The Role for Vitamin and Mineral Supplements in Diabetes Management
D. Enette Larson-Meyer, PhD, RD, FACSM
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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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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.

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

Emphasis on clinical trials and patient outcomes

Clinical Trials
- Randomly-Assigned Clinical Trials
- Efficacy and Safety

But let's look further....

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

Emphasis on clinical trials and patient outcomes

Chromium

FUNCTION:
- Carbohydrate & fat metabolism
- Deemed “glucose tolerance factor” in late 1950’s

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

AI: Adults 19-50 yr = 35 µg men and 25 µg women (>50 yr ↓ 5 µg)
- No UL

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

Schirmer & Heuss, Arch Intern Med, 1959; Institute of Medicine, 2006; Wang and Cefalu Cur Diab Rep, 2010
**Chromium**

**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 4 µg day) for 3 to 24 weeks.

**RESULTS:**
- Improvement in HbA1c (0.55 – 0.8%) → better with CrPic (0.6%, CI=1.06-0.15%).
- 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 (1.50 mg/dL) and HDL (1.6 mg/dL) with CrPic; No impact on Total- and LDL-Cholesterol (15 studies)

**STUDIES: Chromium**

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

**CLINICAL IMPLICATIONS:**
- 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 (-4.9 mg/dL) in patients with T2DM (n=226 poorly control DM on antidiabetic therapy) vs placebo (n=122)**, and improved glucose response following β-blockers, insulin, corticosteroids; gastric neutralizers
- Supplementation improved serum lipids in patients with high cholesterol (total cholesterol 4.9 mg/dL and LDL -12 mg/dL) with some influence on TG
- Studies have not look at combined supplementation vs biotin and chromium alone

**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 its absorption)
- Long-term safety not known
- Some evidence CrPic may be adjuvant therapy for certain subgroups of patients (HbA1c >8% (FPG) 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

AI: Adults 19-70 yr = 30 µg
- ↑ need in patients on hemodialysis or peritoneal dialysis and with biotinidase deficiency

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

**FUNCTION:**
- Cofactor in over 300 metabolic reactions
- Intracellular calcium & potassium homeostasis

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

**UL:** Based on pharmacological agents with diarrhea as endpoint

**Biotin plus Chromium**

**SIDE EFFECTS - previously mentioned for chromium:**
- Risk of adverse advents no different than placebo but long-term safety not known
- Patients with preexisting renal or liver disease more susceptible to adverse effects of chromium
- Cr supplementation can interfere with some medications
- 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 its absorption)
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**Magnesium**

**FUNCTION:**
- Cofactor in over 300 metabolic reactions
- Intracellular calcium & potassium homeostasis

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

**UL:** Based on pharmacological agents with diarrhea as endpoint

**SID EFFECTS:**
- Previously mentioned for chromium
- Patients with preexisting renal or liver disease more susceptible to adverse effects of chromium
- Cr supplementation can interfere with some medications

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

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- Studies have not look at combined supplementation vs biotin and chromium alone

**SIDE EFFECTS:**
- Previously mentioned for chromium
- Patients with preexisting renal or liver disease more susceptible to adverse effects of chromium
- Cr supplementation can interfere with some medications

**PURPORTED FUNCTION IN DIABETES:**
- Mg cofactor in phosphorylation & dephosphorylation reactions in glycolysis (WallPP-)
- Mg deficiency strongly related to insulin resistance
- Protein kinases in insulin signaling and insulin secretion Mg-dependent
- Mg status and/or intake commonly decreased in patients with diabetes
- Mg deficiency strongly related to insulin resistance
- Mg cofactor in phosphorylation & dephosphorylation reactions in glycolysis (WallPP-)}
**Magnesium**

**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

**DOSING:** Various doses/forms, e.g., 360 - 450 mg/day

**RESULTS:**
- Significantly improved FPG in patients with T2DM (↓ 6.6 mg/dL) and GDM, but not patients at risk for diabetes (↓ 9.4 mg/dL)
- No improvement in HbA1c in patients with T2DM
- Improved glucose response after OGTT, and trend for improved IR (HOMA) in patients at risk for DM
- Reduction in systolic (↓ 20.4 mmHg) and diastolic (↓ 8.7 mmHg) blood pressure with 4 mo supplementation

**SIDE EFFECTS:**
- Low pharmacological doses known to cause nausea, abdominal cramps, diarrhea
- RCTs did not find evidence of severe side effects
- Pharmacological doses can cause metabolic hypokalemia, paralytic ileus
- Some diuretics can cause hypermagnesemia

**CLINICAL IMPLICATIONS:**
- Suggestive benefit of magnesium supplementation on improving glucose parameters and blood pressure in diabetic patients, and insulin-sensitivity parameters in those at risk for diabetes → additional studies needed*
- Benefit to maintaining magnesium status through diet high in minimally-processed foods with selective supplementation to maintain normal status.


