“D”-Mystifying Vitamin D and Type 2 Diabetes Mellitus

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Objectives:

1. Review current recommendations for supplementation of vitamin D
2. Evaluate the current literature regarding the benefits of vitamin D use in prevention of type 2 diabetes mellitus
3. Evaluate the current literature regarding the benefits of vitamin D use in the treatment of type 2 diabetes mellitus
4. Discuss the possible clinical benefits of vitamin D supplementation in patients at risk of developing type 2 diabetes mellitus
5. Discuss recommendations for vitamin D supplementation in patients at risk for developing type 2 diabetes mellitus

I. Introduction
A. The prevalence of type 2 diabetes mellitus (DM2) is increasing\(^1\)
   i. In 2001, it was estimated that more than 1 million new cases of DM2 were diagnosed in the United States alone, with an additional 41 million Americans at risk of developing the disease\(^2\)
B. Vitamin D is currently being studied as a treatment for cancer, autoimmune diseases, infectious diseases, and cardiovascular disease\(^3\)
C. Association between vitamin D deficiency and DM2 is unclear\(^1\)

II. Background
A. Vitamin D deficiency
   i. Significance\(^3\)
      a. Vitamin D deficiency results in decreased absorption of calcium and phosphorous with only 10-15% of dietary calcium and 60% of phosphorous being absorbed in the absence of vitamin D
      b. In utero and during childhood, vitamin D deficiency may cause growth retardation and skeletal deformation and can increase risk of hip fracture later in life
      c. In adults, vitamin D deficiency may precipitation or exacerbate of osteoporosis and osteopenia, may cause osteomalacia and muscle weakness, and can increase fracture risk
   ii. Physiology
      a. Vitamin D is a fat soluble vitamin with hormone- like properties\(^4\)
         1. Vitamins are derived from the diet and cannot be synthesized by the body, while hormones are synthesized in the body and affect the function of other cells via hormone receptors
         2. Vitamin D is synthesized in the body and obtained from the diet
            a) Vitamin D3 (cholecalciferol) is synthesized from cholesterol in the body after activation by UV-B light\(^1\)
            b) Vitamin D2 (ergocalciferol) is obtained from dietary consumption of dairy products, fortified cereals, fish, or vitamin D supplements
            c) Vitamin D2 and D3 are then converted to storage form 25-hydroxyvitamin D [25-(OH)D] and active form, 1,25-dihydroxyvitamin D [1,25(OH)\(_2\)D (calcitriol)] in the liver and kidney

Figure 1: Pathways of vitamin D synthesis\(^5\)
iii. Risk factors for vitamin D deficiency
   a. Serum vitamin D levels are frequently lower during winter months due to reduced exposure to sunlight\(^1\)
b. Persons with darker skin tones, such as Africans and South Asians, also exhibit lower serum concentrations of vitamin D, due to increased skin absorption of ultraviolet B light by darker skin pigments.

c. Lifestyle factors, such as obesity and reduced physical activity, may also play a role in vitamin D deficiency due to deposition and subsequent inactivation of vitamin D in adipose tissue.

d. Additional risk factors include advanced age, shut-in status, malabsorption (e.g. celiac disease, etc.), anticonvulsant use, glucocorticoid use.

iv. Recommendations for vitamin D intake
   a. Institute of Medicine
      1. 200 IU/day for age 0-50 years
      2. 400 IU/day for age 51-70 years
      3. 600 IU/day for age 71 or older
      4. 2000 IU maximum daily allowance
      5. Currently in the process of reassessing recommendations
   b. National Osteoporosis Foundation
      1. 800-1000 IU/day for age greater than 50
   c. North American Menopause Society
      1. 800-1000 IU/day for all women
      2. Doses greater than 10,000 IU associated with an increased risk of hypercalcemia and hypercalciuria

v. Screening for vitamin D deficiency
   a. Inactive 25(OH)D is the major circulating vitamin D metabolite and is used to measure serum concentrations.
   b. 25(OH)D should be measured in patients with risk factors for vitamin D deficiency.

