The Role for Vitamin and Mineral Supplements in Diabetes Management

D. Enette Larson-Meyer, PhD, RD, FACSM

Saturday, February 18, 2017

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.

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Disclosures

no financial conflicts of interest

American Diabetes Association. Diabetes Care

Executive Summary: Standards of Medical Care in Diabetes—2014

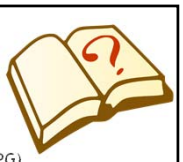
The American Diabetes Association Standards of Medical Care currently do not support the widespread use of vitamin and mineral supplements for diabetes management because of the lack of sufficient evidence.

American Diabetes Association. Diabetes Care

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**

But lets 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

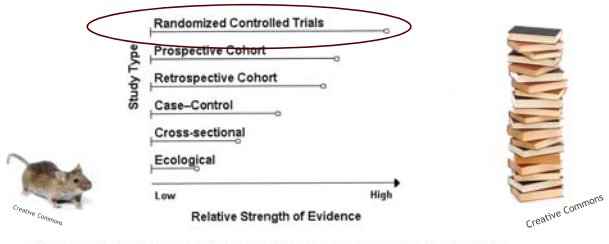


FIGURE 4-1 Ranking study designs: Ranking is shown in descending order of quality from top to bottom; the length of bars is arbitrary and indicates the relative strength of a study design.

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

ELSEVIER

Archives of Medical Research 36 (2005) 250–257

Archives of Medical Research

REVIEW ARTICLE

Complementary Therapies for Diabetes: The Case for Chromium, Magnesium, and Antioxidants

Fernando Guerrero-Romero[a,b] and Martha Rodríguez-Morán[a,b]

[a]Medical Research Unit, Clinical Epidemiology, Mexican Social Security Institute, Durango, Mexico and [b]Research Group on Diabetes and Chronic Illnesses, Durango, Mexico

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A growing body of interest on the possible beneficial role of chromium, magnesium, and antioxidant supplements in the treatment of diabetes has contributed to debate about their value for reaching metabolic control and to prevent chronic complications in diabetic subjects. In this article we use a systematic approach focused on clinically based evidence

Chromium

24 Cr 52.00

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FUNCTION:

- Carbohydrate & fat metabolism
- deemed "glucose tolerance factor" in late 1950's

SOURCES: $CrCl_3$ 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) 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

Schwarz & Mertz, Arch Biochem Biophys, 1959, Institute of Medicine, 2006, Wang and Cefalu Curr Diab Rep 2010

Chromium

24 Cr 52.00

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STUDIES:

- Over 200 human studies → ~28 RCT
- 5 meta-analyses evaluating effect of supplementation on DM management **(2002, 2007, 2010, 2014*, 2015)**

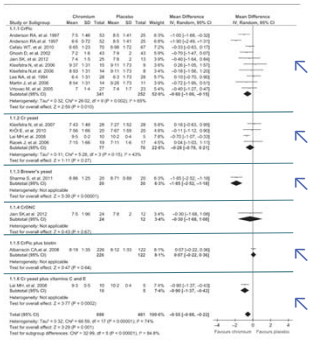
DOSING: 150 -1000 µg/day as $CrCl_3$, Cr Picolinate (salt), Cr-yeast or Brewers Yeast (1.28 to 42 µg day) for 3 to 24 weeks.

RESULTS*:

- Improvement in HbA1c (↓ 0.55 - 0.88%) → better with CrPic (**↓0.6 %**, CI=1.06-0.15%). 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 (↓50 mg/dL)** and **HDL (↑4.6 mg/dL)** with CrPic; No impact on Total- and LDL-Cholesterol (15 studies)

*Suksomboon et al, J Clin Pharm Ther 2014, Yin & Phung, Nutr J, 2015

Effect of Chromium Supplementation On HbA1c



↖ CrPic*

↖ Cr Yeast

↖ Brewers Yeast*

↖ Plus biotin

↖ Plus Vit C & E*

*Suksomboon et al, J Clin Pharm Ther 2014,

Chromium

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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 ß-blockers, insulin, corticosteroids; gastric neutralizers ↓its 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 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)

Suksomboon et al, J Clin Pharm Ther 2014, NIH Office of Dietary Supplements, Wang and Cefalu Curr Diab Rep 2010

Biotin

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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:

- Modulates glucokinase activity → suppresses hepatic glucose output & gluconeogenesis (limits phospoenolpyruvate carboxykinase)
- Acts synergistically with chromium to enhance glucose uptake (pre-clinical)

