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The Effect of Vitamin D Supplementation on Preserving Pancreatic Beta Cell Function in Patients with Newly Diagnosed Type 1 Diabetes

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The Effect of Vitamin D Supplementation on Preserving Pancreatic Beta Cell Function in Patients with Newly Diagnosed Type 1 Diabetes

Abstract

Background: The incidence of type one diabetes is increasing. A diagnosis of type one diabetes comes with serious, lifelong implications including the need to inject exogenous insulin multiple times each day. Failure to adhere to a strict treatment regime can lead to microvascular and macrovascular complications involving the cardiovascular, vascular, renal and ocular systems. Current research is focused on the prevention of diabetes. More specifically, recent research addresses how treatment can be offered to slow disease progression and preserve pancreatic beta cell function. Can adjunctive treatment with vitamin D in patients with newly diagnosed type one diabetes preserve pancreatic beta cell function?

Methods: An exhaustive search of medical literature was conducted using Medline-OVID, CINAHL, EBMR Multifile, Web of Science and NIH clinical trials using the keywords: Vitamin D, type 1 diabetes mellitus, and beta cell function. Relevant articles were assessed for quality using GRADE.

Results: Three studies met inclusion criteria and were included in this systematic review. A two-part, randomized, double blind, placebo-controlled trial with 25 subjects showed supplementation with 1 alpha, 25-Dihydroxyvitamin D3 was safe, but showed no difference in stimulated C-peptide levels between treatment patients and placebo. A randomized, double blind, placebo-controlled trial with 34 subjects showed no difference in stimulated C-peptide levels between patients supplemented with calcitriol or placebo. Finally, a randomized, double blind, placebo-controlled trial with 38 patients showed a higher level of residual C-peptide production in patients treated with cholecalciferol versus placebo. This study also demonstrated moderate evidence towards vitamin D supplementation and subsequent immune-protective benefits.

Conclusion: Overall, there isn’t compelling evidence to show that Vitamin D supplementation can preserve pancreatic beta cell function in patients with newly diagnosed type one diabetes. However, it appears that there is modest evidence to show that vitamin D, specifically in the form of cholecalciferol, has the ability to slow the decline of residual beta cell function. Furthermore, it appears that supplementation with vitamin D is safe and could provide immunity benefits that have yet to be proven.

Keywords: Type 1 diabetes mellitus, vitamin D, beta cell function

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Robert Rosenow

Keywords
Type 1 diabetes mellitus, vitamin D, beta cell function

Subject Categories
Medicine and Health Sciences

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The Effect of Vitamin D Supplementation on Preserving Pancreatic Beta Cell Function in Patients with Newly Diagnosed Type 1 Diabetes

Molly Hamilton

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 10, 2013

Faculty Advisor: Robert P. Rosenow, Pharm.D., O.D.
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Revised 07Dec2009
Biography

Molly Hamilton was born and raised in Northern New Hampshire before travelling to Montana at the age of 18. She completed her undergraduate degree at the University of Montana in Missoula in Health and Human Performance, with a focus on Exercise Science. During her senior year of her undergraduate degree she travelled back to New Hampshire during winter break to complete a wilderness EMT course. After completing her undergraduate degree, Molly went on to work as an Emergency Room Technician in Missoula. During this time she decided that she wanted to pursue a career as a Physician Assistant. Molly is interested in working in Emergency Medicine in Montana.
Abstract

Background: The incidence of type one diabetes is increasing. A diagnosis of type one diabetes comes with serious, lifelong implications including the need to inject exogenous insulin multiple times each day. Failure to adhere to a strict treatment regime can lead to microvascular and macrovascular complications involving the cardiovascular, vascular, renal and ocular systems. Current research is focused on the prevention of diabetes. More specifically, recent research addresses how treatment can be offered to slow disease progression and preserve pancreatic beta cell function. Can adjunctive treatment with vitamin D in patients with newly diagnosed type one diabetes preserve pancreatic beta cell function?

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Results: Three studies met inclusion criteria and were included in this systematic review. A two-part, randomized, double blind, placebo-controlled trial with 25 subjects showed supplementation with 1 alpha, 25-Dihydroxyvitamin D3 was safe, but showed no difference in stimulated C-peptide levels between treatment patients and placebo. A randomized, double blind, placebo-controlled trial with 34 subjects showed no difference in stimulated C-peptide levels between patients supplemented with calcitriol or placebo. Finally, a randomized, double blind, placebo-controlled trial with 38 patients showed a higher level of residual C-peptide production in patients treated with cholecalciferol versus placebo. This study also demonstrated moderate evidence towards vitamin D supplementation and subsequent immune-protective benefits.

