On behalf of the Incredible

[Image of a large group of people]
Study design

22 U.S. sites

n=2423

n=1211

4000 IU/day vitamin D₃

Central Lab

Every 6m: FPG, HbA1c
Every 12m: FPG, HbA1c, 2hPG

Diabetes outcome if
✓ Two (+) tests
✓ One (+) test confirmed on repeat testing

All participants receive current recommendations for pre-diabetes, vitamin D and calcium intake

n=1212

By site, BMI, race

Pittas et al Diabetes Care 2014
Mean serum 25(OH)D level during D2d

“Sufficiency” >20 ng/mL
Cumulative survival rates *free of diabetes, Intention-to-treat*

Hazard ratio for *new-onset diabetes*  
0.88 (95%CI 0.75 to 1.04); p = 0.12

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Vitamin D 4000 IU/d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1212</td>
</tr>
<tr>
<td></td>
<td>6m</td>
<td>1171</td>
</tr>
<tr>
<td></td>
<td>12m</td>
<td>1091</td>
</tr>
<tr>
<td></td>
<td>18m</td>
<td>975</td>
</tr>
<tr>
<td></td>
<td>24m</td>
<td>779</td>
</tr>
<tr>
<td></td>
<td>30m</td>
<td>577</td>
</tr>
<tr>
<td></td>
<td>36m</td>
<td>419</td>
</tr>
<tr>
<td></td>
<td>42m</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>48m</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>54m</td>
<td>13</td>
</tr>
</tbody>
</table>
The primary outcome does not achieve statistical significance

Now what?

- Is there some indication of potential benefit? – **YES**
- Was the trial underpowered? – **Not for the projected 25% reduction**
- Was the trial population appropriate? – **YES**
- Was the treatment regimen appropriate? – **YES**
- Was the primary outcome appropriate or accurately defined? – **YES**
- Was the duration of intervention and follow-up adequate – **YES**
- Were there deficiencies in trial conduct? – **No**
- Is a claim of non-inferiority of value? – **Not applicable**
- Do subgroup findings elicit positive signals? – **YES**
- Can alternative analyses help? – **YES**
- Does additional external evidence exist? – **YES**
- Is there a strong biologic rationale that favors the treatment? – **YES**

Pittas et al JCEM 2020; Pocock and Stone NEJM 2016
Effect of vitamin D supplementation on diabetes prevention according to vitamin D deficiency at baseline

25-hydroxyvitamin D ≥ 12 ng/mL; N=2319

- Hazard ratio for new-onset diabetes: 0.92 (95% CI 0.78 to 1.08)

25-hydroxyvitamin D < 12 ng/mL; N=103

- Hazard ratio for new-onset diabetes: 0.38 (95% CI 0.18 to 0.80)

Post-hoc analysis; Nominal P-value for the interaction term = 0.023
Protocol-specified, exploratory, per-protocol analysis

FOLLOW-UP CENSORED WHEN PARTICIPANTS

- Stopped study pills
- Started diabetes or weight-loss medication
- Took out-of-study vitamin D above study limitation (1000 IU per day)

Hazard ratio for new-onset diabetes

0.84 (95%CI 0.71 to 1.00)

Nominal P=0.04
# Intra-trial 25(OH)D and new-onset diabetes in D2d

<table>
<thead>
<tr>
<th>25(OH)D Level (nmol/L)</th>
<th>Randomized to Placebo</th>
<th>Randomized to Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td><strong>1.23 [0.86 to 1.75]</strong></td>
<td><strong>1.03 [0.76 to 1.38]</strong></td>
</tr>
<tr>
<td>50-74</td>
<td><strong>1.03 [0.76 to 1.38]</strong></td>
<td><strong>0.67 [0.40 to 1.12]</strong></td>
</tr>
<tr>
<td>75-99</td>
<td><strong>0.67 [0.40 to 1.12]</strong></td>
<td><strong>0.47 [0.15 to 1.52]</strong></td>
</tr>
<tr>
<td>100-124</td>
<td><strong>0.47 [0.15 to 1.52]</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Randomized to Placebo**  
  - n=225  
  - Median level, nmol/L: 43, 66, 90, 111, 146  
  - Models adjusted for site, BMI (at baseline), race (white, Black, other), sex, age, physical activity, statin use.

- **Randomized to Vitamin D**  
  - n=22  
  - Median level, nmol/L: 40, 64, 86, 110, 145  
  - Models adjusted for site, BMI (at baseline), race (white, Black, other), sex, age, physical activity, statin use.