McCarty, Med Hypothesis 1999, Singer Diabetes Techinol Ther 2006

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 **HbAIc (↓0.53%)** and **FPG (↓9.5 mg/dL)** in patients with T2DM (n=226 poorly control DM on antidiabetic therapy) vs placebo (n=122)**, and improved glucose response following **OGTT (9.7% ↓ AIC) (n=43)***
- Supplementation improved serum lipids in patients with high cholesterol (**total cholesterol ↓9 mg/dl** and LDL ↓22 mg/dl) with some influence on TG
- Studies have not look at combined supplementation vs biotin and chromium alone

*Singer Diabetes Techinol Ther 2006, **Albarracin et al J Cardiometabolic Synd 2007, Diabetes Metab Res Rev 2008

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

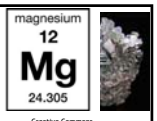
CLINICAL IMPLICATIONS:

2 mg/day plus 600 µg/day *CrPic for 28-90 days may be effective at improving HbA1c and FPG

- Combo may be an effective adjunctive nutritional therapy for those with poorly controlled diabetes with the potential for improving lipid metabolism
- However, more research needed; Evidence limited to few RCTs.

,* Suksomboon et al J Clin Pharm Ther 2014 , Albarracin et al J Cardiometabolic Synd 2007, Diabetes Metab Res Rev 2008

Magnesium



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FUNCTION:

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

SOURCES: Green leafy vegetables, legumes, whole grains, nuts & seeds; milk, meat (med)
Absorption ~50% but high phytates, fiber and phosphates↓

DRI: Adults 19-70 yr = 400-420 mg men and 310-320 mg women; **UL=350***

*UL based on pharmacological agents with diarrhea as endpoint

PURPORTED FUNCTION IN DIABETES:

- Mg cofactor in phosphorylation & dephosphorylation reactions in glycolysis ($MnATP^{2+}$)
- Mg deficiency strongly related to insulin resistance
  - *Protein kinases in insulin signaling cascade and insulin secretion Mg-dependent*
- Mg status and/or intake commonly decreased in patients with diabetes ➡ ↑risk

Sales et al, Clinical Nutr 2011, Hruby et al, J Nutr 2013, Dong et al, Diabetes Care, 2011, Veronese et al Eur J Clin Nutr 2016

Magnesium

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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 (FPG (↓9.4 mg/dL)
- No improvement in HbAlc in patients with T2DM
- Improved glucose response after OGTT (2 hr), and trend for improved IR (HOMA) in patients at risk for DM

related to change in serum Mg

- Reduction in systolic (↓20.4 mmHg) and diastolic (↓8.7 mmHg) blood pressure with 4 mo supplementation

Song et al Diabet Med, 2006, De Paula et al, Sci Rep 2017, Guerrero-Romero & Rodriguez-Moran, J Hum Hypertens 2009, Veronese et al Eur J Clin Nutr 2016

Magnesium

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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
- Hypermagnesemia possible in those with renal insufficiency or taking Mg-containing Meds

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 who have low magnesium status → additional studies needed*
- Magnesium supplementation is well tolerated and is attracting interest in diabetes management, little is known about optimal dose and preparation*
- **Benefit to maintaining magnesium status through diet high in minimally-processed foods with selective supplementation to maintain normal status.**

Sales et al, Clinical Nutr 2011, Guerroro-Romero & Rodriguez-Moran J Hum Hypertens 2009, *Veronese et al Eur J Clin Nutr 2016

Vitamin E

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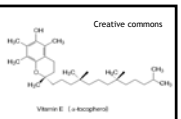
Vitamin E (α-tocopherol)

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

- Overt deficiency rare but present with fat malabsorption

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


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PURPORTED FUNCTION IN DIABETES:

- Inhibits formation of AGE's (animal studies)
- Alleviates long-term OxStress in Pancreatic B cell dysfunction (meta-analysis)

Jin et al, Eur J Pharmacol 2008, Myung et al, BMJ 2013

Vitamin E

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 *overall…*
- 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)

[1] Khodaeian et al, Eur J Clin Invest 2015, Xu et al, PloS ONE, 2014

Vitamin E

SIDE EFFECTS:

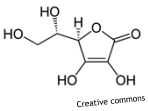
- Effect of long-term, high dose supplementation uncertain
- Potential adverse effects include hemorrhagic toxicity and diminished blood coagulations in patients who are also Vit K compromised
- High dose supplementation >400 IU ↑ risk of all cause mortality*

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%)

Institute of Medicine 2006, Khodaeian et al, Eur J Clin Invest 2015, Xu et al, PloS ONE, 2014, * Miller et al, Ann Intern Med,2005

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)

Steffner et al, Free Radic Bio Med 2001, Will & Byers Nutr Rev 1996

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 ↑RDA

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**

[1] *Khodaeian et al, Eur J Clin Invest 2015, **Tabatabaei-Malazy Xu et al, J Pharm Pharm Sci, 2014

