Effect of 1,25-dihydroxyvitamin D3, Treatment on Insulin Secretion and Muscle Strength in Pre-diabetic Persons

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Title: Effect of 1,25-dihydroxyvitamin D_3 treatment on insulin secretion and muscle strength in pre-diabetic persons.

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Abstract

Pre-diabetes affects over 325 million adults worldwide. These individuals that are predisposed to developing type 2 diabetes mellitus have few options to prevent the progression of the disease other than diet and exercise. Emerging evidence suggests that the active from of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$; also known as calcitriol), contributes to glucose metabolism partly by increasing insulin secretion and also by increasing muscle glucose utilization. We intend to investigate the effects of a low daily dose of $1,25(OH)_2D_3$ on glucose tolerance and muscle function in persons who are susceptible to developing diabetes. This study could provide a new strategy for preventing the progression of type 2 diabetes mellitus with a drug that is already approved for use by the US Food and Drug Administration.

Research Plan

A. Specific Aim

The aim of this study is to assess the effects of $1,25(OH)_2D_3$ on insulin secretion by the pancreas and glucose utilization by skeletal muscle as well as to determine the effects of $1,25(OH)_2D_3$ on muscle strength in pre-diabetic subjects.

Hypothesis: $1,25(OH)_2D_3$ will increase the rate of insulin secretion by pancreatic beta cells and improve glucose uptake in muscle, resulting in improved glucose homeostasis. Secondarily, $1,25(OH)_2D_3$ will increase muscle strength.

Approach: This will be a double blind randomized control trial in pre-diabetic persons. Each participant will be randomly assigned to receive an oral tablet containing 0.25 µg $1,25(OH)_2D_3$ or a placebo tablet for 8 weeks. Identical assessments will be performed both before and after the 8-week intervention period. These assessments will include the 2-hour glucose tolerance test (GTT) and muscle strength testing.

B. Background

Impairments in insulin secretion and glucose disposal affect a third of adults living in the United States (84 million, (CDC 2017)) and approximately 325 million people worldwide (IDF 2017). Over time, these symptoms progress into type 2 diabetes mellitus and then lead to secondary complications such as microvascular (e.g. diabetic nephropathy, retinopathy and neuropathy) and macrovascular (e.g. peripheral vascular and coronary artery disease) diseases.

Early investigations demonstrated a strong link between vitamin D and insulin secretion. In rats, studies had shown that vitamin D deficiency (diet induced) negatively affected insulin secretion (Kadowaki and Norman 1984; Norman et al. 1980). Later, $1,25(OH)_2D_3$ was confirmed to increase insulin

secretion in the vitamin D-deficient rat model (Cade and Norman 1986). On the other hand, observational studies comparing serum $25(OH)D_3$ concentrations and diabetes, as well as randomized control trials with vitamin D_3 supplementation, have not corroborated the link between vitamin D and insulin secretion (Mitri, Muraru, and Pittas 2011; Pittas et al. 2007, 2012, 2019; Wexler 2019). A recent longitudinal clinical trial, known as the Vitamin D and Type 2 Diabetes (D2d) Trial, studied the effects of supplementation with 4,000 IU of vitamin D_3, the tolerable upper intake level (Ross et al. 2011), or placebo for 2.5 years in 2432 participants with pre-diabetes. The results of this trial indicated that vitamin D_3 supplementation (n=1211) had no effect on the incidence of T2DM compared to the placebo group (n=1212) (Pittas et al. 2019). Many clinical trials have focused solely on the relationship between vitamin D_3 intake or serum $25(OH)D_3$ and glucose metabolism and have established that vitamin D_3 and $25(OH)D_3$ do not have an effect on insulin secretion. However, Bonakdaran and colleagues studied patients with chronic renal deficiency and found that 0.5 µg $1,25(OH)_2D_3$, (n=13) given daily for 4 weeks improved glucose utilization compared to placebo-treated controls (n=14) (Bonakdaran et al. 2008). Thus, $1,25(OH)_2D_3$ has been shown to positively affect insulin secretion in CKD patients and we believe that this benefit could be applied to persons with pre-diabetes. Based on these studies, we recognize that $1,25(OH)_2D_3$ itself has a direct hormonal effect on pancreatic beta cells and insulin secretion and that administration of $1,25(OH)_2D_3$, rather than vitamin D_3 or $25(OH)D_3$, may be a key factor in improving glucose homeostasis.

