Research Letter | Diabetes and Endocrinology

Effect of Ergocalciferol on β-Cell Function in New-Onset Type 1 Diabetes: A Secondary Analysis of a Randomized Clinical Trial

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Introduction

Approximately 30% to 50% residual β-cell function may remain at the time of type 1 diabetes (T1D) diagnosis, and this may persist for months or years.1,2 A prolonged partial remission (PR) phase of T1D leads to improved glycemic control and decreased long-term complications.1 We previously reported1 that ergocalciferol significantly decreased circulating tumor necrosis factor (TNF-)α and temporal trends in both hemoglobin A1c (HbA1c) and insulin dose–adjusted A1c (IDAA1c), a marker of PR, compared with placebo. Here, we report the effect size of high-dose ergocalciferol (50 000 IU/wk for 2 months, then biweekly for 10 months) vs placebo on β-cell function, denoted by the ratio of fasting proinsulin to C-peptide (P1:C) and the percent change from baseline in the area under the curve (%ΔAUC) of C-peptide.

Methods

We conducted a post hoc secondary analysis of a single-center, double-blind, placebo-controlled, parallel-group randomized clinical trial of ergocalciferol vs placebo in youths (aged 10-21 years) with newly diagnosed T1D. The trial was conducted at the University of Massachusetts Medical Center (UMMC) in Worcester from October 19, 2017, to April 12, 2021 (ClinicalTrials.gov identifier: NCT03046927). The methodology was published previously.1 The UMMC Institutional Review Board approved the study protocol (Supplement 1) with modifications (Supplement 2).3 We obtained written informed consent from adults and parents and assent from youths (aged <18 years). The study followed the CONSORT reporting guideline.

Exclusion and inclusion criteria were reported previously1 and included fasting C-peptide (>0.1 nmol/L [0.3 ng/mL]) or stimulated C-peptide (>0.2 nmol/L [= 0.6 ng/mL]) and a positive diabetes-associated autoantibody profile. Participants entered a run-in phase of 1 to 2 months, maintained a treat-to-target insulin regimen, and were subsequently randomized to ergocalciferol or placebo.

Table. Fasting Proinsulin, Fasting C-Peptide, and Corresponding PI:Cs During the Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>PI:C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proinsulin, pmol/L</td>
<td>C-peptide, pmol/L</td>
<td></td>
</tr>
<tr>
<td>Ergocalciferol, mo</td>
<td>0</td>
<td>9.56 (16.91)</td>
<td>265.2 (271.6)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5.13 (5.25)</td>
<td>195.7 (133.2)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5.25 (6.60)</td>
<td>152.7 (95.7)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4.68 (4.11)</td>
<td>140.0 (78.4)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2.75 (2.11)</td>
<td>114.5 (69.4)</td>
</tr>
<tr>
<td>Placebo, mo</td>
<td>0</td>
<td>10.08 (19.01)</td>
<td>225.9 (131.7)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6.31 (5.26)</td>
<td>215.0 (126.9)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8.13 (10.99)</td>
<td>238.7 (187.4)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>5.14 (5.01)</td>
<td>146.1 (78.0)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>6.82 (9.51)</td>
<td>166.2 (155.6)</td>
</tr>
</tbody>
</table>

Abbreviation: PI:C, proinsulin to C-peptide ratio.

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Participants completed mixed-meal tolerance tests to estimate C-peptide, fasting glucose, and proinsulin (normal range, 3.6-22 pmol/L) at 0, 3, 6, 9, and 12 months (Table).

The sample size and power calculation were reported previously. Statistical analysis was based on the intent-to-treat principle. We compared differences in fasting PI:C trends between groups using a repeated-measures generalized linear model with normal distribution, logarithmic link function, and unstructured correlations.

We calculated %ΔAUC C-peptide using the trapezoidal method and used a random intercept model adjusted for sex, age, and race to characterize mean %ΔAUC C-peptide from 0 to 12 months. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). Box plots were generated using Prism, version 10 (GraphPad Inc). All tests were 2 sided; $P < .05$ was considered significant. Data analysis was performed from October 5 to November 15, 2023.

Results

Of 48 youths with T1D eligible for the 12-month trial, 36 (24 males [66.7%], 12 females [33.3%]) were randomized to ergocalciferol or placebo (eFigure in Supplement 3). Their mean (SD) age was 13.5 (2.8) years; 2 were Asian (5.6%), 2 were Black (5.6%), 27 (75.0%) were White, and 5 (13.8%) did not

Figure. Fasting Proinsulin, Fasting C-Peptide, and Corresponding Proinsulin to C-Peptide Ratios (PI:Cs)

A and B, Observed (A) and model-predicted (B) PI:C. Trends were generated from a repeated-measures generalized linear model of fasting PI:C. The total number of repeated-measures observations was 149 from 36 participants (18 per group). Three observed values were greater than 0.2; these were considered extreme outliers and were removed (in A). The remaining observations ranged from 0.005 to 0.087. The error distribution was normal, the link function was logarithmic, the repeated-measures correlation was unstructured, and the difference in trends between the 2 groups was significant ($P = .01$). C, Overall analysis of the trends showed that ergocalciferol significantly slowed the decline in percentage AUC C-peptide from baseline compared with placebo ($P = .03$).
report their race. Ergocalciferol significantly decreased fasting PI:C vs placebo (mean [SE], −0.0009 [0.0008] vs 0.0011 [0.0003]; \( P = .01 \); Figure, A and B) for the monthly overall difference in trends. The mean (SD) decrease in \%\Delta AUC C-peptide was similar for both groups in the first 3 months (−10.9 [6.3] vs −8.2 [7.0]; \( P = .99 \)) but subsequently decreased more slowly with ergocalciferol vs placebo (−28.4 [6.2]; \( P < .001 \) vs −41.5 [5.9]; \( P < .001 \)), with a significant reduction in monthly overall temporal trends (mean [SE], −2.8% [0.7] vs −4.7% [0.6]; \( P = .03 \); Figure, C).

Discussion

In this study, ergocalciferol significantly decreased PI:C and slowed the decrease in \%\Delta AUC C-peptide among youths with T1D. We previously showed that ergocalciferol significantly reduced temporal trends in HbA\(_{1c}\), IDAA\(_{1c}\), and TNF-\(\alpha\).\(^1\) Although this randomized clinical trial was limited by its single-center setting, the results suggest a protective action of ergocalciferol on \(\beta\) cells and possible mechanisms of action to prolong PR. Ergocalciferol’s \(\Delta\) effect size for \(\beta\)-cell protection (15%) is comparable to that of imatinib,\(^5\) verapamil,\(^4\) and other agents (15%-19.4%). Thus, vitamin D may be combined with other treatments (eg, teplizumab and baricitinib) to prolong PR.
REFERENCES

SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Trial Protocol. Summary of IRB-Approved Amendments/Modifications to the Investigational Study Protocol With the Associated Dates

SUPPLEMENT 3.
eFigure. CONSORT Flow Diagram

SUPPLEMENT 4.
Data Sharing Statement