vi. Classifications for 25(OH)D levels
   1. Serum concentrations of 0-20 ng/ml considered to be deficient
   2. Serum concentrations 21-30 ng/mL are indicative of insufficiency
   3. Serum concentrations greater than 30 ng/mL (75 nmol/L) are desirable
   4. No justification for serum levels greater than 60 ng/mL (150 nmol/L)

vii. Treatment strategies
   a. National Kidney Foundation treatment recommendations for stage 3 or 4 chronic kidney disease
      1. For 25(OH)D levels less than 5 ng/mL, treat with 50,000 IU weekly for 12 weeks followed by 50,000 IU monthly for 3 months
      2. For 25(OH)D levels of 5-15 ng/mL, treat with 50,000 IU weekly for 4 weeks followed by 50,000 IU monthly for 5 months
      3. For 25(OH)D levels of 16-30 ng/mL, treat with 50,000 IU monthly for 6 months
   b. Expert opinion (see Appendix I)

viii. Ergocalciferol and cholecalciferol are both available as over-the-counter supplements, but only ergocalciferol (D2) is available in prescription strength.
a. Choice of ergocalciferol vs. cholecalciferol is controversial, but many clinicians prefer cholecalciferol.

B. Type 2 diabetes mellitus
   i. DM2 is characterized by decline in β-cell function and increase in insulin resistance over time
      a. Calcium has been shown to play a role in mediation of glucose transport induced by muscle activity
         1. Increased calcium ion concentrations in muscle increases glucose transport activity
         2. Calcium is required for insulin-mediated processes in skeletal muscle and adipose tissue
         3. Calcium depletion may contribute to insulin resistance as disturbance in calcium balance may interfere with insulin release
   b. New hypotheses suggest inflammation may play a role in the development of DM2 by increasing insulin resistance and decreasing β-cell function via cytokine mediated β-cell apoptosis

III. Association between Vitamin D and Type 2 Diabetes
   A. Vitamin D may be protective in those at risk for DM2
      i. Pancreatic β-cell function
         a. Vitamin D receptors (VDRs) are found throughout the body, including in β-cells
         b. Vitamin D appears to play a role in regulation of insulin release in response to glucose intake
            1. Direct effects may be mediated by binding of active form 1,25-OHD to β-cell VDR
            2. Vitamin D may indirectly affect insulin secretion via regulation of calcium-mediated insulin release by regulating calcium influx through cell membranes
      ii. Insulin resistance
         a. Vitamin D may enhance insulin responsiveness for glucose transport by directly stimulating the insulin receptor
         b. Vitamin D may indirectly influence insulin action via regulation of calcium influx through the cellular membrane, thereby ensuring normal calcium-mediated insulin release
      iii. Inflammation
         a. Vitamin D may promote β-cell survival by modulating the effects of inflammatory cytokines and decreasing β-cell destruction
            1. Studies suggest vitamin D may prevent generation of cytokines by interfering with the promoter gene for transcription factors and up-regulation of cytokine binding proteins

IV. Clinical Trials for Increased risk of Type 2 Diabetes and Vitamin D
   A. Observational trials
i. Kirii and colleagues
ii. Knekt and colleagues
iii. Kositsawat and colleagues
iv. Liu and colleagues
v. Pittas and colleagues

B. Prospective trials
i. Avenell and colleagues
ii. Nagpal and colleagues
iii. von Hurst and colleagues
iv. Pittas and colleagues
v. Tai and colleagues


<table>
<thead>
<tr>
<th>Research Design</th>
<th>3799 cohort members from the Framingham Offspring Study followed from 1991-2001 (mean 7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Used questionnaires, physical assessments, and lab tests to collect patient data on dietary intake, height, weight, waist circumference, physical activity, age, sex, smoking status, alcohol consumption, fasting glucose, lipid profile</td>
</tr>
<tr>
<td></td>
<td>Participants excluded for previous diagnosis of DM2, fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL*) or 2-h post-challenge glucose ≥11.1 mmol/L (≥200 mg/dL*)</td>
</tr>
<tr>
<td></td>
<td>Vast majority of participants were Caucasian</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>Used subsample from 1972 cohort to develop and validate a predicted</td>
</tr>
</tbody>
</table>
Multiple linear regression model to relate 25(OH)D concentration to age, sex, BMI, month of blood sampling, vitamin D intake, physical activity, smoking, total energy intake, and alcohol consumption

