Effect of Cholecalciferol as Adjunctive Therapy With Insulin on Protective Immunologic Profile and Decline of Residual β-Cell Function in New-Onset Type 1 Diabetes Mellitus

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Objective: To evaluate the effect of vitamin D3 on cytokine levels, regulatory T cells, and residual β-cell function decline when cholecalciferol (vitamin D3 administered therapeutically) is given as adjunctive therapy with insulin in new-onset type 1 diabetes mellitus (T1DM).

Design and Setting: An 18-month (March 10, 2006, to October 28, 2010) randomized, double-blind, placebo-controlled trial was conducted at the Diabetes Center of São Paulo Federal University, São Paulo, Brazil.

Participants: Thirty-eight patients with new-onset T1DM with fasting serum C-peptide levels greater than or equal to 0.6 ng/mL were randomly assigned to receive daily oral therapy of cholecalciferol, 2000 IU, or placebo.

Main Outcome Measure: Levels of proinflammatory and anti-inflammatory cytokines, chemokines, regulatory T cells, hemoglobin A1c, and C-peptide; body mass index; and insulin daily dose.

Results: Mean (SD) chemokine ligand 2 (monocyte chemoattractant protein 1) levels were significantly higher (184.6 [101.1] vs 121.4 [55.8] pg/mL) at 12 months, as well as the increase in regulatory T-cell percentage (4.55% [1.5%] vs 3.34% [1.8%]) with cholecalciferol vs placebo. The cumulative incidence of progression to undetectable (≤0.1 ng/mL) fasting C-peptide reached 18.7% in the cholecalciferol group and 62.5% in the placebo group; stimulated C-peptide reached 6.2% in the cholecalciferol group and 37.5% in the placebo group at 18 months. Body mass index, hemoglobin A1c level, and insulin requirements were similar between the 2 groups.

Conclusions: Cholecalciferol used as adjunctive therapy with insulin is safe and associated with a protective immunologic effect and slow decline of residual β-cell function in patients with new-onset T1DM. Cholecalciferol may be an interesting adjuvant in T1DM prevention trials.


Type 1 diabetes mellitus (T1DM) is caused by a complex autoimmune process associated with altered humoral and cellular immunity that results in the specific immune destruction of insulin-producing β-cells before and after the diagnosis. There is clear evidence of clinical benefit resulting from preserved β-cell function; in the past few years, intervention trials in patients with new-onset T1DM have been undertaken to silence and/or modulate this altered immune response, aiming to preserve endogenous insulin production.

For editorial comment see page 664

A growing body of evidence from animal and in vitro studies suggests a functional role of vitamin D3 as an adaptive immune system modulator. Most tissues in the body have receptors for the active form of vitamin D3, which are also expressed in activated T and B human lymphocytes. β Cells are able to produce 1,25 dihydroxyvitamin D3 [1,25(OH)2D3], the biologically active form of vitamin D3, with a marked increase in cytosolic calcium after acute application of this vitamin. Immunologic studies in animal models showed that cholecalciferol (vitamin D3 given therapeutically) not only acts to suppress lymphocyte proliferation but also can modify the helper T-cell subtypes 1 and 2 (Th1/Th2) cytokines profile. Cytokines are considered hormones of the immune system that have important functions related to cellular proliferation, differentiation, and survival, and it is widely recognized that Th1 cytokine is associated with cell-mediated immunity and that Th2 cytokine is associated with humoral immune responses. It is believed that T1DM appears to be triggered by Th1 cells, while Th2 cells may be protective.
It also has been reported that exposition of human β cells to 1,25(OH)2D3 protects them from death by reducing expression of major histocompatibility complex class I molecules, inducing expression of antiapoptotic A20 protein and decreasing expression of Fas, a transmembrane cell surface receptor transducing an apoptotic death signal and contributing to the pathogenesis of several autoimmune diseases.