Deficiency of vitamin D has been associated with muscle atrophy and poor diaphragm function (Dzik et al. 2019; Malinovschi et al. 2014). A recent study consisting of 4,157 older adults (>60 years) had shown that vitamin D deficiency (serum [25(OH)D] <30 nmol/L) was associated a three-fold increased incidence of impaired muscle performance and 2-fold increased incidence of impaired muscle strength compared to the vitamin D sufficient group (serum [25(OH)D] >50 nmol/L) (Aspell et al. 2019). Persons with diabetes are particularly susceptible to losses in muscle strength and endurance (Domaski and Ciechanowski 2012; Foley et al. 2007; Ijzerman et al. 2012). Poor muscle function not only accelerates deterioration of health and well-being, but it also impedes recovery following illness or hospitalization. In unpublished preliminary studies, Kumar and colleagues have found that a mouse model severely deficient in $1,25(OH)_2D_3$ experiences a 30% reduction in both muscle strength and fatigue after merely 2 weeks without exogenous $1,25(OH)_2D_3$. Furthermore, our laboratory has shown that human muscle responds to $1,25(OH)_2D_3$ stimulation by increasing mitochondrial function (Ryan et al. 2016). Thus, we believe that $1,25(OH)_2D_3$ in the pre-diabetic populations will offer benefits in muscle function that will reduce losses in mobility and pulmonary diaphragm function.

The overall premise of this research is to investigate the action of a low daily dose of $1,25(OH)_2D_3$ in pre-diabetic persons. Assuming that our hypothesis is valid, these individuals are likely to observe benefits from $1,25(OH)_2D_3$ for improvements in insulin secretion, glucose metabolism, and muscle strength.

C. Significance of Proposed Research

Insulin resistance is an early indication for the development of T2DM. The action of $1,25(OH)_2D_3$ on insulin secretion and glucose utilization may delay or prevent the onset of T2DM in pre-diabetic persons. Additionally, The action of $1,25(OH)_2D_3$ on muscle may maintain and improve muscle function.

D. Design and Methods

Study Design

We will compare insulin secretion and glucose uptake and muscle function before and after 8 weeks of treatment with $1,25(OH)_2D_3$ or placebo in pre-diabetic participants. Men and women will be identified for recruitment to the study based on strict inclusion and exclusion criteria (Table 1 and *Enrollment Criteria*). After assignment to the study group, the participants will be randomly assigned on a first-come-first-serve basis to receive a daily oral table containing either 0.25 µg $1,25(OH)_2D_3$ or placebo for 8 weeks. Before and after the intervention period, assessments will be made that will include a glucose tolerance test (GTT), knee flexor, and grip strength tests.

Table 1: Enrollment Groups

Group	Criteria
1	Men
2	Pre-menopausal Women

Enrollment Criteria

Inclusion criteria:

- Adults, 20 - 45 years old
- Body mass index (BMI) of >24 kg/m^2
- Fasting serum glucose <126 mg/dl

Exclusion criteria:

- BMI ≤24 kg/m^2
- Fasting serum glucose ≥126 mg/dl
- Currently taking calcium and/or vitamin D supplements and unwilling to stop for study duration
- Serum total calcium >10.2 mg/dL
- Serum inorganic phosphorus >4.5 mg/dL
- Pregnancy or breastfeeding
- Diagnosis of Diabetes Mellitus
- Diagnosis of Rheumatoid Arthritis
- Diagnosis of Chronic Obstructive Pulmonary Disease (COPD)
- Renal insufficiency/failure (serum creatinine >1.5 mg/dl men, >1.3 mg/dl women)
- Chronic active liver disease (bilirubin > 1.2 mg/dL, AST >144 IU/L, or ALT >165 IU/L)
- History of chronic hepatitis
- History of depression, anxiety or psychiatric disease
- Active coronary artery disease (unstable angina, myocardial infarction, stroke, and revascularization of coronary, peripheral or carotid artery within 3 months of recruitment)
- Oral warfarin or history of blood clotting disorders
- Platelet count < 100,000 per uL within the last 7 days
- Alcohol consumption greater than 2 glasses/day or other substance abuse
- Untreated or uncontrolled thyroid disorders (outside a TSH range of 0.5 to 10 mIU/L)
- Debilitating chronic disease (at the discretion of the investigators)

- The presence of infections, highly communicable diseases (AIDS, active tuberculosis, venereal disease, hepatitis)
- Any malignancy

Recruitment

A study coordinator will work closely with Dr. Kumar to identify potential candidates for this study. Participants will be recruited from the Research Studies section of the Mayo Classifieds website, and from participants who completed other research studies and agreed to be contacted again for other studies. While most of the information will be provided to potential participants in person, participants may also be contacted by telephone with a brief description of the study and to determine if they are interested in participating. The study coordinator will perform a brief screening questionnaire to determine eligibility to proceed with enrollment. The information gathered from the screening questionnaire will not be stored or used for data analysis if participants do not qualify for the study.

Consent and Screening

Potential participants will report to the Clinical Research and Trials Unit at the Charlton Building or St. Mary's Hospital. A member of the study team will meet the potential participant and then the consent form will be read and discussed in a private area. After receiving consent, the participant will have a urine pregnancy test (if applicable) and screening blood work (fasted). Screening blood work will be processed in a clinical lab and will include: Basic Metabolic Panel (sodium, potassium, bicarbonate, creatinine, BUN, calcium, phosphorous, and albumin), ALT (alanine transaminase), AST (aspartate aminotransaminase), BILIT (total bilirubin), TSH (thyroid stimulating hormone), CBC with differential count including platelets, APT (activated partial thromboplastin time), PT (prothrombin time), GLUCF (glucose fasting) and CDHVD ($1,25(OH)_2D_3$, $25(OH)D_3$). Participants will have a nursing assessment that will include vital signs and a brief physical exam by a study MD.

Study Intervention Agent: 1,25-Dihydroxyvitamin D_3

As per DrugBank, this agent is used to treat refractory rickets (vitamin D resistant rickets), familial hypophosphatemia, hypoparathyroidism, and in the management of hypocalcemia and renal osteodystrophy in patients with chronic renal failure undergoing dialysis. This protocol will use doses that are identical to those used for these other clinical indications.

The Mayo Clinic Pharmacy will prepare $1,25(OH)_2D_3$ tablets containing 0.25 µg of $1,25(OH)_2D_3$ as well as an identical placebo tablet containing 0 µg of $1,25(OH)_2D_3$. Assignment will remain blinded to participant, healthcare providers and members of the study team who have direct participant contact.

Intervention instructions: During screening and prior to receiving the intervention, caloric intake and vitamin and mineral analysis will be estimated by having participants complete the VIOCare Food Frequency questionnaire, with the dieticians in the clinical research unit. A dietician will instruct the participant to adhere to a diet of 400 mg calcium and 800-1000 mg phosphorus while taking $1,25(OH)_2D_3$/placebo agent intervention. These instructions are included to prevent potential development of hypercalcemia and/or hyperphosphatemia as a direct result of $1,25(OH)_2D_3$. After completing screening and baseline assessments, participants will be instructed to take 1 tablet (containing 0.25 µg $1,25(OH)_2D_3$ or placebo) per day for 8 weeks following the completion of Day 3 of baseline assessments (Table 2).