Cox proportional hazards model used to estimate relative risks, 95% CI calculated for tertiles of serum 25(OH)D and incident DM2

After adjustment for waist circumference, diet, parental history of DM2, HTN, low HDL, elevated triglycerides, and impaired fasting glucose, the middle and highest tertiles of 25(OH)D had 30-40% risk reduction in development of DM2 over 7 years (P=0.03)

When adjusted for BMI, physical activity, smoking, and education, OR was 0.60 (95% CI = 0.25-1.48)

When adjusted for sex, OR was 0.28 (CI = 0.10-0.81) for men and 1.14 (CI = 0.60-2.17) for women

Higher vitamin D status is associated with a decreased risk of DM2

Large study, long-term follow-up, adjusted for multiple variables, male and female participants

Observational nature, predicted 25(OH)D score developed for a northern population, only 11% of samples were collected during summer months when vitamin D exposure is highest, subjects were mainly Caucasian

*Conversion factor 0.0555


Double-blind, randomized, placebo-controlled trial conducted in 71 men for 6 weeks

Included Indian men age ≥35 who were centrally obese (waist circumference ≥78 cm)

Excluded FPG >7.0 mmol/L (126 mg/dL*), diabetes, use of oral glucose-lowering medication, insulin, resting BP >140/90 mmHg, HTN, use of antihypertensive medication, cholecalciferol or calcium supplementation within 6 months, chronic renal, hepatic, malignant, or intestinal disease, renal stones, use of medications that might influence insulin secretion, insulin sensitivity, vitamin D, or calcium metabolism within 30 days, febrile illness or infective morbidity within 10 days, grossly damaged liver (serum bilirubin >1.99 mg/dL and serum glutamic
## Methods
- Included Indian men age ≥35 who were centrally obese (waist circumference ≥78 cm)
- Excluded FPG >7.0 mmol/L (126 mg/dL*), diabetes, use of oral glucose-lowering medication, insulin, resting BP >140/90 mmHg, HTN, use of antihypertensive medication, cholecalciferol or calcium supplementation within 6 months, chronic renal, hepatic, malignant, or intestinal disease, renal stones, use of medications that might influence insulin secretion, insulin sensitivity, vitamin D, or calcium metabolism within 30 days, febrile illness or infective morbidity within 10 days, grossly damaged liver (serum bilirubin >1.99 mg/dL and serum glutamic pyruvate transaminase >4 times upper normal limit) or kidney function (serum creatinine >2 mg/dL)
- Subjects randomized to receive 3 supervised doses of 120,000 IU cholecalciferol orally or placebo 2 weeks apart
- 75 g oral glucose load given to test insulin sensitivity immediately following FPG test, blood samples taken at 5, 10, 30, 90, 120, and 180 minutes
- HOMA-IR (hemostasis model assessment of insulin resistance) and HOMA% B (hemostasis model assessment of β cell function) calculated at baseline and 6 weeks

## Statistical Analysis
- Used pilot trial on 30 subjects for power calculations and determination or oral glucose insulin sensitivity index, 40 subjects needed for each group (total 80) for an 80% power to detect a 10% difference in oral glucose insulin sensitivity (primary outcome)
- Mean difference of change tested for normality and compared using unpaired t-test

## Results
- 25(OH)D levels higher in study group at baseline (36.5 ± 14.55 vs. 30.0 ± 12.50 nmol/L, p=0.046)
- Significant increase in 25(OH)D levels in supplement group (35.1 ± 27.28 vs. 0.60 ± 11.61 nmol/L, p=0.000)
- Trend towards increase in oral glucose insulin sensitivity in supplement group (21.17 ± 67.86 vs. -8.89 ± 61.10 ml min⁻¹ kg⁻¹, p=0.055)
- Higher waist-hip ratio (p=0.029) and lower 25(OH)D levels (p=0.010) were significant predictors for improvement in oral glucose insulin sensitivity

*Conversion factor 0.0555²²
III. **von Hurst, et al.** *Vitamin D Supplementation Reduces Insulin Resistance in South Asian Women Living in New Zealand Who are Insulin Resistant and Vitamin D Deficient – A Randomised, Placebo-Controlled Trial*. *British Journal of Nutrition*. 2010;103:549-555.19