There are data showing that supplementation with cholecalciferol in infants, as well as through dietary exposure to vitamin D3 during pregnancy, is associated with reduced risk of human T1DM. In the clinical setting, 2 recent trials found no significant effect of 1,25(OH)2D3 on the preservation of β-cell function after T1DM onset. Nevertheless, the dose and mechanism of action of cholecalciferol in this condition are still under discussion.

Checmokines, chomatactic cytokines that possess the ability to attract and recruit distinct types of cells, have been implicated as recruiters of pathogenic and regulatory T cells to the pancreatic islets, highlighting their role in T1DM pathogenesis and in deceleration of disease onset.

In vivo studies have shown that 1,25(OH)2D3 inhibits the expression of inflammatory cytokines in monocytes, such as interleukin 6 (IL-6), IL-8, IL-12, and tumor necrosis factor, in healthy individuals. The influence of this vitamin on cytokine production by lymphocytes may be another important link between vitamin D3 and the immune system.

The aim of the present study was to evaluate the effect of vitamin D3, [25(OH)D3], the main circulating metabolite of vitamin D3, on peripheral cytokine/chemokine levels, regulatory T cells, and residual β-cell function decrease when given as adjunctive therapy to insulin in patients with new-onset T1DM.

**METHODS**

**DESIGN AND SETTING**

We conducted a prospective 18-month-randomized, double-blind, placebo-controlled study of cholecalciferol concomitant with intensive insulin therapy in patients with new-onset T1DM.

The research protocol (No. 0101/05) was approved by the São Paulo Federal University Ethics Committee, and written informed consent was provided by patients or their guardians. Assent was obtained from children. The study was conducted at the Diabetes Center of São Paulo Federal University, São Paulo, Brazil, from March 10, 2006, through October 28, 2010.

**PARTICIPANTS**

We screened 40 patients with T1DM (according to the American Diabetes Association standards), and 38 were randomized to receive cholecalciferol (n=19) or placebo (n=19). 2 individuals were excluded because they did not meet inclusion criteria. Three patients withdrew from the study: 1 in the placebo group and 2 in the cholecalciferol group because of insufficient adherence. A total of 17 participants in the cholecalciferol group and 18 in the placebo group completed the 18-month follow-up period (Figure 1).

Inclusion criteria were (1) age between 7 and 30 years, (2) disease duration less than 6 months (ie, from first insulin injection), (3) positive test results for islet cell autoantibodies (anti-glutamic acid decarboxylase 65 or antiprotein tyrosine phosphatase), and (4) fasting or 2-hour postmeal stimulated serum C-peptide level of 0.6 ng/mL or more (to convert to nanomoles per liter, multiply by 0.331) during a mixed meal tolerance test (6 mL/kg of body weight [maximum, 360 mL]; Sustagen, Mead Johnson). This test was performed between 7 and 10 AM after an overnight fast, during which only water was ingested. The patients received no short-acting insulin for at least 6 hours before the test. This C-peptide level was chosen according to the protocol of the TrialNet Study Group. Exclusion criteria were severe systemic disease and disorders in calcium metabolism.

**RANDOMIZATION**

Randomization was performed by a pharmacist, without the researchers’ knowledge. Patients were assigned to receive 2000 IU of cholecalciferol (n=17) or placebo (n=18) orally at breakfast daily throughout an 18-month period. We chose this dose because it was associated with reduced risk of type 1A diabetes in a Finnish birth-cohort study. The cholecalciferol and placebo were produced by an independent pharmacy in São Paulo (Millenium) and sent coded to the Diabetes Center.

**INTERVENTION**

After baseline evaluation, patients returned to the Diabetes Center at 1, 3, 6, 9, 12, 15, and 18 months for insulin dosage adjustment, hemoglobin (Hb) A1c measurement, and safety assessment, and to receive their supply of cholecalciferol or placebo (adherence was assessed by drug container return). Evaluation was performed at 0, 6, 12, and 18 months for serum C-peptide, cytokines, and chemokines, as well as peripheral blood regulatory T-cell percentage. The insulin regimen for both trial arms was intensive (multiple [≥3] daily injections associated with glucose self-monitoring [≥3 checks of the glucose level]).