Conclusion: Overall, there isn’t compelling evidence to show that Vitamin D supplementation can preserve pancreatic beta cell function in patients with newly diagnosed type one diabetes. However, it appears that there is modest evidence to show that vitamin D, specifically in the form of cholecalciferol, has the ability to slow the decline of residual beta cell function. Furthermore, it appears that supplementation with vitamin D is safe and could provide immunity benefits that have yet to be proven.

Keywords: Type 1 diabetes mellitus, vitamin D, beta cell function
Acknowledgements

To my fiancée Brendan, my family and friends for their never ending support and love. I would not be where I am today without all of you. Thank You.
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List of Abbreviations

US.....................................................................................................................United States
TID...............................................................................................................Type 1 Diabetes
GAD.................................................................Glutamic Acid Decarobxylase 65
LADA...........................................................Latent Autoimmune Diabetes
NIH............................................................................................................National Institute of Health
GRADE.......Grading of Recommendations, Assessment, Development and Evaluation
1,25(OH)2D3...........................................................1alpha,25-Dihydroxyvitamin D3
AUC..........................................................................................Area Under the Curve
MMTT............................................................................Mixed Meal Tolerance Test
HbA1C..............................................................Glycated Hemoglobin
ADA.........................................................American Diabetes Association
BMI......................................................................................Body Mass Index
IL..............................................................................................Interleukin
TNF..............................................................Tumor Necrosis Factor
CCL.......................................................................................Chemokine Ligand
The Effect of Vitamin D Supplementation on Preserving Pancreatic Beta Cell Function in Patients with Newly Diagnosed Type 1 Diabetes

BACKGROUND

Diabetes affects 25.8 million people, approximately 8.3% of the United States (US) population. It is the seventh leading cause of death in the US. It is estimated that the total yearly cost of diabetes in the US is $174 billion dollars. Diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations and new cases of blindness, along with a major cause of heart disease and stroke in adults in the US. Type One Diabetes (T1D) accounts for approximately 5-10% of all diagnosed cases of diabetes and the incidence is increasing. T1D is an autoimmune disorder in which the body’s own immune system mistakenly destroys the beta cells in the pancreas, the only cells in the body that produce insulin. A diagnosis of T1D comes with a lifetime requirement to inject exogenous insulin. Beta cell destruction occurs during and after clinical disease presentation and is thought to be due to a combination of genetic and environmental factors, including but not limited to viruses, environmental toxins or foods. Extensive research has been conducted to search for a cure, without success at this time. Instead, focus has turned to prevention. Primary prevention studies have taken place in genetically at risk children with attempts to avert the autoimmune destruction. Secondary intervention studies have been attempted in individuals with presence of autoimmune antibodies, but normal insulin secretion as assessed by blood sugar values. Tertiary intervention involves patients that already have clinical evidence of T1D and attempts to preserve their residual beta cell function. A potential link between vitamin D deficiency and T1D has been explored. A birth-cohort study showed that vitamin D supplementation
in the first year of life reduced the risk of developing T1D.\textsuperscript{5} A prospective cross-sectional study showed that frequency of vitamin D deficiency in children with T1D is substantial.\textsuperscript{6} Focus more recently has shifted to tertiary intervention and the use of vitamin D as an immunomodulator to preserve beta cell function in patients with clinically evident T1D.\textsuperscript{3} Can adjunctive treatment with vitamin D in patients with newly diagnosed T1D preserve pancreatic beta cell function?

