D2d Ancillary Study Application

Office Use
Ancillary Study Number: AS14-04 Date Submitted (MM/DD/YYYY): 07/31/2014

Title of Proposal *(81 character limit)*: Parent D and free 25OHD as potential novel predictors of prediabetes progression

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If Principal Investigator is not a member of the D2d study group, please specify:
D2d Co-Investigator:
Institutional Affiliation:

Other Key Persons (biosketch is not required)
Name: Bruce Hollis, M.D. Ancillary Study Role: co-investigator
Name: Ancillary Study Role:
Name: Ancillary Study Role:
Name: Ancillary Study Role:

D2d Ancillary Study Subcommittee Use Only

Ancillary Studies Subcommittee Action: Please Select Date
Steering Committee Action: Please Select Date
DSMB Action: Please Select Date

Approved Applications

Consent form required? Please Select

D2d Ancillary Study Application

Part 1: Research Plan

1a. Anticipated Timeline and Enrollment

Planned Start Date	07/01/2015
Planned End Date	06/30/2020
Anticipated Enrollment	2,049

1b. Hypothesis and Specific Aims

Please describe the question(s) you are asking and what you expect to happen (3/4 page limit).

The only vitamin D measurement now being made in D2d is total 25OHD, long thought to be the most informative measure of vitamin D status. However, parent vitamin D3 (D3) and free 25OHD may be more important than total 25OHD in the pathogenesis of non-skeletal diseases including diabetes. D3 is generally more accessible to cells than 25OHD because it binds less avidly to vitamin D binding protein (DBP), and it may be an important substrate for intracellular production of 25OHD and 1,25(OH)2D. Enzymes that convert D3 to 25OHD and 25OHD to 1,25(OH)2D have been identified in a broad range of cell types, and high concentrations of CYP2R1 mRNA, which encodes 25-hydroxylase, have been found in human pancreas. Total 25OHD includes free 25OHD and 25OHD bound to DBP and albumin. Bound 25OHD enters cells that have the megalin-cubulin endocytotic transport system (e.g. parathyroid gland and kidney), but there is no evidence that it enters the pancreatic beta cell. Therefore, free 25OHD may be more important than total 25OHD for insulin secretion. Genetic variants of DBP differ in frequency across populations, including race groups, and affect concentrations and actions of 25OHD and 1,25(OH)2D. The proposed Ancillary Study will define the relative importance of circulating D3, free 25OHD, and total 25OHD in beta cell function and in clinical measures of diabetes progression. The study uses stored samples and adds no participant or staff burden.

Specific aims:

Aim 1. To investigate the independent and joint abilities of D3, free 25OHD, and total 25OHD to predict progression of beta cell dysfunction (disposition index, DI) and changes in clinical measures (HbA1c, FPG, 2hPG and conversion to T2d) over three years in adults with prediabetes. Hypothesis: In D2d participants randomized to placebo, baseline concentrations of D3 and free 25OHD will be stronger predictors of progression than the baseline concentration of total 25OHD; strengths of these associations may differ by race and/or DBP polymorphisms.

Aim 2. To investigate the independent and joint abilities of D3, free 25OHD, and total 25OHD to predict the effectiveness of vitamin D supplementation in ameliorating beta cell dysfunction (DI) and glucose intolerance (HbA1c, FPG, 2hPG and conversion to T2d). Hypothesis: There will be significant interactions of treatment assignment (vitamin D supplementation or placebo) with baseline concentrations of vitamin D3, free 25OHD, and total 25OHD; lower concentrations of all three metabolites will predict a better treatment response, but these associations will be strongest for vitamin D3 and free 25OHD; these associations may differ by race and/or DBP polymorphisms.

Aim 3. To quantify the effect of supplementation with 4000 IU/d of D3 for 3 yrs, compared with placebo, on changes in serum concentrations of D3, free 25OHD, and total 25OHD in adults with prediabetes. Hypothesis: Percentage increases will be greatest for D3, intermediate for total 25OHD, and smallest for free 25OHD; the relative changes may differ by race and/or DBP polymorphisms.

Aim 4 (Secondary). In parallel with the above aims, to compare the relative importance of the D3, free 25OHD, and total 25OHD as predictors of PTH suppression, following vitamin D supplementation. The relative changes may differ by race and/or DBP polymorphisms.