Vitamin C

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

Institute of Medicine 2006, Khodaeian et al, Eur J Clin Invest 2015, Tabatabaei-Malazy Xu et al, J Pharm Pharm Sci, 2014, Will & Byers Nutr Rev 1996

Vanadium

"Promising TX" per web

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 Phosphotyrosine phosphatase enzyme system → enhancing *insulin receptor phosphorylation and IR-tyrosine kinase*

Pandey et al, Biochemistry, 1998; Verma et al, J Am Coll Nutr, 1998

Vanadium

STUDIES:

- ~5 non-randomized trials (1995 – 2001) in patients with diabetes
- 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)

Smith et al, OJM 2008, Cusi et al, J Clin Endocrinol Metab, 2001) Jacques-Camarena, Ann Nutr Metab 2008

OXFORD UNIVERSITY PRESS

From: **Vanadyl Sulfate Improves Hepatic and Muscle Insulin Sensitivity in Type 2 Diabetes**[1]

. 2001;86(3):1410-1417. doi:10.1210/jcem.86.3.7337

Endogenous Glucose Production

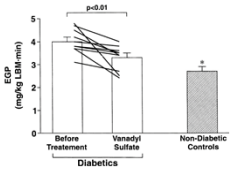


Figure Legend:
Basal EGP before (left column) and after (center column) 6 weeks of vanadyl sulfate treatment in poorly controlled T2DM patients and in matched nondiabetic controls (right column). EGP was significantly reduced by treatment (P < 0.01), but remained significantly higher compared with that in nondiabetic controls (*, P < 0.01, posttreatment vanadyl sulfate vs. nondiabetic controls). Results represent the mean ± se.

OXFORD UNIVERSITY PRESS

From: **Vanadyl Sulfate Improves Hepatic and Muscle Insulin Sensitivity in Type 2 Diabetes**[1]

. 2001;86(3):1410-1417. doi:10.1210/jcem.86.3.7337

Whole body insulin-mediated glucose disposal

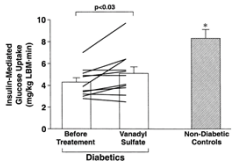


Figure Legend:
Whole body insulin-mediated glucose disposal during the 40 mU/m^2·min euglycemic insulin clamp, performed before (left column) and after (right column) treatment with vanadyl sulfate. Whole body insulin-mediated glucose disposal was significantly improved by vanadyl sulfate treatment (P < 0.03), but remained significantly lower compared with that in matched nondiabetic controls (*, P < 0.01, posttreatment vanadyl sulfate vs. nondiabetic controls). Results represent the mean ± se.

Vanadium

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

Larson-Meyer & Willis, Curr Sports Med Rep 2010, Bouillon Endocrin Rev 2008

Vitamin D

MDLinx Update

Vitamin D linked to diabetes

by Medical Headlines, MDLinx

Learn More

SPECIFIC ACTION:

Direct stimulation of genes expression

- Stimulation of insulin receptor gene (VDR identified on human insulin receptor gene)
- Pancreatic B-cell function (*in-vitro* and in animal models suggest dependence on vit D status) and conversion of pro-insulin to insulin
- Modulation of inflammatory process

STUDIES:

- Meta-analysis addressing supplementation and glycemic control/insulin resistance in patients with DM (2012, 2017) and PreDM (2015)
- 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.**

Grammatikl et al, Rev Endocr Metab Disord 2017, Krul-Poel et al, Eur J Endocrinol 2017, Chagas et al, Nutrients 2012

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 PreDM patients (10 trials) → only those with low status (>20 ng/ml) experienced reductions in FPG **(↓ 2 mg/dL)** and HbA1c **(↓ 1.0 mm/mol)**
- Meta-analysis in patients with T2DM (23 trials; varying vitamin D status) found that only patients in poor control (HbA1>8%) had an improvement in FPG **(↓ 6.5 mg/dL)**.
- Meta-analysis (542 patients with DM) found that supplementation reduced systolic **(↓ 4.6 mmHg, CI=7.7 -1.5)** and diastolic **(↓ 8.7 mmHg, CI=3.5-1.4)** blood pressure
- Evidence from smaller trials suggests vitamin D improves neuropathic symptoms (↓50%) and reduces risk for retinopathy

George et al, Diabet Med 2012, Krul-Poel et al Diabetes Care 2015, Krul-Poel et al, Eur J Endocrinol 2017, Poolsup, 2015, de Paula et al, Sci Rep 2017, Shehab et al Med Princ Pract 2015, Lee & Chen Arch Intern Med 2008, Hermann et al Diabetes Care 2015