Dawson-Hughes et al. Diabetes Care 2020

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Model adjusted for site, BMI (at baseline), race (white, Black, other), sex, age, physical activity, statin use.
Vitamin D and prevention of diabetes: Comparison of available trials

Large, long-term trials specifically designed and conducted to test the effect of vitamin D for diabetes prevention in people with prediabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Pre-diabetes definition Baseline 25OHD</th>
<th>Baseline 25OHD, ng/mL</th>
<th>Intervention</th>
<th>Achieved 25OHD, ng/mL</th>
<th>Follow-up (yrs.)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromsø (Norway)</td>
<td>511</td>
<td>IFG, IGT, iA1c</td>
<td>24</td>
<td>D₃ at 20,000 IU weekly (~2,900 IU daily)</td>
<td>48</td>
<td>Up to 5</td>
<td><strong>0.90 (0.69 to 1.18)</strong></td>
</tr>
<tr>
<td>DPVD (Japan)</td>
<td>1,256</td>
<td>IGT</td>
<td>Not Avail.</td>
<td>Eldecalcitol (active vitamin D analog) daily</td>
<td>NA</td>
<td>Mean 2.6</td>
<td><strong>0.87 (0.68 to 1.09)</strong></td>
</tr>
<tr>
<td>D2d (US)</td>
<td>2,423</td>
<td>IFG, IGT, iA1c</td>
<td>28</td>
<td>D₃ at 4,000 IU daily</td>
<td>52</td>
<td>Mean 2.5</td>
<td><strong>0.88 (0.75 to 1.04)</strong></td>
</tr>
</tbody>
</table>

Jorde et al JCEM 2016; Kawahara et al Diabetes 2017 (abstract; manuscript in preparation)
<table>
<thead>
<tr>
<th>Study Title</th>
<th>PI</th>
<th>EMAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin D supplementation and kidney function</strong></td>
<td>Sun Kim, MD MS</td>
<td><a href="mailto:sunhkim@stanford.edu">sunhkim@stanford.edu</a></td>
</tr>
<tr>
<td><strong>Vitamin D and cancer outcomes</strong></td>
<td>Ranee Chatterjee, MD</td>
<td><a href="mailto:ranee.chatterjee@duke.edu">ranee.chatterjee@duke.edu</a></td>
</tr>
<tr>
<td><strong>Intra-trial exposure to vitamin D and risk of diabetes</strong></td>
<td>Bess Dawson-Hughes, MD</td>
<td><a href="mailto:bess.dawson-hughes@tufts.edu">bess.dawson-hughes@tufts.edu</a></td>
</tr>
<tr>
<td><strong>Reproductibility of a prediabetes classification</strong></td>
<td>Chhavi Chadha, MD</td>
<td><a href="mailto:chhavi.x.chadha@healthpartners.com">chhavi.x.chadha@healthpartners.com</a></td>
</tr>
<tr>
<td><strong>Vitamin D supplementation and insulin resistance sensitivity and secretion</strong></td>
<td>Neda Rasouli, MD</td>
<td><a href="mailto:NEDA.RASOULI@CUANSCHUTZ.EDU">NEDA.RASOULI@CUANSCHUTZ.EDU</a></td>
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</table>
**Hemoglobin glycation index on the diagnosis of prediabetes and diabetes**

PI: Daniel Hsia, MD  
EMAIL: Daniel.Hsia@pbrc.edu

**Vitamin D supplementation and prevention of type 2 diabetes**

PI: Anastassios Pittas, MD MS  
EMAIL: apittas@tuftsmedicalcenter.org

**EHR recruitment approach to trial recruitment**

PI: Vanita Aroda, MD  
EMAIL: varoda@bwh.harvard.edu

**Baseline characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study**

PI: Erin LeBlanc, MD  
EMAIL: Erin.S.LeBlanc@kpchr.org

**Management of incidentally discovered hemoglobin variants**

PI: Michael Lewis, MD  
EMAIL: Michael.Lewis@uvm.edu
Assessment of the NDEP toolkit