The proposed project will contribute to understanding both mechanistic and clinical aspects of vitamin D in prediabetes. It has the potential to affect how the vitamin D requirement is defined, how clinical vitamin D status should be assessed, and how genetic variability may affect vitamin D requirements.

1c. Significance and Brief Background

Please describe the scientific relevance (1 page limit).

Serum vitamin D3 as a potential functional indicator of diabetes progression: Emerging evidence suggests that D3 may be a useful indicator of nutritional vitamin D status as related to prediabetes progression, as D3 is postulated to be an important substrate for the autocrine function of vitamin D in tissues such as the pancreatic beta cell [1]. Historically, 25-hydroxylase capacity was thought to reside solely in the liver. It is now known that many tissues have 25-hydroxylase capacity. Of particular relevance to this application, high concentrations of CYP2R1 mRNA, which encodes 25-hydroxylase, have been found in human pancreas [2], the site of the insulin producing beta cell. The beta cell also has the capacity to convert 25OHD to 1,25(OH)2D [3]. Another factor favoring D3 as a potential substrate for intracellular production of 25OHD is that D3 is loosely bound to DBP and is therefore more readily accessible to diffuse across cell membranes and into cells than is the more tightly bound 25OHD [4]. D3 has a shorter half life than 25OHD (1 day compared with 2 weeks); however, with a daily dosing schedule at 4,000 IU/day, steady access of the autocrine tissues to D3 is anticipated throughout D2d.

Free 25OHD as a potential functional indicator of diabetes progression: Free 25OHD is a viable candidate for a functional indicator of vitamin D status as related to prediabetes progression because it is readily accessible to the pancreatic beta cells and other tissues by simple diffusion. A potential point against free 25OHD as the sole indicator of nutritional vitamin D status is that free 25OHD is present in the circulation in very small quantities [5]. We will assess the level of free 25OHD by measuring it directly and also indirectly, by the method of Bikle [6].

Associations of race and DBP polymorphisms with total 25OHD, free 25OHD, and diabetes risk: Total 25OHD and its free fraction are influenced by polymorphisms in the DBP gene (Gc). The distributions of two single nucleotide polymorphisms (SNPs) in this gene, rs7041 and rs4588, as well as the protein isoforms they distinguish, primarily Gc1F, Gc1S, and Gc2, may explain some of the known race difference in total 25OHD (lower in AAs than whites). The DBP isoforms differ in concentration and in affinity for vitamin D metabolites [7-9], and thus influence their transport, half-life, and access to cells. Their frequencies differ considerably by race and also within race (Gc1F: 67% in AAs, 15% in white; Gc1S: 18% in AAs, 56% in whites; Gc2: 10% in AAs, 27% in whites) [10]. It is uncertain whether free 25OHD differs by race [11,12]. Conflicting findings may result from effects of DBP polymorphism on estimation of free 25OHD by indirect measure [11]. Directly measured free 25OHD has not been compared across race or DBP polymorphisms. Small studies in healthy Canadians [13] and US colorectal cancer patients [14] suggest that the Gc2 isoform may influence changes in total 25OHD with supplementation. The effects of DBP polymorphism on supplement-related increases in D3 and free 25OHD have not been examined. Limited data suggest that DBP polymorphism may be related to diabetes risk in some populations. The Gc1F isoform was associated with lower fasting insulin, lower insulin resistance, and lower diabetes prevalence relative to the Gc1S isoform in Japanese adults [15,16]. The frequency of the Gc1F allele in Japan is about 48%, midway between that of AAs and US whites [10]. In contrast, no similar association was observed in several populations of European origin, groups in which the Gc1F allele is uncommon [17-19]. The potential association of DBP polymorphism with diabetes risk has not been investigated in African or AA populations. Such an investigation would be of interest because poor vitamin D status may be more weakly associated with diabetes risk in AAs than in US whites [20, 21].

Serum D3 and free and total 25OHD as potential indicators of PTH levels and PTH suppression: Serum 25OHD and PTH are widely observed to be inversely associated. The relative importance of the three candidate functional indicators of PTH status (D3, free 25OHD and total 25OHD) has not been assessed in a head-to-head study. The parathyroid cell has the megalin-cubulin transport system [22] which allows bound 25OHD to be transported into this cell by endocytosis. We therefore postulate that, in contrast to the case for diabetes progression, total 25OHD may be a more robust predictor of PTH status (and of PTH response to vitamin D supplementation) than either D3 or free 25OHD.