METHODS

An exhaustive search of medical literature was conducted using Medline-OVID, CINAHL, EBMR Multifile and Web of Science using the keywords: vitamin D, type 1 diabetes mellitus, and beta cell function. The bibliographies of these articles were extensively scanned for relevant articles. Inclusion criteria included recent diagnosis of T1D (less than six months), patients positive for islet autoantibodies (anti-glutamic acid decarboxylase 65 (GAD) or anti IA-2), and any form of vitamin D supplementation (calcitriol, cholecalciferol, etc). Exclusion criteria included patients with latent autoimmune diabetes (LADA), comparison to treatment other than placebo, and animal studies. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).\textsuperscript{7}

RESULTS

Preliminary searches yielded 19 articles for review. However after screening with established inclusion and exclusion criteria three articles remained.\textsuperscript{8,9,10} All three were randomized controlled trials (see table I). Furthermore, a search on the NIH clinical trials
site reveals there are no active studies regarding vitamin D supplementation to preserve pancreatic beta cell function in patients with newly diagnosed T1D.

Walter et al Study

This randomized, double blinded, placebo controlled trial\(^8\) was a two part study. Part one was a safety assessment of 0.25 microgram doses of 1alpha,25-Dihydroxyvitamin D\(_3\) (1,25(OH)\(_2\)D\(_3\)), and part two investigated supplementation of 1,25(OH)\(_2\)D\(_3\) versus placebo in patients with newly diagnosed T1D and compared residual beta cell function. Twenty-five patients were enrolled in part one of the study from hospitals and outpatient clinics in Bavaria, Germany between November 2000 and 2006. Twenty-one completed the study, with a 16% loss to follow up. Patients received 0.25 micrograms 1,25(OH)\(_2\)D\(_3\) daily at breakfast for nine months and were followed for an additional 18 months. Primary outcomes of safety measured were plasma levels of calcium, phosphate, alkaline phosphatase and creatinine, urinary calcium excretion and kidney ultrasound. Part two of the study enrolled 40 patients and 38 patients completed the study, with a 5% loss to follow up. Twenty-two patients were randomized to receive 0.25 micrograms 1,25(OH)\(_2\)D\(_3\) daily for nine months, and 18 received placebo. Randomization was performed by an independent pharmacy where they coded the medication before sending it to the Diabetes Research Institute. Primary outcome evaluated was the area under the curve (AUC) for stimulated C peptide release 0-120 minutes after a mixed meal tolerance test (MMTT) comprised of Boost High Protein 360mL collected at baseline, month 9 and month 18. Secondary outcomes evaluated included: peak C peptide level after MMTT at eighteen months, daily insulin requirement and Glycated Hemoglobin level (HbA1C).\(^8\)
All patients were similar between part one and part two of the study, including treatment and placebo patients. Eligibility criteria included: age 18-39 years old (part one: median 31.2 +/- 7.3 years, part two: treatment-median 31.4 +/- 6.8 years, placebo-median 24.0 +/- 6 years), duration of treatment with insulin less than two months (part two: treatment-median 35.0 days, placebo-median 40.0 days), and had a positive result on test for islet autoantibodies (anti-GAD antibodies or anti-IA-2 antibodies), normal values for plasma calcium, phosphate, alkaline phosphatase and creatinine and were compliant with an adequate insulin treatment regime. Exclusion criteria included: disorders in calcium metabolism, kidney disease, malignancy, arterial hypertension, pregnant or lactating women and women of child-birthing age that weren’t performing an effective contraception technique.8

All three groups (part one and treatment and placebo in part two) were statistically evaluated for safety efficacy. Plasma levels of calcium, alkaline phosphatase, phosphate and creatinine and 24-hour urine excretion of calcium were not significantly different in any patients, those treated with 1,25(OH)2D3 or placebo (see table II). Adverse events were reported in 10% of patients and included upper respiratory tract infection and rhinitis but were evenly dispersed in both treatment and placebo groups and likely not secondary to 1,25(OH)2D3 supplementation.8

In part two of the study, the primary outcome measured was AUC C-peptide, which was decreased about 40% in both the treatment and placebo group (treatment-baseline 90.8 +/- 30.3, month 18 58.4 +/- 47.7, placebo- baseline 98.1 +/- 33.0, month 18 58.0 +/-33.7). Secondary outcomes measured included: peak C peptide after MMTT,
daily insulin dose and HbA1C. Mean results were not significantly different in treatment versus placebo for any of the secondary outcomes (see table III).  

Overall, Walter et al. proved that supplementation with 0.25 micrograms 1,25(OH)\textsubscript{2}D\textsubscript{3} is safe, but does not provide significant reduction in loss of pancreatic beta cell function, as assessed by production of stimulated C-peptide.  