**Vitamin E**

**FUNCTION:**
- Non-specific chain breaking antioxidant, prevents hemolysis of RBC
- Protects PUFA's in membrane and phospholipids in plasma LDL

**SOURCES:** Vegetable oils & spreads, wheat germ, unprocessed cereal grains, nuts, fruits & vegetables, fatty meats
- Overt deficiency rare but present with fat malabsorption

**RDA:** Adults 19-70 yr = 15 mg  men, 75 mg  women  UL=1000 mg/day

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

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

**DOSING:** 150-800 mg/day / 200 – 1600 IU for 4 to 27 weeks (↑↑ RDA)

**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
- However, reduction in HbA1c and fasting insulin found in patients with low Vit E status (↓ 0.58%, ↓ 9 pmol/L) and in patients withHbA1c ≥8% (↓ 0.5%, 1 ↓ 0.7 pmol/L)

**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%)


**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  men, 75 mg  women  UL=2000 mg
- May be 35 mg/day higher in diabetes (↑ Blood sugar competes with Vit C tissue uptake and promotes urinary losses)

**PURPORTED FUNCTION IN DIABETES:**
- Insulin action, glycemic control, endothelial function, ↓ OxStress
- Necessary to optimize insulin secretion (cultured islet cells)

**SIDE EFFECTS:**
- Effect of long-term, high dose supplementation uncertain
- Potential for some benefit 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:**
- Numerous studies evaluating effect of supplementation on insulin resistance and glycemic control
- 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
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**PURPORTED FUNCTION IN DIABETES:**
- Insulin action, glycemic control, endothelial function, ↓ OxStress
- Necessary to optimize insulin secretion (cultured islet cells)


**Vitamin C**

**STUDIES:**
- Two recent meta-analyses evaluating Vit C supplementation on insulin resistance & glycemic markers in T2DM
- 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**

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

**RESULTS:**
- Vitamin C supplementation did not improve HOMA-IR but authors concluded “non statistical improvement in insulin resistance”**
- 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 concentrations and tended to improve triglycerides**


**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 (may ↑oxalate formation)

**CLINICAL IMPLICATIONS:**
- Patients with hyperglycemia have elevated Vit C requirements
- Some evidence high dose Vit C supplementation influences glycemic control
- Vit C may Impact OxStress/endothelial function – serum concentration and dose needed for OxStress may be different than other functions)
- Prudent that patients with diabetes select diet high in fruits and vegetables

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**Vanadium**

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

**DRI:** No RDA or AI; UL=1.8 mg

**SOURCES:** Mushrooms, shellfish, black pepper, parsley, dill seed, beer, wine
- Grains (13-30%) and Beverages (26-57%) make up significant daily sources
- Absorption ~5%

**PURPORTED FUNCTION IN DIABETES (animal and in-vitro studies):**
- Insulin-like effects in liver, skeletal muscle, adipose tissue
- Stimulates glucose uptake either directly or by inhibiting PTP enzyme system → enhancing insulin receptor phosphorylation and IR-tyrosine kinase


**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

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**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
- Vitamin D Receptor (VDR) detected in pancreatic B-cells, skeletal muscle, liver, adipose tissue and neuronal cells
- Polymorphisms in VDR associated with altered insulin sensitivity/function

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**Tabatabaei-Malazy Xu et al, J Pharm Pharm Sci, 2014**
Vitamin D

**SPECIFIC ACTION:**
- Direct stimulation of genes expression
- Stimulation of insulin receptor gene (VDR identified on human insulin receptor gene)
- Pancreatic B-cell function (dependent on vitamin D status in vitro and in animal models) and conversion of pro-insulin to insulin
- Modulation of inflammatory process

**STUDIES:**
- RCTs 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 changes in vitamin D status.

**CLINICAL IMPLICATIONS:**
- Evidence from smaller trials suggests vitamin D improves neuropathic symptoms and is a protective factor against diabetic retinopathy.
- Meta-analysis (6 RCTs evaluating influence of vitamin D on diabetic retinopathy) showed vitamin D reduced the risk of diabetic retinopathy.

**SIDE EFFECTS:**
- Toxicity rare, reported in literature as accidental overdose
- Symptoms due to hypercalcemia, fatigue, nausea, back pain, tissue calcification
- U-shape association between vitamin D and diabetic neuropathy identified (case-control), may be a narrow optimal vitamin D range for DM patients

**FUNCTION:**
- Normal blood formation & Neurological function
- Direct stimulation of genes and inflammation (2012)

**PURPOSED FUNCTION IN DIABETES:**
- Modulation of inflammatory process
- Direct stimulation of genes expression
- Stimulation of insulin receptor gene
- Pancreatic B-cell function
- Conversion of pro-insulin to insulin

**RESULTS:**
- Meta-analysis (6 RCTs evaluating influence of vitamin D on diabetic retinopathy) showed vitamin D reduced the risk of diabetic retinopathy.
- Meta-analysis in patients with T2DM (23 trials; varying vitamin D status) found that supplementation reduced systolic blood pressure by 4.6 mmHg, CI=7.7 –1.5, and diastolic blood pressure by 8.7 mmHg, CI=3.5-1.4.

**DOSING:** protocols vary, i.e., 1000 IU/day to 50,000 IU/month for various durations.

Vitamin B12

**STUDIES:**
- Meta-analysis (6 RCTs) evaluating B12 status in patients treated with metformin vs. placebo
- Meta-analysis (7 RCTs) of effect of supplementation with B complex vitamin (including cyanocobalamin) on glycemic control in patients with diabetes, 2012
- 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.

**FUNCTION:**
- Normal blood formation & Neurological function
- 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
- Megaloblastic anemia, weakness, fatigue, SOB, palpitations, neuropathy
- Prudent recommendation is for all patients with diabetes to take MVI containing B12 - more research needed on efficacy of B12 supplementation

**SIDE EFFECTS:**
- No adverse effects known from food or cyanocobalamin supplementation in healthy individuals
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 inhibitors
- 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