This proposed study will provide insight into which vitamin D measure(s) are the best functional indicators of vitamin D status for predicting progressive glucose intolerance and PTH suppression in adults with prediabetes. This knowledge gained would have widespread benefit to the clinical community and will enhance the return of the investment in the D2d study.

1d. Innovation & Impact

Please describe the research innovation and potential impact (1/2 page limit).

To our knowledge, this ancillary study is the only study specifically designed and powered to perform a 'head to head' comparison of three candidate vitamin D measures to determine the most appropriate functional indicator of vitamin D status as it pertains to progression of prediabetes. D2d is a unique study to evaluate whether D3 or free 25OHD levels are more or less predictive than the current standard, total 25OHD, of clinically important outcomes related to progressive glucose intolerance. In addition, we will be able to determine whether or not the vitamin D compound(s) that most strongly predict progression to diabetes are the same as those that predict the skeletal response to vitamin D, as assessed by PTH suppression. This is important because it will potentially influence the choice of vitamin D compound(s) to be measured in the clinical setting. In recent years, measurement of total 25OHD levels has increased dramatically. For example, Medicare reimbursements for 25OHD tests increased 83-fold between 2000 and 2010; a total of 1300 tests per 10,000 patients were reimbursed in 2010 [23]. This unusually large increase was thought to be due to numerous publications advocating increasing use and measurements of this vitamin as well as by increasing media coverage of those publications. Independent of whether all of those measurements were needed, it is clearly important to choose the most appropriate functional indicator of vitamin D status when making a measurement. This ancillary study has the strong potential to change the paradigm or to provide strong support for the current choice of total 25OHD as the preferred clinical measure of vitamin D status.

1e. Research Approach

Please address the following: (1 and 1/2 page limit)

- *Study type (e.g. interventional or observational)*
- *Population and setting (inclusion/exclusion criteria)*
- *Study design (e.g. details of study procedures, outcome assessments, confounders, bias)*
- *Schedule of assessments*
- *Sample size (power) calculations*
- *Data analysis plan*

Study Type. The ancillary study adds only selected measurements in stored blood samples and involves no additional data collection. It involves use of 1 ml of stored serum from the baseline and year 3 time points for the measurements described below. It will also use 10 micrograms of DNA from the archive. The remaining of the data are collected as part of D2d and will be made available to the Ancillary Study team by the D2d Coordinating Center.

Population. All D2d participants who gave written consent to provide serum and DNA for the archive and to have those samples used for ancillary study purposes will be eligible to participate in this Ancillary study. To date, 86% of the subjects enrolled have given their consent for use of both their serum and DNA for ancillary study purposes. If that proportion remains the same, and if the actual dropout rate equals the projected rate of 5% per year, then the number of subjects available to participate in this ancillary study is projected to be 2,049 at baseline and 1,756 at the 3-year visit. Of these, the projected number of African Americans is 625 at baseline and 536 at the 3-year or final visit.

Measures added in the Ancillary Study. New measures to be made in the baseline and 3-yr visit serum samples include: D3, DBP, albumin, free 25OHD (directly and indirectly measured -- see below),1,25(OH)2D, PTH, CRP, and IL-6. Also, two SNPs (rs7041 and rs4588) will be determined in stored DNA.

Please continue Research Approach on next page.

MEASUREMENTS/METHODS

1) Vitamin D3 - by LC/MS/MS
2) DBP – by ELISA using polyclonal antibody
3) Albumin - by ELISA
4) Serum free 25OHD - We propose to measure free 25OHD by two methods, one indirect and one direct. Formal validation of either method in a population with prediabetes (or in any population) would require a "gold standard" method for comparison and there is currently no such gold standard. Nevertheless, we believe that our approach will provide the best estimates possible of free 25OHD given current technologies.
- the indirect method [6] is derived from concentrations of total 25OHD, DBP, and albumin and from a single affinity constant of DBP with 25OHD. This method does not account for differences in DBP affinities for 25OHD, but we will be making assessments of DBP variants whose affinities are known, and so can correct calculated free 25OHD levels appropriately.
- the direct assay is Future Diagnostic immunoassay. This method is unbiased for variations in DBP concentrations and for DBP affinities. It has a detection limit of 1.9 pg/ml and CV of 6.9-15.7% [12].
5) Serum 1,25(OH)2D – By RIA, the traditional method, rather than LC/MS/MS because the traditional method requires less serum (250 rather than 1000 microliters).
6) Serum PTH - by Liaison
7) Serum CRP and IL-6 –These measures are included as potential covariates in analyses of the data related to Ancillary Study aims 1-3.
8) In extracted DNA, we will measure two single-nucleotide polymorphisms in the Gc gene, rs7041 and rs4588.