**Bizzarri et al Study**

This randomized, double blinded, placebo controlled trial compared the effects of calcitriol (the active form of vitamin D 1,25-dihydroxyvitamin D3) versus placebo in patients with newly diagnosed T1D and residual pancreatic beta cell function. Thirty-four subjects were enrolled and 27 completed the trial, with a 20% loss to follow up. Eligibility criteria included: diagnosis according to American Diabetes Association (ADA), age 18-35 years old (median 18 years old), duration of insulin therapy less than three months and baseline C peptide levels greater than 0.25 nmol/l.

Fifteen patients were randomized to receive 0.25 micrograms calcitriol and 12 were randomized to receive placebo. At baseline, 16 of 34 subjects had clinical evidence of vitamin D deficiency, and at study completion at 24 months vitamin D levels were slightly increased in calcitirol group (+3.9%) and slightly decreased in placebo group (-8.0%). Primary outcome measured was AUC\textsubscript{0-120 minutes} after Boost High-Protein standardized liquid meal and was not significantly different between treatment and placebo groups at baseline or after twelve months (treatment- baseline 69.9 +/- 24.8, month 12 49.7 +/- 30.4, placebo- baseline 72.5 +/- 37.7, month 12 56.2 +/- 39.7). A secondary outcome measured was mean rate of decline in fasting C peptide (month 12-treatment 17.7%, placebo 28.4%, month 24- treatment 44.4%, placebo 42.5%). Of note,
vitamin D deficiency at diagnosis was not associated with decreased residual beta cell function at twenty-four months (C-peptide levels of vitamin D deficient patients- 0.19 +/- 0.09, C peptide levels of non-vitamin D deficient patients- 0.22 +/- 0.16).\textsuperscript{9}

Overall, this study was a designed as a second trial with calcitriol, following up the Walter et al\textsuperscript{8} study and was designed to use patients that were younger at diagnosis with a defined level of basal C-peptide at baseline, and also to assess baseline vitamin D status and association with residual beta cell function. It was found that serum vitamin D levels were only modestly altered by supplementation, and that calcitriol did not provide preservation of residual beta cell function in patients with clinically evident T1D. Also, calcium and phosphate levels were within normal limits for the duration of the study and no adverse events were reports in treatment or placebo groups. This study was limited by a small sample size, although statistical analyses were performed prior to study onset and it was determined that an adequate sample size was 26.\textsuperscript{9}

**Gabbay et al Study**

This randomized, double blinded, placebo controlled trial\textsuperscript{10} investigated the effects of cholecalciferol supplementation versus placebo in patients with newly diagnosed T1D and effect on residual beta cell function. Thirty-eight patients began the study at the Diabetes Center of Sao Paulo Federal University in Brazil, and 35 patients completed the follow-up (a 7% loss). Eligibility criteria included: age between 7 and 30 years (treatment 13.5 +/- 5.1, placebo 12.5 +/- 4.8), length of time since first insulin injection (treatment 2.2 +/- 1.2 months, placebo 2.7 +/- 1.7 months), positive test for islet cell autoantibodies (anti GAD or anti protein tyrosine phosphatase) and fasting or 2-hour post-prandial stimulated serum C-peptide greater than 0.6 ng/mL. Exclusion criteria
included: severe systemic disease and disorders in calcium metabolism. Seventeen patients were randomized to receive 2000IU cholecalciferol daily and 18 patients received placebo, with randomization performed by a pharmacist and the pills were produced and concealed in an independent pharmacy. Patients were similar in regards to baseline characteristics, with the exception of differences in HbA1C (see table III).\textsuperscript{10}

Primary outcome measured was cumulative incidence of stimulated C peptide to an undetectable level at 18 months. C peptide was stimulated with a MMTT (mixed meal tolerance test) that was 6mL/kg of body weight performed between seven and ten in the morning after an overnight fast, and patients received no insulin for at least six hours prior to assessment. Overall, patients being treated with cholecalciferol were less likely to have an undetectable C peptide level, and had improved residual beta cell function versus placebo (undetectable C-peptide level, treatment group-6.2%, placebo group-37.5%, RR-16.5%, RRR- 83.5%, ARR- 31.3%, NNT-4). A number of secondary outcomes were assessed at baseline, and months 6, 12 and 18 without significant differences appreciated between treatment and placebo groups (see table IV).\textsuperscript{10}