<table>
<thead>
<tr>
<th>Research Design</th>
<th>➢ Randomized placebo-controlled, double-blind trial following 106 women for 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>➢ Included women with hypovitaminosis D (serum 25(OH)D &lt; 50 nmol/L) + insulin resistance (hemostasis model assessment, HOMA-IR ≥ 1.93 calculated as [(fasting serum insulin x fasting plasma glucose)/22.5], and/or TAG/HDL cholesterol ratio ≥ 3.0)</td>
</tr>
<tr>
<td></td>
<td>➢ Excluded fasting plasma glucose ≥ 7.2 mmol/L (130 mg/dL*), medication for DM2, vitamin D supplementation ≥ 25 mcg (1000 IU) daily</td>
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<tr>
<td></td>
<td>➢ Subjects randomized to receive 100 mcg (4000 IU) cholecalciferol daily or placebo for 6 months</td>
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<tr>
<td></td>
<td>➢ Fasting blood samples and anthropometric assessments obtained at baseline and 6 months, blood test at 3 months to monitor for adverse events, computer model used to calculate insulin sensitivity (HOMA2 %S) and β-cell function (HOMA 2 %B)</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>➢ 42 subjects required for each arm (total 84 patients) for an 80% power</td>
</tr>
</tbody>
</table>
to detect a 5% significance

- Primary outcome was change in HOMA-IR
- Mann-Whitney $U$ test used to compare groups, Wilcoxon test used to compare baseline and endpoint measures within groups, Kruskal-Wallis test and post hoc tests + Bonferroni adjustments used to compare $>2$ independent groups/conditions, Friedman’s ANOVA and post hoc tests used to compare $>2$ related groups, 2 tailed $p$-values set at $<0.05$, Pearson’s correlations used for normally distributed data, Spearman’s correlations used for non-parametric data

### Results

- N=42, vitamin D group and N=39, placebo group completed the study
- 91% of subjects were Indian
- The vitamin D group had a significantly greater increase in 25(OH)D levels from baseline than the placebo group (49 nmol/L vs. 8 nmol/L, $p<0.001$) at 6 months
- Insulin resistance (HOMA-IR) decreased in the vitamin D group and increased in the placebo group (-0.25 vs. 0.36, $p=0.03$) at 6 months
- Insulin sensitivity (HOMA2 %S) increased in the vitamin D group and decreased in the placebo group (5.9 vs. -5.9, $p=0.003$) at 6 months, no difference seen at 3 months, no change seen at 25(OH)D levels $<80$ nmol/L
- No difference in change in fasting plasma glucose between groups

### Authors’ Conclusion

- Insulin sensitivity improved with vitamin D supplementation at 6 months with serum concentrations $>80$ nmol/L but did not improve at 3 months

### Strengths

- Randomized, placebo controlled trial, longer duration than previous studies

### Weaknesses

- Did not meet power, did not assess compliance

*Conversion factor 0.0555$^{22}$

### V. Summary of Evidence for Increased Risk of Type 2 Diabetes and Vitamin D

#### A. Research findings

i. Large observational studies show a possible link between increased vitamin D levels and decreased risk for DM2$^{12-16}$

ii. Small, short-term RCTs showed possible increase in insulin sensitivity with vitamin D supplementation$^{18,19}$

iii. Duration of treatment with vitamin D as well as serum levels of 25(OH)D may play a role in improvement of insulin sensitivity

#### B. Additional questions
i. Studies were conducted in mostly Caucasian populations; results in other ethnicities are unknown

ii. Optimal target level for serum vitamin D is not established

iii. Ideal dose and schedule for vitamin D supplementation are not established

iv. The protective effects of vitamin D in patients with diagnosed DM2 and more advanced β-cell dysfunction are unclear