POWER

In the expected 878 placebo completers (i.e. with data at baseline and 3 years), we would have at least 80% power at the 0.05 alpha level to detect a difference between correlation coefficients of one vs. another vitamin D metabolite with each outcome variable that is 0.128 or higher, using a two-sided z test. This is a conservative estimate because it is based on the assumption that the vitamin D metabolites are themselves not correlated. If this assumption is untrue, power will be better than 80% . In quantifying the effect of vitamin D supplementation on the three vitamin D metabolites in the 1,756 completers, the minimal treatment group differences we could detect are 0.23 ng/ml for D3, 0.16 ng/ml for total 25OHD, and 0.21 pg/ml for free 25OHD.

DATA ANALYSIS

Aim 1: The first step in testing this hypothesis will be to determine whether D3 and free 25OHD have larger R^2 than total 25OHD in univariate and, if appropriate, multivariate regression adjusting for other predictors of progression. If they are larger, the second step will be to determine whether, when the strongest of these predictors is entered into the regression model, the two other variables still contribute. If either D3 or free 25OHD captures most of the information in these three related risk factors, that will be compelling. We can use standard methods to test for interactions with race and DBP polymorphisms.
Aim 2: We will first model D3, free 25OHD, and total 25OHD as continuous variables, as that will be most sensitive method for detecting interaction. If we show interaction, we can create strata for these variables, e.g., quartiles, and describe the effects of vitamin D supplementation in the strata. We will then compare the regression coefficients of D3, free 25OHD, and total 25OHD.
Aim 3: We can perform univariate and multivariate analyses to estimate the effects of vitamin D supplementation on the three vitamin D measures, and again would like to be able to test whether they are significantly different.
Aim 4: Similar to Aim 1.

1f. References Cited
Please attach a list of references (PDF format document) with the application.

Part 2: Description of Data

2a. Required Sources of Data
Please select all that apply:

- ☑ Existing data collected as part of D2d study
  If yes, please complete ***D2d Ancillary Study Data Request Form***
- ☑ New data derived through use of stored biological specimens collected as part of D2d study
  If yes, please complete ***D2d Ancillary Study Specimen Request Form***
- ☐ New data derived through direct contact with D2d participants (e.g. procedure, survey, observation)
  If yes, please complete question *2b*
  If available, please include a copy of the proposed protocol with your application.

2b. New Data Acquisition, *if applicable*
Please describe the additional procedures, interventions or surveys required for new data acquisition and address the need for additional visits and/or the prolongation of existing visits. (1/2 page limit).

None.

Part 3: Facilities & Resources

3a. D2d Collaborating Clinical Sites

Please note: By marking the box next to a site(s), the ancillary study PI has secured the commitment of the site(s) to the proposed ancillary study to allow generation of new data by direct contact with D2d participants at the site.

Please select all D2d collaborating clinical sites that have agreed to participate in the proposed Ancillary Study.

- ☐ Atlanta VA Medical Center
- ☐ Baylor College of Medicine
- ☐ Beth Israel Medical Center
- ☐ Duke University Medical Center
- ☐ Florida Hospital Translational Research Institute
- ☐ HealthPartners Research Foundation
- ☐ Los Angeles Roybal
- ☐ Maine Medical Center Research Institute
- ☐ Medical University of South Carolina
- ☐ MedStar Health Research Institute
- ☐ NIDDK Phoenix
- ☐ Northwestern University
- ☐ Pennington Biomedical Research Center
- ☐ Stanford University Medical Center
- ☐ Tufts Medical Center
- ☐ Tulane University Health Sciences
- ☐ University of Kansas Medical Center
- ☐ University of Nebraska Medical Center
- ☐ University of Tennessee Health Science Center
- ☐ University of Texas Southwestern Medical Center

3b. Description of Clinical Laboratory Facilities, *if applicable*

Please describe clinical laboratory facilities and where and how bio-specimens will be handled (e.g. storage, shipping of biological material; laboratory staff experience).