Vitamin D RCT

- Double-blind RCTs in 60 patients with DM , CAD and **low vitamin D status (<20 ng/mL)**
- **Given 50,000 IU every 2 weeks**
- Matched and block randomized patients based on age, sex, BMI and dosage/type medications
- Controlled for and assessed diet and physical activity

RESULTS

- Vitamin D status increased by 7 ± 1 ng/mL
- ↓**FPG** (-15 ±7 mg/dL vs. +19 ±7)
- ↓ **Serum insulin** (-2.7 ±1.1 mg/dL vs. ++1.8 ±1.1)
- ↓ HOMA-IR and B cell function (QUICKI)

Farrokhian et al, J Nutr, 2017

Vitamin D

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 (serum 25(OH)D) important in "at risk" patients
- Maintaining sufficient vitamin D status **(>20-30 ng/mL)** essential in all patients; may ↓ progress from PreDM to DM and ↓ risk of DM complications
- Future trials should include larger N's and account for changes in vitamin D status with supplementation

Larson-Meyer & Willis Curr Sports Med Rep 2010, Abbasi et al, J Nutr 2015, Grammatiki Rev Endocr Metab Disord 2017, Holick et al J Clin Endocrinol Metab 2011

Vitamin B12

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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 (atrophic gastritis)

PURPORTED FUNCTION IN DIABETES:

- Long-term treatment with metformin decreases B12 status
- B12 deficiency **↑s** severity of peripheral neuropathy in DM patients and may be important in its management

Lu et al, PLoS One, 2014, Sun, Lai & Lu, Acta Neurol Taiwan, 2005

Vitamin B12

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 ↓s B12 status** → effect is dose & duration 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 affective than nortriptyline for symptomatic painful diabetic neuropathy; sublingual B12 as effective as neuromuscular injections

Lu et al, PLoS One, 2014, Sun, Lai & Lu, Acta Neurol Taiwan, 2005, Talaei et al Int J Food Sci Nutr 2009

Vitamin B12

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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
  - Megoblastic anemia, weakness, fatigue, SOB, palpitations, neutropenia
- Prudent recommendation is for **all** patients with diabetes to take MVI containing B12 → more research needed on efficacy of B12 supplementation

Institute of Medicine 2006, Haeusler, Parry-Strong & Krebs, N Z Med J 2014, Lu et al, PLoS One, 2014, ADA, Diabetes Care 2017

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

Valdés-Ramos et alEndocr Metab Immune Disord Drug Targets 2015, Gunasekara et al Diabetes Metab Syndr Obes 2011, Barringer et al Ann Int Med 2003, Smolek et al Clin Opthalmol 2013

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?

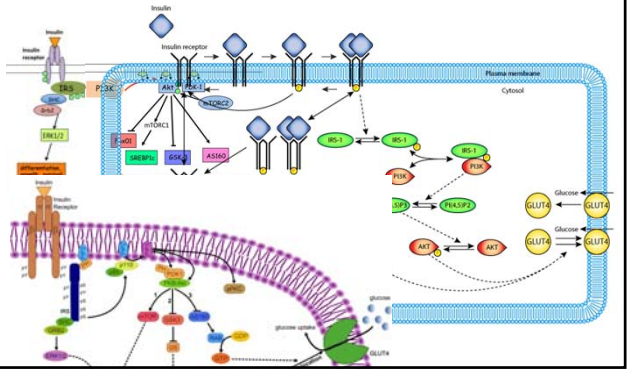
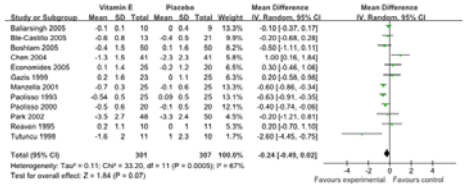
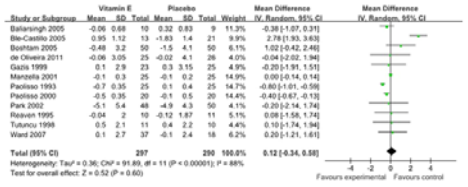


Figure 2. Forest plot of randomised controlled trials investigate the effect of vitamin E supplementation on HbA1c.



Xu R, Zhang S, Tao A, Chen G, Zhang M (2014) Influence of Vitamin E Supplementation on Glycaemic Control: A Meta-Analysis of Randomised Controlled Trials. PLOS ONE 9(4): e95008. doi:10.1371/journal.pone.0095008
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.



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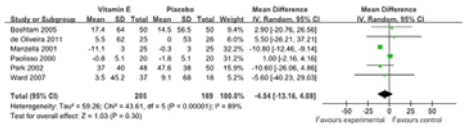
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0095008

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



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