplementation

**STUDIES:**
- Several targeted meta-analyses of supplementation on glycemic control and blood pressure in patients with diabetes or at risk for diabetes (2006, 2016, 2016)
- Recent meta-analysis of 12 RCT in patients with Diabetes and 6 RCT in those at risk
- **Related to change in serum Mg**
- No improvement in HbA1c in patients with T2DM
- Improved glucose response after OGTT (2 hr), and trend for improved IR (HOMA) in patients at risk for DM

**RESULTS:**
- Magnesium supplementation can interfere with some medications
- However, more research needed; Evidence limited to few RCTs.

**CLINICAL IMPLICATIONS:**
- Risk of adverse events no different than placebo but long-term safety not known
- Patients with preexisting renal or liver disease more susceptible to adverse effects of chromium
- Effective adjunctive nutritional therapy for those with poorly controlled diabetes with the potential for improving lipid metabolism

**FUNCTION:**
- Non-specific chain breaking antioxidant, prevents hemolysis of RBC; protects PUFA’s in cell membrane and phospholipids in plasma LDL

**SOURCES:**
- Vegetable oils & spreads, wheat germ, unprocessed cereal grains, nuts, fruits & vegetables, fatty meats

**DRI:** Adults 19-70 yr = 15 mg UL=1000 mg/day

**PURPORTED FUNCTION IN DIABETES:**
- Inhibits formation of AGE’s (animal studies)
- Improves long-term OxStress in pancreatic B cell dysfunction (meta-analysis)

**SIDE EFFECTS:**
- Low pharmacological doses known to cause nausea, abdominal cramps, diarrhea
- RCTs did not find evidence of severe side effects

**FUNCTION:**
- Inhibits formation of AGE’s (animal studies)
- Improves long-term OxStress in pancreatic B cell dysfunction (meta-analysis)
Vitamin C

**FUNCTION:**
- Hydrophilic antioxidant; regenerates vitamin E
- Biosynthesis of collagen, carnitine, neurotransmitters

**SOURCES:**
- Most fruits & vegetables including: citrus fruits, peppers, tomatoes, potatoes, strawberries, spinach, cruciferous vegetables

**RDA:** Adults 19-70 yr = 90 mg/day; women = 75 mg/day

**SIDE EFFECTS:**
- High dose Vit C generally considered safe
- Sudden increases in vitamin C can cause osmotic diarrhea & promote renal excretion
- High doses not recommended for individuals with renal stones, hyperoxaluria, or with compromised renal function

**CLINICAL IMPLICATIONS:**
- Necessary to optimize insulin secretion (cultured islet cells)
- Insulin action, glycemic control, endothelial function, OxStress
- Acts as “insulin mimetic”

**STUDIES:**
- Two recent meta-analyses evaluating effect of supplementation on insulin resistance and glycemic control
- RCT in 425 patients with T2DM/controls evaluating insulin resistance (HOMA-IR)
- 14 RCT in 363 patients (mostly with T2DM) evaluating glycemic control

**RESULTS:**
- Supplementation did not improve HOMA-IR but authors concluded “non statistical improvement in insulin resistance”
- Supplementation did not improve HbA1c, FPG or fasting insulin overall...
- However, reduction in HbA1c and fasting insulin found in patients with low Vit E status
- Supplementation impacted FPG (+20 mg/dL) and tended to reduced HbA1c (−0.46%, CI= -1.75 to 0.84 )
- Doses >1000 mg/day may be needed
- Supplementation also reduced total cholesterol (−15.2 mg/dL) and LDL (−12.6 mg/dL)

**DOSING:**
- 120 to 1250 mg/day (typically) for 4 to 16 weeks, but as long as 9 yrs

**CLINICAL IMPLICATIONS:**
- Risk benefit would suggest little promise
- Potential for some benefit in patients with low vitamin E status or who are in poor control (HbA1c >8%)

Vitamin E

**FUNCTION:**
- Hydrophilic antioxidant; regenerates vitamin E
- Biosynthesis of collagen, carnitine, neurotransmitters

**SOURCES:**
- Mushrooms, shellfish, black pepper, parsley, dill seed, beer, wine
- Grains (13-30%) and Beverages (26-57%) make up significant daily sources

**RDA:** No RDA or AI; UL=2000 mg

**SIDE EFFECTS:**
- Effect of long-term, high dose supplementation uncertain
- Potential adverse effects include hemorrhagic toxicity and diminished blood coagulations in patients who are also Vit K compromised

**CLINICAL IMPLICATIONS:**
- Risk benefit would suggest little promise
- Potential for some benefit in patients with low vitamin E status or who are in poor control (HbA1c >8%)

**STUDIES:**
- Three RCT (92 patients/controls with T2DM; 6 double blind) with HOMA-IR
- 26 observational studies (82,176 patients) and 12 RCT (10,769 patients) with glycemic data
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**DOSING:**
- 150- 800 mg/day / 200 – 1600 IU for 4 to 27 weeks (+ RDA)

**CLINICAL IMPLICATIONS:**
- Risk benefit would suggest little promise
- Potential for some benefit in patients with low vitamin E status or who are in poor control (HbA1c >8%)

