No Protective Effect of Calcitriol on β-Cell Function in Recent-Onset Type 1 Diabetes

The IMDIAB XIII trial

Carla Bizzarri, MD[1]
Dario Pitocco, MD[2]
Nicola Napoli, MD[3]
Enrico Di Stasio, MD[2]
Daria Maggi, MD[3]
Silvia Manfrini, MD[3]
Concetta Suraci, MD[4]
Maria Gisella Cavallo, MD[5]
Marco Cappa, MD[1]
Giovanni Ghirlanda, MD[2]
Paolo Pozzilli, MD[3]
the IMDIAB Group*

OBJECTIVE — We investigated whether supplementation of the active form of vitamin D (calcitriol) in recent-onset type 1 diabetes can protect β-cell function evaluated by C-peptide and improve glycemic control assessed by A1C and insulin requirement.

RESEARCH DESIGN AND METHODS — Thirty-four subjects (aged 11–35 years, median 18 years) with recent-onset type 1 diabetes and high basal C-peptide >0.25 nmol/l were randomized in a double-blind trial to 0.25 μg/day calcitriol or placebo and followed-up for 2 years.

RESULTS — At 6, 12, and 24 months follow-up, A1C and insulin requirement in the calcitriol group did not differ from the placebo group. C-peptide dropped significantly ($P < 0.001$) but similarly in both groups, with no significant differences at each time point.

CONCLUSIONS — At the doses used, calcitriol is ineffective in protecting β-cell function in subjects (including children) with recent-onset type 1 diabetes and high C-peptide at diagnosis.

Diabetes Care **33:1962–1963, 2010**

Vitamin D deficiency has been associated with type 1 diabetes (1). Several studies suggest that vitamin D supplementation in early childhood decreases the risk of developing type 1 diabetes (2,3). The aim of this pilot trial was to investigate whether the supplementation of the active form of vitamin D (calcitriol) in subjects with recent-onset type 1 diabetes is able to protect residual β-cell function (C-peptide) and to improve metabolic control.

RESEARCH DESIGN AND METHODS

— Patients with recent-onset type 1 diabetes (17 female and 17 male subjects; aged 11–35 years, median 18 years) were studied. Criteria for inclusion were *1*) diagnosis according to the American Diabetes Association, *2*) age at presentation between 11 and 35 years, *3*) duration of clinical disease (since the beginning of insulin therapy) <12 weeks, and *4*) baseline C-peptide >0.25 nmol/l.

A double-blind trial was designed with patients randomized to 0.25 μg/daily calcitriol (the active form of vitamin D, 1.25-dihydroxyvitamin D3) or placebo and followed-up for 2 years. The study was approved by ethical committees of the participating institutions, with informed consent signed by patients or parents, where appropriate.

Guidelines for insulin therapy

The same protocol for insulin treatment as in previous IMmunotherapy of DIABetes (IMDIAB) trials (4) was applied.

Investigations and follow-up

Fasting C-peptide, A1C, and 25(OH) vitamin D levels were evaluated up to 24 months. Stimulated C-peptide meal test was performed at baseline and at 12 months using a Boost High-Protein standardized liquid meal, with blood samples drawn at baseline and 30, 60, and 120 min. C-peptide was evaluated by chemiluminescence on an ADVIA Centaur analyzer and serum 25-hydroxyvitamin D (25OHD) by radioimmunoassay (Diasorin), detecting both forms of 25OHD.

Statistical power and analysis

The number of patients to be included in the trial was calculated from setting a difference in basal C-peptide of 0.12 nmol/l at 2 years after diagnosis between the calcitriol and placebo groups. Setting α (probability of type 1 error) equal to 0.05 and β (probability of type 2 error) equal to 80%, the required sample size was 26 patients for a two-sided test. To ensure an appropriate sample size, 34 patients were recruited to allow for drop outs. Multiple comparison by ANOVA was used to compare treatment groups across time points with Bonferroni correction where appropriate.

RESULTS

— Twenty-seven subjects (79.4%) completed the trial, 15 in the calcitriol group and 12 in the placebo group. Overall, there were 16 of 34 subjects (47%) with a significant vitamin D deficiency (blood levels <20 ng/ml), whereas at 24 months 25OHD levels were slightly increased in the calcitriol group (+3.9%) and reduced in the placebo group (−8.0%).

At 6, 12, and 24 months, A1C, C-peptide, and insulin requirement values did not differ between calcitriol and placebo groups. The area under the curve of C-peptide response ($AUC_{0-120\ min}$) was not significantly different in the calcitriol versus placebo group at baseline (calcit-

From the [1]Department of Endocrinology and Diabetes, Bambino Gesù Children's Hospital, Rome, Italy; the [2]Department of Diabetology, Catholic University, Rome, Italy; the [3]Department of Endocrinology and Diabetes, University Campus Bio-Medico, Rome, Italy; the [4]Department of Diabetology, Sandro Pertini Hospital, Rome, Italy; and the [5]Department of Medical Therapy, University Sapienza, Rome, Italy.
Corresponding author: Paolo Pozzilli, p.pozzilli@unicampus.it.
Received 10 May 2010 and accepted 9 June 2010.
*A complete list of the members of the IMDIAB Group can be found in the APPENDIX.
DOI: 10.2337/dc10-0814. Clinical trial registry no. NCT01120119, clinicaltrials.gov.

riol group: 69.9 ± 24.8 nmol/l × 120 min; placebo group: 72.5 ± 37.7; $P = 0.658$) or after 12 months (calcitriol group: 49.7 ± 30.4 nmol/l × 120 min; placebo group: 56.2 ± 39.7; $P = 0.845$).