**OUTCOME MEASURES**

Complete blood cell count, aminotransferase levels, and phosphate and alkaline phosphatase levels were evaluated by automated chemistry analyzers (Advia 120 and 2400; Siemens, Germany).

The HbA1c level was measured in whole blood using high-performance liquid chromatography (Tosoh Bioscience, normal value, 3.5%-6.0%). Serum C-peptide level was measured by an immunofluorometric assay (AutoDelfia) with a detec-
The cholecalciferol and placebo groups were similar in terms of age (mean [SD], 13.5 [5.1] vs 12.5 [4.8] years), sex (male, 61% vs 59%), Tanner stage 1 (44% vs 38%), and duration of disease (2.2 [1.2] vs 2.7 [1.7] months).

Serum concentrations of 25(OH)D$_3$ in the cholecalciferol-treated group (basal, 26.34 [6.49] vs 6 months, 60.88 [21.64] ng/mL; $P < .001$) increased during this period and were maintained until the end of the study. In the placebo group, there was a nonsignificant ($P = .38$) variation in the 25(OH)D$_3$ serum levels during the same period (basal, 25.76 [5.68] vs 6 months, 28.57 [8.77] ng/mL). The 25(OH)D$_3$ serum levels exhibited a trend to be higher in the treatment group than in the placebo group (65.02 [25.95] vs 40.52 [10.35] ng/mL; $P = .06$) at 18 months. Plasma ionized calcium concentrations were similar in the cholecalciferol and placebo groups at basal conditions (1.31 [0.08] vs 1.33 [0.05] ng/mL) and at 18 months (1.35 [0.47] vs 1.29 [0.05] ng/mL). Other safety determinants (complete blood cell count and amino-transferase, phosphorus, and alkaline phosphatase levels) also were within the reference ranges in both groups. No clinical adverse events were reported during the study.

The groups were similar in terms of body mass index and insulin dosage (U/kg/d) at baseline and during the study (Table 1). The HbA$_1c$ level was significantly higher in the cholecalciferol group than in the placebo group at the beginning of the study and fell significantly after 6 months in the cholecalciferol group ($P = .05$), with no significant difference in the other time points between the 2 groups.

There were no significant differences in sera concentrations of IL-12, IL-6, IL-1B, IL-8, IL-10, chemokine IL-8, and chemokine IL-99 between the groups at baseline and during follow-up (Table 2). A significant decrease in IL-12 serum levels was detected in the first 6 months of study in both groups ($P = .05$).

In the cholecalciferol group, interferon gamma-inducible protein 10 (CXCL10) levels were significantly higher at baseline (148.1 [100.2] pg/mL vs 93.4 [47.4] pg/mL; $P = .02$) compared with the placebo group, as well as chemokine ligand 2 (CCL2) at 12 months (184.6 [101.1] pg/mL vs 121.4 [55.8] pg/mL; $P = .04$) and with a trend of higher values until the end of the study ($P = .07$) in the cholecalciferol group (Table 2). After regression analysis, IL-6 was the only independent factor.