Vanadium

**FUNCTION:**
- Found in all cells; function not yet understood
- Acts as “insulin mimetic”

**SOURCES:**
- Mushrooms, shellfish, black pepper, parsley, dill seed, beer, wine
- Grains (13-30%) and Beverages (26-57%) make up significant daily sources

**DOSING:**
- No RDA or AI; UL = 1.8 mg

**SIDE EFFECTS:**
- Radiation of liver, skeletal muscle, adipose tissue
- Absorption -- 5%

**CLINICAL IMPLICATIONS:**
- Potential for some benefit in patients with low vitamin E status or who are in poor control (HbA1c >8%)

**STUDIES:**
- Two recent meta-analyses evaluating effect of supplementation on insulin resistance and glycemic control
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**DOSING:**
- 120 to 1250 mg/day (typically) for 4 to 16 weeks, but as long as 9 yrs

**CLINICAL IMPLICATIONS:**
- Risk benefit would suggest little promise
- Potential for some benefit in patients with low vitamin E status or who are in poor control (HbA1c >8%)
**Vanadium**

**STUDIES:**
- 1 RCT in patients with impaired glucose tolerance (IGT) (2008)

**DOSING:** 75-150 mg/day *Vanadyl Sulfate (BID/TID) for 2 - 6 weeks

**RESULTS:**
- Improvement in HbA1c (0.3 – 1.0%↓) and FPG (23 - 34 mg/dL ↓) in patient with DM
- No effect of supplementation on insulin sensitivity in patients with IGT
- Decreased basal endogenous glucose production and enhanced skeletal muscle insulin sensitivity in patients (n=11) with poorly controlled diabetes (via euglycemic clamp)


**SIDE EFFECTS:**
- Mild GI effects consistently reported (diarrhea, abdominal upset)
- Sx decrease over time and may be reduced if dose is titrated upward

**CLINICAL IMPLICATIONS:**
- Results intriguing
- However, no high quality studies to support effectiveness; side effects consistently present

Smith et al, OJM 2008, Cusi et al, J Clin Endocrinol Metab 2001)

**Vitamin D**

**FUNCTION:**
- Calcium absorption & homeostasis, bone health; Inflammatory modulation, immune function
- Modulation of expression of > 200-1000 genes

**SOURCES:** Fatty fish, fortified milk, some yogurt, margarine and OJ, egg yolk, sun-dried mushrooms, meat from sun exposed animals and Sensible Sun Exposure

**RDA:** Adults 19-70 yr = 600 IU  Adults> 70 yr = 800 IU  UL=4000 mg

**PURPORTED FUNCTION IN DIABETES:**
- Not completely understood → Gene Expression
- Vitamin D Receptor (VDR) detected in pancreatic B-cells, skeletal muscle, liver, adipose tissue and neuronal calls
- Polymorphisms in VDR associated with altered insulin sensitivity/function

**STUDIES:**
- Meta-analysis evaluating influence of supplementation on blood pressure (2017) and inflammation (2012)
- Several trials looking at macro/microvascular complications of DM.
- No studies adequately account for differences in vitamin D status.

**Vitamin D**

**DOSING:** protocols vary, i.e., 1000 IU/day to 50,000 IU/wk and influence of status for various durations

**RESULTS:**

- RCT in 275 patients with well-controlled T2DM found no benefit of supplementation on glycemic control except in patients with very low status (>12 ng/ml) who experienced significant reductions in HbA1c with supplementation. Similar results in meta-analyses of PrediDM patients (10 trials) only those with low status (<20 ng/ml) experienced reductions in FPG (↓2.3 mg/dL) and HbA1c (↓1.8 mmol/L).

- Meta-analysis in patients with T2DM (23 trials; varying vitamin D status) found that only patients in poor control (HbA1c >8%) had an improvement in FPG (↓8.7 mmHg, CI=3.5-1.4) blood pressure reductions in FPG (↓50%) and reduces risk for retinopathy.

- Progress from PreDM to DM and supplementation of vitamin D (serum 25(OH)D) important in “at risk” patients.

- Double-blind RCT in 60 patients with DM, CAD and low vitamin D status (20 ng/ml) jeden 50,000 IU every 2 weeks

- Matched and blocked randomized patients based on age, sex, BMI and dosage/type medications

- Controlled for diet and physical activity

**SIDE EFFECTS:**

- Toxicity rare → reported in literature as accidental overdose

- Symptoms due to hypercalcemia → fatigue, nausea, back pain, tissue calcification

- A U-shape association between vitamin D and diabetic neuropathy identified (case-control) → may be a narrow optimal vitamin D range for DM patients

**CLINICAL IMPLICATIONS:**

- Insufficient evidence to support routine vitamin D supplementation; evaluation of status important in “at risk” patients

- Maintaining sufficient vitamin D status (>20-30 ng/mL) essential in all patients; may ↓progress from PrediDM to DM and ↓risk of DM complications

- Future trials should include larger N’s and account for changes in vitamin D status with supplementation