E. Assessments

Participants will undergo a series of assessments for initial baseline measurements and post-intervention measurements (Table 2). Both baseline and post-intervention evaluations will include a questionnaire, glucose tolerance, lower extremity strength testing (knee flexor), and upper extremity strength testing (grip strength). During the intervention phase, serum calcium and phosphorus levels will be monitored at every two weeks.

Questionnaire: The NIH-funded Patient-Reported Outcomes Measurement Information System Global-10 (PROMIS 10) is a brief, 10-question, multiple-choice survey that approximates a person's perceived physical and mental health (Hays et al. 2009). The questionnaire will be delivered as a written survey or in electronic format on a handheld tablet at the consent and screening visit as well as at the final visit for post-intervention assessments.

Glucose Tolerance Test (GTT): After an overnight fast, subjects will present to the Clinical Research and Trials Unit (CRTU). The subjects will ingest a drink containing 75g glucose. Venous blood will be obtained for measurement of glucose, insulin, and C-peptide concentrations over a 120 min period at 0, 10, 20, 30, 60, 90 and 120 minutes (Dalla Man et al. 2005; Sathananthan et al. 2012). All blood will be immediately placed on ice, centrifuged at 4^{o}C, separated, and stored at -80^{o}C until assay. Glucose will be measured using a Yellow Springs glucose analyzer, C-Peptide will be measured by ELISA assay using EMD Millipore (Billerica, MA) reagents, and insulin will be measured using a chemiluminescence assay with reagents obtained from Beckman (Chaska, MN). At the time of study, glucose values at 0 and 120 minutes will be used to categorize glucose tolerance status and exclude subjects with T2DM. Data obtained from GTT will provide fasting, peak, and nadir insulin concentrations. Additional calculations will be used to determine area above basal (AAB) or area under the curve (AUC) during the postprandial period using the trapezoidal rule as previously described (Vella et al. 2007). Insulin action (S_i) and β-Cell responsivity indices (ϕ) will be calculated (Cobelli et al. 2014) from the plasma glucose, insulin and C-peptide concentrations observed during the experiments using the appropriate minimal model (Breda et al. 2001), incorporating age-associated changes in C-peptide kinetics (Cauter et al. 1992). The disposition index (DI) will be calculated as $DI = \phi \cdot S_i$, which determines if β-cell function is appropriate for the prevailing insulin action.

Lower Extremity Strength Test: Participants will undergo measurements at the Motion Analysis Laboratory. Dominant knee flexor musculature strength will be assessed via a computerized multi-joint testing system (Humac Norm System; CSMi Medical Solutions Stoughton, MA). Subjects will be positioned and stabilized on the testing apparatus using standardized protocols. The axis of the knee joint will be aligned with the center of rotation of the dynamometer arm and the lower leg will be strapped to the lever arm just proximal to the angle. Participants will be buckled in at the waist, shoulders and the distal part of the thigh. Peak torque will be assessed at a knee angle of 60^{o} flexion. Participants will be verbally encouraged to perform at their maximum. Torque generated by the subject in an isometric contraction will be measured and recorded. Three isometric strength testing repetitions will be performed for each muscle group. Each isometric muscle contraction will be held for 5s and a 30s rest period will be observed between contractions. The largest value from three trials will be used.

Upper Extremity Strength Test: Isometric handgrip strength will be measured in the Motion Analysis Laboratory. Dominant hand grip strength will be tested using a custom designed digital grip dynamometer (NK Biotechnical Engineering Co., Minneapolis, MN). The measurements will be performed with participants sitting upright, feet flat on the floor, elbow flexed to 90º, and forearm in neutral position. Standardized verbal encouragement will be given for each contraction. Three maximal repetitions (30s rest between attempts) will be recorded. The largest value from three trials will be used.