There were a number of surrogate outcomes assessed at baseline, and month 6, 12 and 18 as well. They included inflammatory markers and immune cells: interleukin twelve (IL-12), Tumor Necrosis Factor (TNF), Chemokine IL-10, IL-10, Chemokine Ligand Two (CCL2) and regulatory T cells. There was an increased amount of CCL2 (baseline:treatment-192.3 +/- 92.0, placebo-168.5 +/- 87.8, month 18:treatment- 221.9 +/- 257.2, placebo-136.6 +/- 69.1) and regulatory T cells(baseline:treatment-3.34 +/-1.8, placebo-2.78 +/-1.7, month 18:treatment-3.75 +/-1.6, placebo-3.20 +/-1.5) in the treatment group.\textsuperscript{10}
Overall results show that the primary outcome of residual beta cell function as a measure of stimulated C-peptide release favored the group treated with 2000IU cholecalciferol. Also, the increased level of CCL2 in the treatment group may work in an anti-inflammatory fashion and, in conjunction with TNF, prevent autoimmune destruction of beta cells. One limitation of this study was the difference in HbA1C at baseline of the treatment group (9.25% +/-2.17%) versus placebo (7.73% +/-2.16%). However HbA1C became very similar by the first follow up at month six.\textsuperscript{10}

**DISCUSSION**

Vitamin D is an inexpensive, easily accessible supplement with many proposed health benefits. The question remains whether one of these benefits includes preservation of pancreatic beta cell function in patients with newly diagnosed T1D. Both Walter et al\textsuperscript{8} and Bizzarri et al\textsuperscript{9} showed little to no effect of vitamin D on patient important outcomes including daily insulin requirement and HbA1c levels. However, the safety assessment in Walter et al\textsuperscript{8} showed no difference in minor adverse events between treatment and placebo, and no adverse events that could be attributed to the medication in either group. All three studies\textsuperscript{8,9,10} primarily assessed capability of pancreatic beta cells to release C peptide. Steffes et al\textsuperscript{11} showed that beta cell function as a measure of stimulated C peptide release was a good prognostic indicator for patients with T1D. This included reducing incidences of retinopathy and nephropathy in patients with higher, and more sustained levels of C peptide (and insulin) secretion.\textsuperscript{11} Gabbay et al\textsuperscript{10} also assessed many other surrogate outcomes including inflammatory markers and plasma levels of specific auto-immune cells. New research in T1D targets immunotherapy to preserve beta cell function. Keymeulen et al\textsuperscript{12} found that short term treatment with CD3 antibody preserved
residual beta cell function for up to 18 months in T1D. However, every patient in the study experienced adverse events including: fever, headache, viral syndrome, arthralgia and gastrointestinal symptoms. Pescovitz et al conducted a study comparing Rituximab, an anti CD20 monoclonal antibody versus placebo in preserving beta cell function. Rituximab was found superior to placebo in preserving beta cell function in T1D for one year, however it had significantly more side effects than placebo (57 patients with 392 reported adverse events, placebo 30 people with 148 reported adverse events). Gabbay et al was the only study to show that vitamin D supplementation, specifically in the form of cholecalciferol, was able to preserve pancreatic beta cell function in patients with newly diagnosed T1D. This outcome was assessed based on progression of C peptide to an undetectable level at month 18. Results showed that 37.5% of patients in the placebo group had non-existent beta cell function as a function of C peptide release, while only 6.2% of patients in the treatment group had such a decline in their beta cell function. Based on the finding in the Steffes et al study it can be assumed that these results would directly correlate with patient important outcomes, including, but not limited to, decreasing daily insulin requirements, improving HbA1C levels and preventing future systemic complications. There are many possible explanations for the remarkable results supporting treatment in Gabbay et al as compared to the other two studies. Patients were younger overall in the Gabbay et al study and also had a higher level of baseline beta cell function as measured by a higher level of fasting or stimulated C peptide than either of the other two studies. Also, in the first two studies the active form of vitamin D was used (1,25(OH)2D3 as opposed to 25-hydroxyvitamin D3 in the Gabbay et al study. 
Further data was extrapolated from Gabbay et al\textsuperscript{10} including an increase in IL-10, CCL-2, and regulatory T cells in the patients treated with cholecalciferol. According to Batagglia et al\textsuperscript{14} in an animal study on non-obese diabetic mice, rapamycin (an immunosuppressant drug) plus IL-10 protected mice from developing diabetes and induced long-term tolerance.\textsuperscript{14} It has also been proposed that auto-immune diseases, including the beta cell destruction in T1D, is induced by dysfunction of immune cells. A decreased amount or dysfunctional population of regulatory T cells contributes to the development of T1D along with decreased levels of CCL2 that tend toward anti-inflammatory effects.\textsuperscript{15} It can be inferred then that the increased levels of IL-10, CCL2 and regulatory T cells could work together to prevent autoimmune destruction of pancreatic beta cells.\textsuperscript{10} Future research should be conducted to confirm the immune-protective capabilities of cholecalciferol on pancreatic beta cells and rule out a chance outcome from this study. Research should also explore the implications of these altered levels of cytokines, chemokines and regulatory T cells and their impact on T1D progress and patient important outcomes.