### Table 1. Changes in Clinical, Metabolic, and Endocrine Variables in Patients With New-Onset T1DM During the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cholecalciferol (n = 17)</th>
<th>Placebo (n = 18)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting C-peptide, ng/mL</td>
<td>0.65 (0.45)</td>
<td>0.92 (0.83)</td>
<td>.25</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.88 (0.85)</td>
<td>0.76 (0.71)</td>
<td>.66</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.55 (0.42)</td>
<td>0.55 (0.35)</td>
<td>.99</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.45 (0.34)</td>
<td>0.43 (0.49)</td>
<td>.91</td>
</tr>
<tr>
<td>Stimulated C-peptide, ng/mL</td>
<td>1.55 (0.91)</td>
<td>1.83 (1.03)</td>
<td>.40</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.74 (1.57)</td>
<td>1.43 (0.97)</td>
<td>.47</td>
</tr>
<tr>
<td>Month 6</td>
<td>1.26 (1.03)</td>
<td>1.18 (1.04)</td>
<td>.84</td>
</tr>
<tr>
<td>Month 12</td>
<td>1.10 (1.03)</td>
<td>0.96 (1.08)</td>
<td>.73</td>
</tr>
<tr>
<td>Hemoglobin A$_1c$, %</td>
<td>9.25 (2.17)</td>
<td>7.73 (2.16)</td>
<td>.05</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.34 (1.56)</td>
<td>7.40 (2.14)</td>
<td>.93</td>
</tr>
<tr>
<td>Month 6</td>
<td>7.72 (1.96)</td>
<td>7.57 (1.65)</td>
<td>.81</td>
</tr>
<tr>
<td>Month 12</td>
<td>8.29 (2.06)</td>
<td>8.91 (2.71)</td>
<td>.53</td>
</tr>
<tr>
<td>Daily insulin dose, U/kg/d</td>
<td>0.52 (0.19)</td>
<td>0.43 (0.19)</td>
<td>.19</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.57 (0.24)</td>
<td>0.56 (0.20)</td>
<td>.92</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.72 (0.18)</td>
<td>0.69 (0.28)</td>
<td>.79</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.81 (0.37)</td>
<td>0.80 (0.27)</td>
<td>.91</td>
</tr>
<tr>
<td>Body mass index$^b$</td>
<td>18.5 (3.0)</td>
<td>18.6 (2.5)</td>
<td>.75</td>
</tr>
<tr>
<td>Baseline</td>
<td>18.7 (3.0)</td>
<td>19.0 (2.1)</td>
<td>.55</td>
</tr>
<tr>
<td>Month 6</td>
<td>18.7 (2.8)</td>
<td>19.3 (2.7)</td>
<td>.51</td>
</tr>
<tr>
<td>Month 12</td>
<td>19.5 (2.8)</td>
<td>20.5 (4.2)</td>
<td>.83</td>
</tr>
</tbody>
</table>

Abbreviation: T1DM, type 1 diabetes mellitus.

* SI conversion factors: To convert C-peptide to nanomoles per liter, multiply by 0.331; to convert hemoglobin A$_1c$ to a proportion of total hemoglobin, multiply by 0.01.

* Between-group comparisons.

$^b$ Calculated as weight in kilograms divided by height in meters squared.
associated with CCL2 (β = 49.23; P = .02). No association was found between chemokines/cytokines and serum C-peptide or metabolic variables during the monitoring period.

Percentages of regulatory T cells were not significantly different in either group at baseline (P = .75), but increased significantly at 12 months of the follow-up study in the cholecalciferol group (P = .04). The percentage of these cells in peripheral blood was not associated with any clinical or other immunologic variables studied.

During the follow-up period, there was a decrease in the antiglutamic acid decarboxylase 65 titer of 60% (baseline vs 18 months; P = .05) in the cholecalciferol group, and antiprotein tyrosine phosphatase titers showed great variability, with a paradox increase of 160% (P = .02) up to 18 months with cholecalciferol vs placebo.

Interestingly, stimulated serum C-peptide was enhanced in the first 12 months (12% vs −35%; P = .01) and had less decay until 18 months (−14% vs −46%) in the cholecalciferol group compared with the placebo group (P = .03) (Figure 2).

The cumulative incidence of progression to undetectable fasting serum C-peptide (≤0.1 ng/mL) fasting serum C-peptide during the 18 months of monitoring reached 18.7% in the cholecalciferol group and 62.5% in the placebo group (P = .01), and stimulated C-peptide reached this level in 62.2% of the cholecalciferol group and 37.5% of the placebo group (P = .047) (Figure 3A and B).