VI. Clinical Trials for Treatment of DM2 with Vitamin D

A. Prospective trial
   i. Luo and colleagues\textsuperscript{23}

B. Randomized controlled trial
   i. Jorde and colleagues\textsuperscript{24}


<table>
<thead>
<tr>
<th>Research Design</th>
<th>➢ Prospective trial in 109 Chinese patients followed for 3 months</th>
</tr>
</thead>
</table>
| Methods        | ➢ Included age >50, DM2, 25(OH)D \( \leq 50 \text{ nmol/L} \)  
                 ➢ Excluded current use of vitamin D supplementation  
                 ➢ 21 of 39 vitamin D deficient subjects treated with cholecalciferol 2,000 IU daily for 3 months  
                 ➢ 25(OH)D, PTH, calcium, and phosphate measured at baseline and monthly |
| Statistical Analysis | ➢ Chi-square test used for categorical data, two-sample t-test, Mann Whitney U test, or chi-square test used to compare groups with 25(OH)D levels <50 and \( \geq 50 \text{ nmol/L} \), paired t-test or Wilcoxon signed-rank test used to test difference from baseline in subjects treated with vitamin D, Pearson’s coefficient used to assess relationship between vitamin D and metabolic syndrome, inflammatory markers, and BMI  
                       ➢ P values set at \( <0.05 \) |
| Results         | ➢ Subjects had DM2 diagnosis \( \geq 7 \text{ years} \)  
                 ➢ No association between vitamin D deficiency and metabolic syndrome within DM2 |
## Results
- Subjects had DM2 diagnosis ≥ 7 years
- No association between vitamin D deficiency and metabolic syndrome within DM2
- No impact of vitamin D deficiency on glycemic control
- No difference in response to vitamin D based on presence or absence of metabolic syndrome

## Authors’ Conclusion
- There is no association with hypovitaminosis D and metabolic syndrome or glycemic control in well-established Chinese DM2

## Research Design
- Randomized placebo controlled trial following 36 patients with DM2 for 6 months

## Methods
- Included males and females age 21-75 years with DM2 ≥ 1 year and treated with medium long-acting insulin at bedtime + metformin and stable A1cs of 7.0-9.5% ≥ 3 months, serum calcium levels <2.55 mmol/L
- Excluded past medical history of coronary infarction, angina pectoris, stroke, renal stone disease, and sarcoidosis
- Subjects randomized to receive 20,000 IU of cholecalciferol twice weekly or placebo for 6 months
- All other vitamin D supplements discontinued at inclusion without washout period, insulin and metformin doses remained constant during the study
- Lab tests including plasma glucose, serum insulin, C-peptide, serum fructosamine, A1c, serum calcium, parathyroid hormone, 25(OH)D, (1,25(OH)2D), and fasting lipid profile, as well as blood pressure, height, weight, waist and hip circumference measured at baseline and 6 months
- HOMA method used to calculate basal insulin sensitivity \([(\text{fasting plasma insulin (pmol/L)} \times \text{fasting plasma glucose (mmol/L)})/135]\) and secretion \([(\text{fasting plasma insulin (pmol/L)} \times 3.33)/(\text{fasting plasma glucose (mmol/L)} 3.5)]\)
**Statistical Analysis**
- Primary outcome was change in A1c after 6 months
- 70 subjects needed for an 89% power to detect a 0.5% difference in A1c (p < 0.05)
- Used 2 sided statistical tests including Student’s t-test used to compare groups at baseline, ANCOVA used to compare changes from baseline

**Results**
- 36 subjects enrolled, 4 in the vitamin D group lost to follow-up
- Found no difference in A1c change at 6 months (vitamin D -0.2 ± 0.9% and placebo -0.2 ± 0.5%, p=0.9)
- 1,25(OH)₂D levels significantly higher in treatment group vs. placebo (p=0.001)
- No difference in compliance between groups
- No difference in glucose metabolism between groups

**Authors’ Conclusion**
- Cholecalciferol 40,000 IU weekly for 6 months did not improve A1c, insulin secretion, or insulin resistance in patients with DM2

**Strengths**
- RCT, used large doses of vitamin D for longer duration

**Weaknesses**
- Small study, did not meet power, insulin and metformin may have masked effect of vitamin D, patients were not vitamin D deficient at baseline and may have had decreased response to vitamin D

**VII. Summary of Evidence for Treatment of DM2 with Vitamin D**

A. Research findings
   i. One small prospective trial did not show an association between glycemic control and vitamin D deficiency²³
   ii. One small RCT did not show an improvement in A1c, insulin secretion, or insulin resistance²⁴