Serum assays for vitamin D3, DBP, albumin, free 25OHD, 1,25(OH)2D, and PTH will be performed at Heartland Assays, LLC (Ames, Iowa) on a total of 1.0 ml of serum. Heartland Assays is a highly respected analytical laboratory run by Dr. Ron Horst, who set up and oversees the assays. For the DBP and PTH assays (requiring 50 and 250 microliters, respectively), the serum must not have been thawed previously. Once previously thawed serum is okay for the other measures.

Serum CRP and Il-6 will be assayed at Tufts CTRC. These assays require 350 microliters of serum (300 for CRP and 50 for Il-6). Once previously thawed serum could be used.

The DNA (10 ng) will also be analyzed at Tufts CTRC.

Part 4: Potential Burden on the D2d study

*Please describe the potential burden of the ancillary study **on the D2d study** in relation to the following and provide ways to minimize the burden:*

4a. Participant Burden and Potential for Compromising Participant Retention

None - this study uses archived samples and clinical information that is currently being collected in D2d only.

4b. Participant Safety and Confidentiality

Please describe measures taken to ensure participant safety and confidentiality and address plan for data management (secure storage, monitoring etc.).

No personal identifiers will be used in the computer files; subjects will be identified by unique subject and visit numbers (a given subject's ID for each visit is different).

4c. Burden on Collaborating Clinical Sites

No added burden.

4d. Regulatory Requirements

Please describe how informed consent will be obtained and describe plan for local IRB approval. If available, please attach a copy of the informed consent form.

Only subjects who have consented to ancillary studies and to DNA analysis will be included in this study.

Part 5: D2d Support

Please note: The costs associated with the use of resources (D2d or other) must be included in the plans for funding the ancillary study. All negotiated services must be documented in a letter of commitment from the provider of such services.

Please select resources at the D2d Coordinating Center or D2d Central Laboratory that will be required. There will be a fee associated with these services:

- ☑ Data extraction and transfer
- ☑ Specimen selection and transfer
- ☐ Data analyses *(depending upon staff availability, proposed analyses may be conducted by the analytical team at the D2d Coordinating Center*)
- ☐ Other study-specific services for studies that will collect new data in real time

Part 6: Funding

6a. Funding Source(s)

Please describe ancillary study funding source(s) or plans to apply for funding.

We plan to submit an RO1 application for this study in September or October, 2014.

6b. Planned Date of Submission to Funding Agency 10/01/2014

Part 7: NIH Biosketch

*Please attach NIH Biosketches **for PI only** with your application upon submission.*

D2d Ancillary Study Application

Part 8: Acknowledgement of D2d Ancillary Studies Policies & Procedures

I have read and agree to abide by the policies and procedures for D2d Ancillary Studies as described in the document titled: *D2d Ancillary Studies Policies and Procedures & Instructions for Submission of Proposals*, and specifically regarding the presentation and publication of ancillary study results and data sharing policies.

Principal Investigator Signature _____ Date _____
(e-signature accepted)

Part 9: Attachments

Please indicate all documents that are included with your application:

- ☑ NIH Biosketches for PI only ***(required for all applications)***
- ☑ References Cited ***(required for all applications)***
- ☑ D2d Ancillary Study Data Request Form
- ☑ D2d Ancillary Study Specimen Request Form

Please note: The following forms are not required with application, but are required *prior to study initiation:*

- ☐ Ancillary Study Proposal
- ☐ Ancillary Study Manual of Procedures
- ☐ Informed Consent Form *(required for studies involving generation of new data via direct contact with D2d participants)*
- ☐ IRB Approval Letter

Final steps to submission:
Save a copy of this form to your computer.
Click on the "Submit" button, which will open an email and automatically attach application. In that email, attach additional documents checked above to complete application then send.

Submit

Thank you for your interest in the D2d Study

D2d Ancillary Study Specimen Request Form

Office Use
Ancillary Study Number AS14-04 Date Submitted (MM/DD/YYYY) 07/31/2014

Title of Proposal
(81 character limit)
Parent D and free 25OHD as potential novel predictors of prediabetes progression

Principal Investigator Bess Dawson-Hughes, M.D.
Institutional Affiliation Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

1. Sample Specifications

Please select all that apply:

Age Range
- (•) All *(30 years and older)*
- ( ) Other, please specify: _____

Sex
- (•) All
- ( ) Female
- ( ) Male

Race
- (•) All
- ( ) White
- ( ) Black
- ( ) Asian
- ( ) Other, please specify: _____

Ethnicity
- (•) All
- ( ) Hispanic
- ( ) Non-Hispanic

D2d Ancillary Study Specimen Request Form

2. Specimens Requested

Please indicate treatment group and time-point (in months, starting with baseline) for each specimen type requested. Specimens not collected at a particular time-point are indicated with a dash.