**PI:** Roshni Devchand, MPH
**EMAIL:** rdevchand@hagersharp.com

Financial management of large, multi-center trials

**PI:** Olivia Lovegreen
**EMAIL:** OLovegreen@tuftsmedicalcenter.org

Rational and design of D2d

**PI:** Anastassios Pittas
**EMAIL:** apittas@tuftsmedicalcenter.org
Manuscripts in Progress and Future Directions
<table>
<thead>
<tr>
<th>Project Title</th>
<th>PI</th>
<th>EMAIL</th>
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</thead>
<tbody>
<tr>
<td>Baseline insulin and cardiovascular risk</td>
<td>Sangeeta Kashyap, MD</td>
<td><a href="mailto:KASHYS@ccf.org">KASHYS@ccf.org</a></td>
</tr>
<tr>
<td>Quality of life and mood assessment</td>
<td>Rowena Dolor, MD</td>
<td><a href="mailto:rowena.dolor@duke.edu">rowena.dolor@duke.edu</a></td>
</tr>
<tr>
<td>Participant retention</td>
<td>Vanita Aroda, MD</td>
<td><a href="mailto:varoda@bwh.harvard.edu">varoda@bwh.harvard.edu</a></td>
</tr>
<tr>
<td>Effect of vitamin D supplementation on incident CVD</td>
<td>Cyrus Desouza, MD</td>
<td><a href="mailto:cdesouza@unmc.edu">cdesouza@unmc.edu</a></td>
</tr>
<tr>
<td>Dietary patterns impacting risk of type 2 diabetes</td>
<td>Emily Newbold, PhD</td>
<td><a href="mailto:enewbold@kumc.edu">enewbold@kumc.edu</a></td>
</tr>
</tbody>
</table>

Submitted
Safety and tolerability of vitamin D
PI: Karen Johnson, MD
EMAIL: kjohnson@uthsc.edu

Prevalence of NAFLD/NASH in D2d cohort and progression to diabetes
PI: Richard Pratley, MD
EMAIL: Richard.Pratley.MD@AdventHealth.com

Racial and ethnic differences of glycemia
PI: Erin LeBlanc, MD
EMAIL: Erin.S.LeBlanc@kpchr.org

Diabetes and statin use
PI: Jean Park, MD
EMAIL: Jean.Y.Park@medstar.net

Vitamin D impacts on glycemia
PI: Daniel Hsia, MD
EMAIL: Daniel.Hsia@pbrc.edu
Effect of vitamin D by race weight status

PI: Ranee Chatterjee, MD
EMAIL: ranee.chatterjee@duke.edu

Vitamin D supplementation and bone related outcomes

PI: Lisa Ceglia, MD
EMAIL: lceglia@tuftsmedicalcenter.org

Natural history of pre-diabetes

PI: Anastassios Pittas, MD MS
EMAIL: apittas@tuftsmedicalcenter.org

Meta-analysis of trials on the effect of vitamin D on diabetes

PI: Anastassios Pittas, MD MS
EMAIL: apittas@tuftsmedicalcenter.org
OVERVIEW

- Fully screened 3,969 people
- Randomized 2,423 people with prediabetes to either 4,000 IU vitamin D₃ or placebo
- Followed for a median of 2.6 years (diabetes) / 3.0 years (other outcomes)

STORED REPOSITORY SAMPLES *analyses require funding

- Urine (baseline and annually)
- Serum and plasma blood samples (baseline, month 6, and annually)
- Whole blood for DNA (baseline only)

SUPPORT

The D2d Coordinating Center can provide statistical support.

DATA POINTS (*available at baseline only)

- Demographics: DOB, sex, race, ethnicity
- Socioeconomic data: education, marital status, employment status, household income
- Medical history (structured data fields for menopausal status, history of gestational diabetes and cancer, smoking history)
- Family history of diabetes and cancer
- Sunlight-related lifestyle data
- Medications for hypertension, lipid- and glycemia-lowering, osteoporosis, weight loss, and aspirin
- Supplemental vitamin D and calcium intake
- Vital signs: blood pressure, height, weight, waist*
- Dietary intake (FFQ) and physical activity (IPAQ)
- Quality of life (at M24 only)
- Study pill adherence
- Adverse events (adjudicated nephrolithiasis, cancer, and serious cardiovascular events)
- Fasting blood measures: WBC*, Hgb*, HCT*, ALT*, AST*, platelets*, serum calcium, serum creatinine, calculated eGFR, HbA1c, glucose, insulin, CRP, urine calcium creatinine ratio, urine albumin creatinine ratio, 25-hydroxyvitamin D (total, D₂, and D₃), total cholesterol, HDL, LDL, triglycerides
- At 30 min and 120 min post 75-g glucose load: glucose, insulin, C-peptide
- C-Telopeptide, osteocalcin, and parathyroid hormone (on a subset of participants)
Have an idea? Contact the D2d Coordinating Center at D2d@tuftsmedicalcenter.org