All three studies\textsuperscript{8,9,10} are randomized control trials so they start at a high level of validity, but each study has significant risks to overall quality. Regarding methodology, all three studies\textsuperscript{8,9,10} were adequate as they each were double blinded with allocation concealment and none of the studies had to be stopped early. However, Walter et al\textsuperscript{8} had a 16\% loss to follow up and Bizzarri et al\textsuperscript{9} had a 20\% loss to follow up. Regarding prognostic factors, Gabbay et al\textsuperscript{10} had significant differences between baseline HbA1c of treatment versus placebo group, however it would have appeared to be an advantage to the placebo group as the levels were higher in the treatment group. Regarding directness
of evidence, all three studies\textsuperscript{8,9,10} were highly reliant upon surrogate outcomes, primarily C-peptide. The assumption had to be made that C-peptide is a good measure of pancreatic beta cell function, which is a good indicator of overall T1D prognosis. Also, Gabbay et al\textsuperscript{10} was heavily based on surrogate outcomes including levels of pro-inflammatory and anti-inflammatory cytokines, chemokines and regulatory T cells and an inference must be made that these surrogate outcomes would have an impact on patient important outcomes. Finally, regarding precision, all three studies\textsuperscript{8,9,10} were limited by small sample sizes. Walter et al\textsuperscript{8} had 65 patients between part one and part two, Bizzarii et al\textsuperscript{9} had 34 subjects and Gabbay et al\textsuperscript{10} had 38 patients. None of the studies\textsuperscript{8,9,10} were downgraded for publication bias (See Table I). Therefore, the overall quality of evidence is low; however, with the safety profile of vitamin D, supplementation carries a low risk of harm.

\textbf{CONCLUSION}

T1D is a chronic disease that requires daily monitoring and can lead to serious, systemic complications. Extensive research has been completed exploring the etiology of T1D, searching for a cure and trying to halt disease progression. It appears that vitamin D deficiency, either in utero or during the first year of life, can increase likelihood of developing T1D. Furthermore, it appears that T1D disease progression can be altered by immunomodulating medications, many of which have serious adverse side effects. Recent research on vitamin D has shown possible immune-protective capabilities. Overall, there isn’t compelling evidence to show that vitamin D supplementation can preserve pancreatic beta cell function in patients with newly diagnosed T1D. However, it appears that there is modest evidence to show that vitamin D in the form of
cholecalciferol has the ability to slow the decline of residual beta cell function. Furthermore, it appears that supplementation with vitamin D is safe and could provide additional immune-protective benefits that have yet to be proven.
References


8. Walter M, Kaupper T, Adler K, Foersch J, Bonifacio E, Ziegler AG. No effect of the 1alpha,25-dihydroxyvitamin D3 on beta-cell residual function and insulin


**Table I: Characteristics of Reviewed Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walter et al 8</td>
<td>RCT</td>
<td>Serious Limitations a</td>
<td>No serious indirectness</td>
<td>Serious Imprecision b</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
<td>Bizzarri et al 9</td>
<td>RCT</td>
<td>Serious Limitations c</td>
<td>No serious indirectness</td>
<td>Serious Imprecision d</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
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<td>Important</td>
</tr>
<tr>
<td>Gabbay et al 10</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>Serious Indirectness e</td>
<td>Serious Imprecision f</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Low</td>
<td>Important</td>
</tr>
</tbody>
</table>

a- 16% loss to follow up 

b- small sample size, 65 patients

c- 20% loss to follow up

d- small sample size, 27 patients

e- strong use of surrogate outcomes including levels of proinflammatory and anti-inflammatory cytokines, chemokines and regulatory T cells

f- small sample size, 35 patients
### Table II- Baseline Characteristics (Walter et al study)