Please note:

Each vial of **serum or plasma** contains **0.5 mL**
Each vial of **whole blood** contains **2 mL**
Each vial of **urine** contains **1.5 mL**

Specimen Type	Placebo									Vitamin D								
	0	6	12	18	24	30	36	42	48	0	6	12	18	24	30	36	42	48
DNA	☒	-	-	-	-	-	-	-	-	☒	-	-	-	-	-	-	-	-
Whole Blood	☐	-	☐	-	☐	-	☐	-	☐	☐	-	☐	-	☐	-	☐	-	☐
Serum	☒	☐	☐	-	☐	-	☒	-	☐	☒	☐	☐	-	☐	-	☒	-	☐
Plasma	☐	☐	☐	-	☐	-	☐	-	☐	☐	☐	☐	-	☐	-	☐	-	☐
Urine without preservative	☐	-	☐	-	☐	-	☐	-	☐	☐	-	☐	-	☐	-	☐	-	☐
Urine with acid preservative	☐	-	☐	-	☐	-	☐	-	☐	☐	-	☐	-	☐	-	☐	-	☐

Final steps to submission:
Save a copy of this form to your computer.
Attach to D2d Ancillary Study application and submit in a single email to: D2d@TuftsMedicalCenter.org.

D2d Ancillary Study Data Request Form

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Principal Investigator Bess Dawson-Hughes, M.D.
Institutional Affiliation Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

1. Data Requested

Please indicate required time assessments for each outcome category requested.

Outcome Category	Time Assessed									End of study	
	Base	M03	M06	M12	M18	M24	M30	M36	M42	M48	Conf*
Medical History	☒	☐	☐	☐	☐	☐	☐	☒	☐	☐	☐
Physical Examination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vital Signs	☒	☐	☐	☐	☐	☐	☐	☒	☐	☐	☐
Waist Circumference	☒	-	-	-	-	-	-	-	-	-	-
Non-Study Medication Review	☒	☐	☐	☐	☐	☐	☐	☒	☐	☐	☐
Food Frequency Questionnaire	☒	-	-	-	-	-	-	-	-	☐	☐
Physical Activity Questionnaire	☒	-	-	☐	-	☐	-	☒	-	☐	-
Study Pill Adherence	☐	-	☐	☐	☐	☐	☐	☐	☐	☐	☐
HbA1c, Fasting Plasma Glucose	☒	-	☐	☒	☐	☒	☐	☒	☐	☐	☐
2-hour Plasma Glucose (OGTT)	☒	-	-	☒	-	☒	-	☒	-	☐	☐
Plasma Glucose after 30 min (OGTT)	☒	-	-	☒	-	☒	-	☒	-	☐	-
25-hydroxyvitamin D	☒	-	-	☒	-	☒	-	☒	-	☐	-
Serum Insulin, fasting	☒	-	-	☒	-	☒	-	☒	-	☐	-
Serum Insulin, after 30 min (OGTT)	☒	-	-	☒	-	☒	-	☒	-	☐	-
Urine Albumin-Creatinine Ratio	☒	-	-	☒	-	☒	-	☒	-	☐	-
Urine Calcium-Creatinine Ratio	☒		-	☒	-	☒	-	☒	-	☐	-

***Conf = a confirmatory visit to confirm the diagnosis of diabetes.**

2. Comments

If necessary, please use the space below to provide additional comments.

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Ancillary Studies Bibliography

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12. Schwartz JB, Lai J, Lizaola B, Kane L, Markova S, Weyland P, Terrault NA, Stotland N, Bikle D (2014) A comparison of direct and calculated free 25(OH) Vitamin D levels in clinical populations. J Clin Endocrinol Metab jc20133874.

13. Fu L, Yun F, Oczak M, Wong BY, Vieth R, Cole DE (2009) Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. Clin Biochem 42:1174-1177.

14. Muindi JR, Adjei AA, Wu ZR, Olson I, Huang H, Groman A, Tian L, Singh PK, Sucheston LE, Johnson CS, Trump DL, Fakih MG (2013) Serum vitamin D metabolites in colorectal cancer patients receiving cholecalciferol supplementation: correlation with polymorphisms in the vitamin D genes. Horm Cancer 4:242-250.