Regression analysis showed that body mass index (β = 0.09, P = .047), insulin dose (β = −1.20, P = .006), and HbA1c (β = −0.16, P = .02) were independently related to stimulated serum C-peptide.

This placebo-controlled trial of cholecalciferol, 2000 IU/d, involved patients with new-onset type 1DM, including children, who had significant residual β-cell function, so that a possible effect of this vitamin could be detected. We found that stimulated serum C-peptide was enhanced during the first year after diagnosis and showed a significantly smaller decline after 18 months (the primary end point) with cholecalciferol compared with placebo.

Abbreviations: CCL2, chemokine ligand 2; CXCL, interferon gamma–inducible protein 10; IL, interleukin; T1DM, type 1 diabetes mellitus; TNF, tumor necrosis factor.

Table 2. Changes in IL-12, TNF, CXCL10, CCL2, and Regulatory T Cells in Patients With New-Onset T1DM During the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholecalciferol</td>
<td>Placebo</td>
</tr>
<tr>
<td>IL-12, pg/mL</td>
<td>Baseline</td>
<td>12.5 (17.5)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>3.5 (7.3)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>6.4 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>3.9 (5.0)</td>
</tr>
<tr>
<td>TNF, pg/mL</td>
<td>Baseline</td>
<td>9.3 (157)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>1.9 (6.3)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>4.6 (8.9)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>2.2 (3.8)</td>
</tr>
<tr>
<td>Chemokine IL-10, pg/mL</td>
<td>Baseline</td>
<td>148.1 (100.2)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>104.9 (57.1)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>113.9 (99.2)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>204.2 (311.9)</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>Baseline</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>1.5 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>2.0 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>1.4 (1.0)</td>
</tr>
<tr>
<td>CCL2, pg/mL</td>
<td>Baseline</td>
<td>192.3 (92.0)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>139.2 (45.2)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>184.6 (101.1)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>221.9 (257.2)</td>
</tr>
<tr>
<td>Regulatory T cells, %</td>
<td>Baseline</td>
<td>3.34 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>4.09 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>4.55 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Month 18</td>
<td>3.75 (1.6)</td>
</tr>
</tbody>
</table>

Figure 2. Analysis of the percentage of change in stimulated C-peptide level at 0, 6, 12, and 18 months in patients with new-onset type 1 diabetes treated with cholecalciferol or placebo. Limit lines indicate standard deviation.

Figure 3. A cumulative incidence of progression to undetectable fasting C-peptide (A) and stimulated C-peptide (B) (≤0.1 ng/mL) in patients with new-onset type 1 diabetes treated with cholecalciferol or placebo. The number of patients was unchanged, with 17 in the cholecalciferol group and 18 in the placebo group.

COMMENT

This placebo-controlled trial of cholecalciferol, 2000 IU/d, involved patients with new-onset T1DM, including children, who had significant residual β-cell function, so that a possible effect of this vitamin could be detected. We found that stimulated serum C-peptide was enhanced during the first year after diagnosis and showed a significantly smaller decline after 18 months (the primary end point) with cholecalciferol compared with placebo.
Our results also suggest, in a clinical setting, a preliminary mechanism of action of cholecalciferol supplementation, demonstrating increased levels of peripheral CCL2 as well as the percentage of regulatory T cells in the cholecalciferol-treated group. Chemokine ligand 2 is a potent factor in the polarization of T<sub>H0</sub>0 cells toward a T<sub>H1</sub>/T<sub>H2</sub> phenotype. However, T<sub>H1</sub>/T<sub>H2</sub> imbalance does not necessarily mean that T<sub>H1</sub> is only proinflammatory and T<sub>H2</sub> is only anti-inflammatory; instead, the interplay between those cytokines and defects in regulatory T cells probably determine the fate of β cells in T1DM.

Taken together, the increase of CCL2 serum levels and regulatory T cells by cholecalciferol treatment in patients with new-onset T1DM may collaborate to delay the autoimmune destruction of the β cells.