Fasting C-peptide dropped significantly in both groups during follow-up ($P < 0.001$). Mean rate of decline in fasting C-peptide after 12 months was 17.7% in the calcitriol group and 28.4% in the placebo group. After 24 months, the rate of C-peptide decline was 44.4% in the calcitriol group and 42.5% in the placebo group. At 12 months, the $AUC_{0-120\ min}$ of C-peptide dropped significantly in both the calcitriol ($P < 0.03$) and control ($P < 0.04$) groups. No differences were observed in the mean C-peptide response after mixed meal at different time points between the two groups. Vitamin D status did not influence residual β-cell function. Likewise, vitamin D deficiency at diagnosis was not associated with lower residual β-cell function at 24 months (C-peptide in patients with 25OHD levels <20 ng/ml: 0.19 ± 0.09 nmol/l vs. 0.22 ± 0.16 nmol/l in patients with 25OHD levels >20 ng/ml; $P = 0.408$). Calcium and phosphate levels remained within normal limits throughout the follow-up, and no adverse events were reported in any patient.

CONCLUSIONS — In the first pilot trial with calcitriol, Walter et al. (5) reported no differences in fasting C-peptide, AUC C-peptide, and peak C-peptide after a mixed meal between treated and placebo groups at 9 and 18 months. A1C and insulin requirement were also similar between the groups. In the aforementioned study, no threshold of C-peptide level at study entry was defined. We designed a trial in which patients were younger at diagnosis, including also children, and should have had basal C-peptide levels at entry >0.25 nmol/l so that a possible effect of calcitriol on disease progression could have been detected. We have shown that calcitriol does not affect residual β-cell function in such patients, even those of younger age. Similar to the German trial describing a mean C-peptide decrease of ~40% at 18 months, in our study, decline of C-peptide after 24 months was 44.4% in the calcitriol group and 42.5% in the placebo group. These findings substantially confirm the data from combined studies collected by the TrialNet Research Group on decline of C-peptide (6).

In the study by Walter et al. (5), serum concentrations of the active form of vitamin D 1.25(OH)2D3 were determined only in 13 patients in the safety phase, at baseline, and after 9 months of treatment, and they increased significantly (24.6 vs. 30.3 pg/ml; $P < 0.02$). On the contrary, we found that plasma levels of 25OHD were only modestly modified by the oral supplementation of calcitriol.

In view of the association of supplementation of vitamin D early in life with a risk reduction of type 1 diabetes (2,3,7), it is likely that the protective effects of vitamin D may be beneficial in modulating the initiation of the autoimmune process. However, supplementation after disease onset does not induce any beneficial effect.

In conclusion, the results of this trial indicate that, at the doses used, calcitriol is ineffective in preserving residual β-cell function.

Acknowledgments — This study was supported by a grant from Ministero Università e Ricerca Scientifica (Progetti di Interesse Nazionale PRIN) to P.P., principal investigator.

No potential conflicts of interest relevant to this article were reported.

C.B. researched data, contributed to the discussion, and wrote the manuscript. D.P. researched data, contributed to the discussion, and wrote the manuscript. N.N. researched data, contributed to the discussion, and wrote the manuscript. E.D.S. reviewed/edited the manuscript. D.M. researched data and contributed to the discussion. S.M. researched data and contributed to the discussion. C.S. researched data, contributed to the discussion, and wrote the manuscript. M.G.C. researched data, contributed to the discussion, and wrote the manuscript. M.C. reviewed/edited the manuscript. G.G. reviewed/edited the manuscript. P.P. reviewed/edited the manuscript.

Calcitriol and placebo tablets were prepared by pharmacist Dr. Raffaele Marzano, who is greatly acknowledged for his contribution.

APPENDIX

Members of the IMDIAB Group

M. Altomare, E. Astorri, I. Barchetta, D. Benevento, G. Beretta Anguissola, C. Bizzarri, R. Buzzetti, M. Capizzi, M. Cappa, M.R. Cassone Faldetta, M.G. Cavallo, L. Cipolloni, E. Cipponeri, F. Costantino, A. Crinò, E. Di Stasio, E. Fioriti, G. Ghirlanda, C. Guglielmi, A. Lauria, D. Maggi, S. Manfrini, A.R. Maurizi, C. Moretti, L. Morbiducci, N. Napoli, A. Palermo, P. Patera, D. Pitocco, R. Portuesi, P. Pozzilli, R. Scrocca, S. Spera, R. Strollo, C. Suraci, C. Tubili, D. Tuccinardi, L. Valente, N. Visalli.

References

1. Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. Diabetologia 2005;48:1247–1257
2. The EURODIAB Substudy 2 Study Group. Vitamin D supplements in early childhood and risk for type I (insulin dependent) diabetes mellitus. Diabetologia 1999;42:51–54
3. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500–1503
4. Pitocco D, Crinò A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, Anguissola GB, Visalli N, Suraci C, Matteoli MC, Patera IP, Cavallo MG, Bizzarri C, Pozzilli P, the IMDIAB Group. The effects of calcitriol and nicotinamide on residual pancreatic beta-cell function in patients with recent-onset type 1 diabetes (IMDIAB XI). Diabet Med 2006;23:920–923
5. Walter M, Kaupper T, Adler K, Foersch J, Bonifacio E, Ziegler AG. No Effect of the 1α,25-dihydroxyvitamin D3 on β-cell residual function and insulin requirement in adults with new-onset type 1 diabetes. Diabetes Care 2010;33:1443–1448
6. Palmer JP. C-peptide in the natural history of type 1 diabetes. Diabetes Metab Res Rev 2009;25:325–328
7. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child 2008;93:512–517