**Vitamin B12**

**SIDE EFFECTS:**

- Toxicity rare → reported in literature as accidental overdose

- Symptoms due to hypercalcemia → fatigue, nausea, back pain, tissue calcification

- A U-shape association between vitamin D and diabetic neuropathy identified (case-control) → may be a narrow optimal vitamin D range for DM patients

**FUNCTION:**

- Blood formation & Neurological function

**SOURCES:** Foods of animal origin, B12-fortified foods

**RDA Adults** = 2.4 µg  
**UL None**

- Advisable those > 50 yr meet needs with supplement B12 or fortified foods

**PURPOSED FUNCTION IN DIABETES:**

- Long-term treatment with metformin decreases B12 status

- B12 deficiency → severity of peripheral neuropathy in DM patients and may be important in its management

**STUDIES:**

- Meta-analysis (6 RCT) evaluating B12 status in patients treated with metformin vs. placebo

- Meta-analysis (7 RCT) of effect of supplementation with B complex vitamin (including cyanocobalamin) or methylcobalamin alone (dating 1954 - 2004) on pain, vibration perception thresholds, autonomic symptoms, electrophysiological measures

- Single-blind RCT (100 patients) evaluating B12 supplementation vs. nortriptyline (n=50 each) on treatment of painful diabetic neuropathy

**DOSING:** Oral or injection for 4 to 16 weeks

**RESULTS:**

- Metformin ↓B12 status = effect is dose dependent

- B12 supplementation alone or with B vitamins had overall beneficial effect on neuropathy management but symptomatic relief (pain, paresthesia) greater than electrophysiological changes; many studies not good quality

- Parenteral B12 more effective than nortriptyline for symptomatic painful diabetic neuropathy; sublingual B12 as effective as neuremamucillic injections

- Double-blind RCT in 60 patients with DM, CAD and low vitamin D status (20 ng/ml) jeden 50,000 IU every 2 weeks

- Matched and blocked randomized patients based on age, sex, BMI and dosage/type medications

- Controlled for diet and physical activity

**SIDE EFFECTS:**

- No adverse effects known from food or cyanocobalamin supplementation in healthy individuals

**CLINICAL IMPLICATIONS:**

- Monitor biochemical and clinical signs of B12 deficiency in patients taking metformin

- Serum B12 <220 pmol/L = deficiency

- Megablastic anemia, weakness, fatigue, SOB, palpitations, neuropenia

- Prudent recommendation is for all patients with diabetes to take MVI containing B12 → more research needed on efficacy of B12 supplementation
Multivitamin

PURPORTED FUNCTION IN DIABETES:
▶ Improve glycemic control, prevent diabetes complications

STUDIES:
Numerous human studies looked at MVI or combination of various vitamins
▶ A single-blind RCT in 96 T2DM patients supplemented with MVI or MVI plus zinc sulfate vs placebo for 4 months found reductions in blood glucose (↓6 mg/dL), HbA1c (↓0.91%), and improvement of lipid profile with MVI plus Zn supplementation
▶ Double-blind RCT in 130 T2DM patients found that MVI supplementation for 1 year reduced incidence of infections (43% vs 73%)
▶ Open label, uncontrolled study in 10 patients found that high dose supplementation with folate, pyridoxine and B12 reduced symptoms of retinopathy


To Summarize and Conclude....
▶ MNT for diabetes management should ensure consumption of foods rich in magnesium, vitamin E, vitamin C and vitamin B12 and ensure vitamin D sufficiency through sun exposure, diet and/or supplementation
▶ Supplemental doses of chromium picolinate, magnesium, vitamin C, vitamin D and vitamin B12 may be beneficial (at least over short-term) for some patients with diabetes
▶ Patients in poor glycemic control
▶ Patients with low nutrient status.
▶ Some results suggest impact of certain vitamin & mineral supplements similar to alpha-glucosidase inhibitors & DPP-4 inhibits
▶ Practitioners should continue to follow the research on vitamin and mineral supplementation in diabetes management

Evaluation

Although there is some supportive evidence, many individual trials and Meta-analyses did not:
▶ Monitor/control for diet, exercise, lifestyle change, medication use
▶ Monitor/control for nutrient status (difficult for some nutrients)
▶ Evaluate T1DM or GDM → most of the studies on T2DM
▶ Perform sub-group analysis to determine which patients may benefit

Supplements for Diabetes Management
▶ There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. C
▶ Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. A
▶ There is insufficient evidence to support the routine use of micronutrients such as chromium, magnesium, and vitamin D to improve glycemic control in people with diabetes. C
▶ There is insufficient evidence to support the use of cinnamon or other herbs/supplements for the treatment of diabetes. C
▶ It is reasonable for individualized meal planning to include optimization of food choices to meet recommended daily allowance/dietary reference intake for all micronutrients. E

Questions?
Figure 2. Forest plot of randomised controlled trials investigate the effect of vitamin E supplementation on HbA1c.


http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0095008

Figure 3. Forest plot of randomised controlled trials investigate the effect of vitamin E supplementation on fasting glucose.


Figure 4. Forest plot of randomised controlled trials investigate the effect of vitamin E supplementation on fasting insulin.