Quantification of 25(OH)D<sub>3</sub> in serum is the best indicator of overall vitamin D status. The important forms of vitamin D are cholecalciferol (vitamin D<sub>3</sub>) and ergocalciferol (vitamin D<sub>2</sub>). However, the potency of ergocalciferol is less than one-third that of cholecalciferol, and more than 95% of 25(OH)D measurable in serum is usually 25(OH)D<sub>3</sub>. The cholecalciferol and placebo groups had insufficient (<30 ng/mL) levels of 25(OH)D<sub>3</sub> at baseline. Low serum levels of vitamin D<sub>3</sub> have usually been reported in T1DM. The vitamin D<sub>3</sub> serum level in newly diagnosed T1DM patients with new-onset T1DM may collaborate to delay the autoimmune destruction of the β cells.

Many studies demonstrate that glucotoxicity might also influence cytokine and chemokine production. Therefore, the higher levels of CXCL10 in the cholecalciferol group than in the placebo group may be explained by the higher HbA<sub>1c</sub> level in the treatment vs placebo group at the beginning of the study.

To our knowledge, the influence of cholecalciferol as an adjunct to insulin therapy and glycemic control in cell-mediated immunity and proinflammatory cytokines has been not studied in T1DM. We analyzed the evolution of proinflammatory and anti-inflammatory cytokines/chemokines and regulatory T cells in our patients during cholecalciferol supplementation. In the first 6 months of the study, we saw overall diminished inflammatory cytokine secretion (IL-12, IL-6, IL-1β, and tumor necrosis factor) in both groups. In general, it was related to improvement in metabolic control and anti-inflammatory effects of insulin. However, after this period, we observed 3 benefits for the patients’ immunologic profiles: (1) a tendency to increase IL-10, (2) a significant increase of CCL2, and (3) an increase in regulatory T cells, which might have contributed to the less-progressive β-cell decay in the cholecalciferol group.

There are data potentially involving IL-10-dependent regulatory T-cell pathways on recovery of β-cell function even after the clinical onset of T1DM. An increase of CCL2 may suggest a shift toward helper T-cell immunity; however, this has been described as occurring with routine insulin therapy during the first 2 years after diagnosis in a group of children with newly diagnosed T1DM. With respect to cholecalciferol supplementation associated with increase in the percentage of regulatory T cells, this was recently reported in apparently healthy individuals who had taken 140 000 U of cholecalciferol monthly for 3 months.

Finally, we cannot rule out that the lesser decay of serum C-peptide shown in the cholecalciferol group could be mediated by its direct action on β-cell function, increasing the levels of cytosolic calcium that is important for the movement of insulin granules and insulin secretion.
Overall, we showed that cholecalciferol doses of 2000 IU/d concomitant with insulin therapy is safe and related to protective immunologic profile and slow decline of residual β-cell function in new-onset T1DM. Cholecalciferol can be an interesting adjuvant in combination with immunosuppressant drugs in T1DM prevention studies.

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Author Contributions: Dr Gabbay had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gabbay, Duarte, and Dib. Acquisition of data: Gabbay, Sato, and Finazzo. Analysis and interpretation of data: Gabbay and Dib. Drafting of the manuscript: Gabbay, Sato, and Finazzo. Critical revision of the manuscript for important intellectual content: Gabbay, Duarte, and Dib. Obtained funding: Dib. Administrative, technical, and material support: Gabbay, Sato, and Dib. Study supervision: Dib.

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lates with serum 25-hydroxyvitamin D, but not with 1,25-dihydroxyvitamin D,

Correction

Error in Acknowledgments. In the Article titled “Selective Protection Against Extremes in Childhood Body Size, Abdominal Fat Deposition, and Fat Patterning in Breastfed Children” by Crume et al., published in the May issue of the Archives (2012;166[5]:437-443), an error occurred in the Acknowledgments section on page 442. A stray line of type (“had no role in the study.””) between the “Role of the Sponsor” and “Additional Contributions” sections should have been deleted.