B. Additional questions
   i. Studies were small in size and did not meet power or did not report power calculations
   ii. Studies were relatively short in duration, effect of long-term vitamin D supplementation is not known

**VIII. Discussion**

A. Evidence shows a possible link between increased vitamin D levels and reduction of insulin resistance in patients at increased risk for DM2
   i. Larger studies were observational in nature
   ii. Small RCTs were relatively short in duration
iii. Studies were conducted in mostly Caucasian populations
iv. No optimal target level for serum vitamin D has been established with regard to reduction of risk for DM2
v. No ideal dose or schedule for vitamin D supplementation has been established

B. Small studies were unable to show improvement in DM2 with vitamin D supplementation
   i. Studies were short in duration
   ii. Studies either did not meet power or did not report power
   iii. Cannot draw conclusions from available evidence

IX. Clinical Recommendations and Conclusions

A. Patients with risk factors for vitamin D deficiency including those at increased risk for DM2 may benefit from being screened for vitamin D deficiency
B. Patients with vitamin D deficiency and insufficiency should be supplemented with vitamin D to achieve recommended normal serum levels
C. Larger randomized placebo controlled studies of longer duration are needed in populations at risk for DM2
   i. Greater proportions of ethnic minority participants are needed
   ii. Optimal dose and treatment duration with vitamin D need to be established
D. Larger RCTs of longer duration are needed in patients with DM2
Appendix I: Strategies for Prevention and Treatment of Vitamin D Deficiency in Adults

<table>
<thead>
<tr>
<th>Deficiency Cause</th>
<th>Prevention and Maintenance</th>
<th>Treatment</th>
</tr>
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</table>
| Inadequate sun exposure, age >50 | ➢ 800-1000 IU vitamin D₃ daily  
➢ 50,000 IU vitamin D₂ every 2-4 weeks  
➢ Increased sun exposure or tanning bed use | ➢ 50,000 IU vitamin D₂ weekly for 8 weeks, repeat if 25(OH)D <30 ng/mL                                                                       |
| Pregnancy, lactation      | ➢ 1000-2000 IU vitamin D₃ daily  
➢ 50,000 IU vitamin D₂ every 2 weeks  
➢ Maintenance 50,000 IU vitamin D₂ every 4 weeks | ➢ 50,000 IU vitamin D₂ weekly for 8 weeks, repeat if 25(OH)D <30 ng/mL                                                                       |
| Malabsorption syndromes   | ➢ Increased sun exposure  
➢ 50,000 IU vitamin D₂ daily to weekly  
➢ Maintenance 50,000 IU vitamin D₂ weekly | ➢ Tanning bed use  
➢ 50,000 IU vitamin D₂ every 1-2 days                                                                                                     |
| Medication                | ➢ Increased sun exposure  
➢ 50,000 IU vitamin D₂ every 2-7 days  
➢ Maintenance 50,000 IU vitamin D₂ every 1, 2, or 4 weeks | ➢ 50,000 IU vitamin D₂ every 1-2 weeks for 8-10 weeks                                                                                      |
| Obesity                   | ➢ 1000-2000 IU vitamin D₃ daily  
➢ 50,000 IU vitamin D₂ 1-2 times weekly  
➢ Maintenance 50,000 IU vitamin D₂ every 1, 2, or 4 weeks | ➢ 50,000 IU vitamin D₂ weekly for 8-12 weeks, repeat if 25(OH)D <30 ng/mL                                                                       |
| Nephrotic syndrome        | ➢ 1000-2000 IU vitamin D₃ daily  
➢ 50,000 IU vitamin D₂ 1-2 times weekly  
➢ Maintenance 50,000 IU vitamin D₂ every 4 weeks | ➢ 50,000 IU vitamin D₂ biweekly for 8-12 weeks, repeat if 25(OH)D <30                                                                       |
<table>
<thead>
<tr>
<th>Chronic kidney disease stage</th>
<th>Duration</th>
<th>Vitamin D Protocol</th>
<th>25(OH)D &lt; 30 ng/mL Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>2-4 weeks</td>
<td>1000-2000 IU vitamin D₃ daily</td>
<td>50,000 IU vitamin D₂ weekly for 8 weeks, repeat if 25(OH)D &lt; 30 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50,000 IU vitamin D₂ 1-2 times weekly</td>
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<tr>
<td></td>
<td></td>
<td>Maintenance 50,000 IU vitamin D₂ every 2-4 weeks</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease stage 4-5</td>
<td>2-4 weeks</td>
<td>1000-2000 IU vitamin D₃ daily</td>
<td>Calcitriol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50,000 IU vitamin D₂ every 2 weeks</td>
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</table>
### Appendix II: Evidence of Proposed Mechanisms for Benefit of Vitamin D in DM2