Table 2: Timeline of the study

Consent, Screening, and Baseline Assessments (complete within 5 days)	
Day 1	Consent and Screening Completion of the PROMIS 10 Questionnaire Food Frequency Questionnaire Nutrition Consult with Dietitian Urinalysis (women only) • HCG Fasting Blood Draw • Basic Metabolic Panel, ALT, AST, BILIT, TSH, CBC, APT, PT, GLUCF, PTH, CDHVD ($1,25(OH)_2D_3$, $25(OH)D_3$), calcium, and phosphorus
Day 2	Glucose Tolerance Test • Glucose, insulin, glucagon and C-peptide, at fasting and at 10, 20, 30, 60, 90 and 120 minutes following oral glucose bolus Knee Flexor Strength Test Grip Strength Test Physical Exam with Physician ***Begin Intervention with $1,25(OH)_2D_3$ or Placebo***
Intervention	
Week 2	Blood Draw: calcium and phosphorus
Week 4	Blood Draw: calcium and phosphorus
Week 6	Blood Draw: calcium and phosphorus
Week 8	***Begin Post-Intervention Assessments***
Post-Intervention Assessments (complete within 2 days of taking last tablet)	
Day 1	Fasting Blood Draw • CDHVD ($1,25(OH)_2D_3$), calcium, and phosphorus Glucose Tolerance Test • Glucose, insulin, glucagon and C-peptide, at fasting and at 10, 20, 30, 60, 90 and 120 minutes following oral glucose bolus Knee Flexor Strength Test Grip Strength Test Completion of PROMIS 10 Questionnaire

F. Statistics and Analyses

Power calculations for determining sample sizes were performed in JMP Pro 14 by using previously published variances on DI and ϕ that describe beta cell function in pre-diabetic persons (Sathananthan et al. 2012) (Table 3).

Table 3: Power calculations for determining sample size

Parameter	Expected Outcome (mean ± sd)	Total Sample Size
DI	1920 ± 321 (10^{-14}dl/kg/min^2 per pmol/l)	28
ϕ	63.8 ± 7.5 (10^{-9} min^{-1})	15
		47

* Total N to detect a 20% difference with 85% power between two groups of N/2.

Analysis: Data will be analyzed as a repeated measures analysis of variance (ANOVA) with the independent variable as $1,25(OH)_2D_3$ or placebo and the dependent variable as assessments made before and after intervention. The main effect will be an analysis of the study groups pooled across gender and hormonal status to compare intervention with placebo. Additional co-variables to be considered in the analyses will be sex and menopausal stage per study group affiliation, as well as age, race, and others as post-hoc analyses.

G. Endpoints

Primary: Completion of final blood collection and GTT.
Secondary: Completion of PROMIS 10 Questionnaire.

Human Subjects

Risks to the subjects

Human Subjects Involvement and Characteristics: All protocols and all techniques to be used will be approved by the Mayo Clinic Institutional Review Board (IRB) prior to initiation of any studies. Subject characteristics and inclusion/exclusion criteria have been clearly specified above. Our plan is to complete the study on 50 participants with 25 in each group. We are anticipating a target accrual of 75 subjects to account for anticipated dropout in order to have 50 participants complete the study.

Sources of Materials. Samples of blood and urine obtained during the study will be used exclusively for research purposes. No use will be made of pre-existing specimens.

Urine: Urine samples will be collected from women for pregnancy testing.
Blood: One blood draw will occur during the screening visit (approximately 15 mL). A glucose tolerance test will be performed at baseline that will include seven blood draws (approximately 1 mL of blood from each draw) periodically over the course of 2 hours. Every 2 weeks during the intervention, a small sample of blood (1 mL) will be collected to monitor calcium and phosphorus levels. At completion of 8 weeks of intervention, another GTT will be performed and 5 mL of blood will be collected for post-intervention analysis. This analysis will include calcium, phosphorus, $25(OH)D_3$, $25(OH)D_2$, $1,25(OH)_2D_3$, and $1,25(OH)_2D_2$. All specimens will be processed internally and stored in the study team laboratory.