15. Hirai M, Suzuki S, Hinokio Y, Chiba M, Kasuga S, Hirai A, Toyota T (1998) Group specific component protein genotype is associated with NIDDM in Japan. Diabetologia 41:742-743.

16. Hirai M, Suzuki S, Hinokio Y, Hirai A, Chiba M, Akai H, Suzuki C, Toyota T (2000) Variations in vitamin D-binding protein (group-specific component protein) are associated with fasting plasma insulin levels in Japanese with normal glucose tolerance. J Clin Endocrinol Metab 85:1951-1953.

17. Klupa T, Malecki M, Hanna L, Sieradzka J, Frey J, Warram JH, Sieradzki J, Krolewski AS (1999) Amino acid variants of the vitamin D-binding protein and risk of diabetes in white Americans of European origin. Eur J Endocrinol 141:490-493.

18. Malecki MT, Klupa T, Wanic K, Cyganek K, Frey J, Sieradzki J (2002) Vitamin D binding protein gene and genetic susceptibility to type 2 diabetes mellitus in a Polish population. Diabetes Res Clin Pract 57:99-104.

19. Ye WZ, Dubois-Laforgue D, Bellanne-Chantelot C, Timsit J, Velho G (2001) Variations in the vitamin D-binding protein (Gc locus) and risk of type 2 diabetes mellitus in French Caucasians. Metabolism 50:366-369.

20. Scragg R, Sowers M, Bell C (2004) Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 27:2813-2818.

21. Harris SS, Pittas AG, Palermo NJ (2012) A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. Diabetes Obes Metab 14:789-794.

22. Lundgren S, Carling T, Hjalm G, Juhlin C, Rastad J, Pihlgren U, Rask L, Akerstrom G, Hellman P (1997) Tissue distribution of human gp330/megalin, a putative Ca(2+)-sensing protein. J Histochem Cytochem 45:383-392.

23. Shahangian S, Alspach TD, Astles JR, Yesupriya A, Dettwyler WK (2014) Trends in laboratory test volumes for Medicare Part B reimbursements, 2000-2010. Arch Pathol Lab Med 138:189-203.

BIOGRAPHICAL SKETCH

NAME Bess Dawson-Hughes, MD	POSITION TITLE Professor of Medicine; Director, Bone Metabolism Laboratory
eRA COMMONS USER NAME DAWSON-HUGHES1	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Randolph-Macon College, Lynchburg, VA	B.A.	06/64	Chemistry
Tufts University School of Medicine, Boston, MA	M.D.	06/75	Medicine
St. Elizabeth's Hospital, Boston, MA	Post-Doctoral	06/77	Residency, Internal Medicine
Brigham & Women's Hospital, Boston, MA	Post-Doctoral	06/81	Fellowship, Research

A. Personal Statement *(relevant to the proposed study)*

I am pleased to participate as the principal investigator on the proposed Ancillary Study to D2d entitled "Parent D and free 25OHD as potential novel predictors of prediabetes progression". I am an active member of the D2d team and serve on the D2d Executive Committee, the Steering Committee, and the Ancillary Studies Committee (as chair). I am trained in endocrinology and for the last 25 years I have conducted clinical research in the area of *vitamin D, bone and muscle metabolism*. My work has included *large, long-term clinical trials,* including a multi-center trial in which procedures and measurements were calibrated across five collaborating sites, as well as smaller metabolic studies, as shown below. *I have also participated in the development of national and international guidelines on vitamin D, most recently having served as the Chair of the IOF position statement on vitamin D recommendations for older adults and have applied such knowledge in the study design of the proposed study. I have collaborated extensively with the Principal Investigator, Dr. Pittas, on several past and ongoing NIH-funded studies, as documented in publications cited in our biosketches. Dr. Pittas and I have demonstrated the ability to work closely and effectively together and I enjoy working with someone as talented and motivated as he is.* I have also collaborated extensively with Dr. Susan Harris. It is a pleasure to add Dr Bruce Hollis to this team – he brings expertise in vitamin D assays which is critical to the success of this project. Emerging evidence has raised the possibility that total 25OHD may not be the most appropriate measure of vitamin D status as it relates to diabetes risk. The logical next step is to do a careful comparative analysis of the candidates, vitamin D3, free 25OHD and total 25OHD as predictors of prediabetes progression. Understanding the role of these vitamin D metabolites, alone and in combination, is important whether or not the treatment with 4000 IU of vitamin D3 per day in D2d affects the rate of progression to diabetes. I am looking forward to continuing my active involvement in this ancillary study to gain a better understanding of how vitamin D affects the beta cell and to enhance the value of the D2d study as a whole.