<table>
<thead>
<tr>
<th></th>
<th>Calcium (mmol/L)</th>
<th>Alkaline Phosphatase (IU/mL)</th>
<th>Phosphate (mmol/L)</th>
<th>Creatinine (mg/dL)</th>
<th>24-h calcium urine excretion (mmol/24h)</th>
<th>AUC C-peptide (nmol/L x 120 min)</th>
<th>Fasting C-peptide (nmol/L)</th>
<th>Peak C-peptide (nmol/L)</th>
<th>A1C (%)</th>
<th>Daily Insulin Dose (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatmen</strong></td>
<td>2.4 +/- 0.1</td>
<td>67 +/- 19</td>
<td>1.2 +/- 0.2</td>
<td>0.8 +/- 0.1</td>
<td>6.3 +/- 3.2</td>
<td>90.8 +/- 30.3</td>
<td>0.33 +/- 0.12</td>
<td>1.00 +/- 0.37</td>
<td>8.4 +/- 2.1</td>
<td>24.9 +/- 12.6</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>2.5 +/- 0.1</td>
<td>65 +/- 26</td>
<td>1.2 +/- 0.2</td>
<td>0.8 +/- 0.1</td>
<td>6.1 +/- 3.2</td>
<td>98.1 +/- 33.0</td>
<td>0.34 +/- 0.13</td>
<td>1.10 +/- 0.36</td>
<td>8.3 +/- 1.6</td>
<td>24.6 +/- 8.9</td>
</tr>
</tbody>
</table>

### Table II- Outcomes Measured-Month 18 (Walter et al study)

<table>
<thead>
<tr>
<th></th>
<th>AUC C-peptide (nmol/L x 120 min)</th>
<th>Fasting C-peptide (nmol/L)</th>
<th>Peak C-peptide (nmol/L)</th>
<th>A1C (%)</th>
<th>Daily Insulin Dose (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatmen</strong></td>
<td>58.4 +/- 47.7</td>
<td>0.19 +/- 0.18</td>
<td>0.66 +/- 0.52</td>
<td>6.1 +/- 0.6</td>
<td>35.6 +/- 19.2</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>58.0 +/- 33.7</td>
<td>0.22 +/- 0.15</td>
<td>0.63 +/- 0.34</td>
<td>6.3 +/- 0.8</td>
<td>34.9 +/- 18.1</td>
</tr>
</tbody>
</table>

### Table II-Baseline Characteristics and Outcomes Measured Month 18 (Gabbay et al study)

<table>
<thead>
<tr>
<th></th>
<th>Fasting C-peptide (ng/mL)</th>
<th>Stimulated C-peptide (ng/mL)</th>
<th>A1C (%)</th>
<th>Daily Insulin Dose (IU/kg/d)</th>
<th>Body Mass Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatmen</strong></td>
<td>0.65 +/- 0.45</td>
<td>1.55 +/- 0.91</td>
<td>9.25 +/- 2.17</td>
<td>0.52 +/- 0.19</td>
<td>18.5 +/- 3.0</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>0.92 +/- 0.83</td>
<td>1.83 +/- 1.03</td>
<td>7.73 +/- 2.16</td>
<td>0.43 +/- 0.19</td>
<td>18.5 +/- 2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Fasting C-peptide (ng/mL)</th>
<th>Stimulated C-peptide (ng/mL)</th>
<th>A1C (%)</th>
<th>Daily Insulin Dose (IU/kg/d)</th>
<th>Body Mass Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatmen</strong></td>
<td>0.45 +/- 0.34</td>
<td>1.0 +/- 1.03</td>
<td>8.29 +/- 2.06</td>
<td>0.81 +/- 0.37</td>
<td>19.5 +/- 2.8</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>0.43 +/- 0.49</td>
<td>0.96 +/- 1.08</td>
<td>8.91 +/- 2.71</td>
<td>0.80 +/- 0.27</td>
<td>20.5 +/- 4.2</td>
</tr>
</tbody>
</table>