Potential Risks:
The following are potential risks for this study

a) Blood will be withdrawn. The total blood withdrawn throughout the 8-week study will be approximately 40 mL.
b) The study agent, $1,25(OH)_2D_3$, has potential risks that are considered rare at the dosage in use. These risks include hypercalcemia, hyperphosphatemia, weakness, headache, nausea, vomiting, sleepiness, dry mouth, constipation, muscle pain, bone pain, or a metallic taste.

Adequacy of Protection Against Risks

Feasibility, Recruitment, and Informed Consent: Volunteers will be initially recruited from individuals who have previously indicated a desire to participate in research. Each willing participant will meet one of the investigators who will explain the scientific rationale, the procedures and the potential risks involved in the study. The consent form will be approved by the Mayo Clinic IRB prior to use. Informed written consent from the participant will be obtained by one of the investigators prior to participation. An electronic note will be entered in each participant's medical record regarding the consent and a copy of the consent will be electronically kept with the participant's medical record. A copy of the consent will be offered to the subject and the original kept with the investigators records.

Protection against risk: All protocols and all techniques to be used will be approved by the Mayo Clinic IRB prior to initiation of any studies. All participants will have the Mayo Clinic paging operator available to them 24 hours a day to contact the investigators for any problems. The Clinical Research and Trials Unit (CRTU) also has an on-call physician available 24 hours a day to contact for problems or concerns in the event that the study MD does not respond to calls or pages. The following protection will be taken for the risks identified above:

a) The amount of blood drawn is within the amounts acceptable by the institution. There is an institutional electronic tracking system to ensure that a patient is not in more than one study at a time.
b) A Data Safety and Monitoring Plan (DSMP) will be utilized for patient safety. Investigators and the CRTU have had extensive experience in all procedures and aspects of the study. The investigative team will review any participant safety issues as delineated in the DSMP.
c) Subject protection is as listed in the above section. Confidentiality of all medical records is strictly maintained by established procedures. The original study data are kept in the Principal Investigator's laboratory/office and are entered into a secure Mayo firewall allocated for use by only the study team. All data are reviewed by the Principal Investigator. All investigators carry pagers. Volunteers have access to the Mayo Clinic paging operator 24 hours a day.
d) The risks to the subjects are small being primarily those of blood withdrawal.
e) Participants will have their serum calcium and phosphorus levels repeatedly checked following administration of $1,25(OH)_2D_3$ or placebo. Participants who develop an increase in their calcium or phosphorus level above the institutional upper limit of normal (defined values) will be taken off the intervention, referred to their primary healthcare provide, and have their blood calcium and phosphorus reassessed after two weeks or until the concentrations return to within normal limits.

Potential Benefits of Proposed Research to the Subjects and Others

Evidence for the impact of $1,25(OH)_2D_3$ on glucose metabolism and muscle function is steadily increasing. When administered in low doses, this treatment may be a reliable option that is currently

approved by the US Food and Drug Administration, for improving glucose metabolism in persons who are prone to T2DM. Participants included in this study may experience benefits that could enhance their general health and fitness and prevent development of T2DM.

Protection of Human Research Participants

The personnel identified in the application have completed the required education on the protection of human research participants. The institution has established a formal program entitled the Mayo Investigator Training Program (MITP). The MITP is a web-based educational course designed to provide all personnel involved in human subjects research with training about human subject protection. All Mayo personnel engaged in human subject research are required to complete the course and recertify themselves every two years. The primary objectives of the course are to provide the historical framework for current human subject protection regulations and to explore the evolving issues related to human subject research. The course is divided into four sections:

1. Course introduction and general overview
2. History section which explores examples of unethical behavior in human subject research
3. Review of major human subject protection issues
4. Discussion of the various roles and responsibilities of individuals involved in human subject research.

At the conclusion of the instruction, individuals are required to complete a thirty-question assessment.

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