<table>
<thead>
<tr>
<th>Proposed Mechanism</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Improvement in pancreatic β-cell function via direct effect on insulin secretion  | ➢ Presence of VDRs in pancreatic β-cells  
➢ Presence of vitamin D response element in human insulin gene promoter  
➢ Transcriptional activation of human insulin gene by 1,25-OHD                                                                         |
| Improvement on insulin action via direct and indirect effect on insulin responsiveness | ➢ Presence of VDR in skeletal muscle  
➢ Vitamin D stimulates expression of insulin receptor and enhances responsiveness for glucose transport in vitro  |
| Improvement in systemic inflammation via effects on inflammatory cytokines        | ➢ Vitamin D interacts with promoter region of cytokine genes to interfere with transcription and action  
➢ Vitamin D down-regulates activation of encoder genes for cytokines  
➢ Vitamin D interferes with generation of cytokines by up-regulating expression of binding proteins |
### Appendix III: Additional Trials for Increased Risk of DM2 and Vitamin D

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirii, et al.(^1)(^2)</td>
<td>Observational trial in 59,796 Japanese patients</td>
<td>Questionnaires</td>
<td>Found calcium intake was inversely associated with diabetes risk in higher vitamin D intake, OR 0.62 (95% CI 0.41-0.94) for men and 0.59 (95% CI 0.38-0.91) for women</td>
</tr>
<tr>
<td>Knekt, et al.(^1)(^3)</td>
<td>Nested case-control in 7503 Finnish patients</td>
<td>Surveys</td>
<td>Age adjust OR of DM2 between highest and lowest quartiles of vitamin D was 0.60 (95% CI = 0.37-0.96)</td>
</tr>
<tr>
<td>Kositsawat, et al.(^1)(^4)</td>
<td>Retrospective analysis of 9,773 subjects from National Health and Nutrition Examination Survey (NHANES)</td>
<td>Examined association between 25(OH)D levels and A1c</td>
<td>25(OH)D levels were inversely associated with A1c levels in subjects age 35-74 years (P=0.0045) and in subjects without a history of DM2 (P=0.0282)</td>
</tr>
<tr>
<td>Pittas, et al.(^1)(^6)</td>
<td>Observational trial in 83,779 nurses</td>
<td>Questionnaires</td>
<td>23% risk reduction of DM2 with &gt;800 IU vitamin D daily vs. &lt;200 IU daily</td>
</tr>
<tr>
<td>Avenell, et al.(^1)(^7)</td>
<td>Subgroup analysis of RCT in 5292 osteoporosis patients, age ≥70</td>
<td>Subjects randomized to receive cholecalciferol 800 IU daily, 1000 mg calcium daily, both, or placebo for 24-62 months</td>
<td>Found no difference in development of DM2 or increase in need for DM2 medications</td>
</tr>
<tr>
<td>Pittas, et al.(^1)(^8)</td>
<td>Ancillary analysis of double-blind, parallel-group, single-center, RCT in osteoporosis patients</td>
<td>Subjects supplemented with 700 IU cholecalciferol and 500 mg calcium or placebo for 3 years</td>
<td>Higher rates of DM2 in placebo vs. calcium and vitamin D (81% vs. 70%, p=0.28)</td>
</tr>
<tr>
<td>Tai, et al.(^1)(^9)</td>
<td>Prospective trial in 33 subjects with vitamin D insufficiency</td>
<td>Subjects treated with two 100,000 IU doses of cholecalciferol weeks apart</td>
<td>Found no difference in blood glucose mean or insulin sensitivity</td>
</tr>
</tbody>
</table>
References