B. Positions and Honors

Positions and Employment

1977 - 1978	Chief Resident in Medicine, St. Elizabeth's Hospital Brighton, MA
1978 – 1982	Endocrine Fellow, Harvard Medical School, Brigham and Women's Hospital
1982 - 1986	Assistant Medical Officer, USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University, Boston, MA (In charge of l4-bed Metabolic Research Unit)
1982 - 1987	Assistant Professor of Medicine, Tufts University School of Medicine, Boston, MA
1982 -	Director, Bone Metabolism Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
1992 - 1995	Associate Professor of Medicine, Tufts University School of Medicine, Boston, MA
1995 -	Senior Scientist, Tufts University, Boston
1996 -	Professor of Medicine, Tufts University School of Medicine, Boston, MA.

Other Experience and Professional Memberships and Honors

1975	Alpha Omega Alpha
1981 – 1982	Individual National Research Service Award, Harvard Medical School
1995	Bolton L. Corson Medal for research, The Franklin Institute
1990 – 2012	Board of Trustees National Osteoporosis Foundation
1995 – 2003	Associate Editor of Journal of Bone and Mineral Research
1997 - 2000	American Society for Bone and Mineral Research - Council member
1998 - 2000	American Society for Clinical Nutrition - Council member
1998 - 2005	International Bone and Mineral Society Council member
2000 – 2004	Advisory Council, NIAMS
2002 – 2005	President, National Osteoporosis Foundation (NOF)
2004 -	General Secretariat (VP) and Trustee, International Osteoporosis Foundation (IOF)
2012	International Osteoporosis Foundation President's Award
2012 -	Board of Directors of Center for the Advancement of Science in Space (CASIS)
2014	NOF Lawrence G. Raisz Memorial Lecture Award, NOF Annual meeting
2014	Thompson-Reuters "Highly cited researcher" (top 1% in clinical research in years 2002-2012)

C. Selected Peer-Reviewed Publications or Manuscripts *in press* (selected out of 210)

Most relevant to the current application (in chronological order).

1. **Dawson-Hughes B**, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med*, 1991; 115:505-12.
2. **Dawson-Hughes B**, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rates of bone loss in postmenopausal women randomized to two dosages of vitamin D. *Am J Clin Nutr*, 1995;61:1140-5.
3. **Dawson-Hughes B**, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*, 1997; 337:670-6.
4. Pittas AG, **Dawson-Hughes B**, Li T, Willett WC, Van Dam RV, Manson JE and Hu FB. Vitamin D and Calcium Intake in Relation to type 2 Diabetes. *Diabetes Care* 2006:29(3): 650-6. ***
5. Pittas AG, Harris S, Stark P and **Dawson-Hughes B**. The Effects of Calcium and Vitamin D Supplementation on Blood Glucose and Markers of Inflammation in Non-diabetic Adults. *Diabetes Care* 2007:30(4):980-986 ***
6. Pittas AG, Qi S, Manson JE, **Dawson-Hughes B** and Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care* 2010:33(9):2021-3 [PMC2928356] ***
7. Mitri J, **Dawson-Hughes B** and Pittas AG. The effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity and glycemia in adults at high risk for diabetes. The CaDDM randomized controlled trial *AJCN* 2011:94(2):486-294 [PMC3142723] ***
8. Pittas AG, Nelson J, Mitri J, Hillmann W, Garganta C, Nathan DM, Hu FB and **Dawson-Hughes B**. Vitamin D status and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program randomized controlled trial. *Diabetes Care* 2012:35(3):565-573 [PMC Pending]. ***
9. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley J.A., Meyer HE, Pfeifer M, Sanders KM, Staehelin HB, Theiler R, **Dawson-Hughes B**. A pooled analysis to define vitamin D dose requirements for fracture prevention in seniors. *N Engl J Med* 2012; 367: 40-49.
10. **Dawson-Hughes B**, Harris SS, Palermo NJ, Ceglia L, Rasmussen H. Meal conditions affect the absorption of supplemental vitamin D_3 but not the plasma 25-hydroxyvitamin D response to supplementation. J Bone Miner Res 2013;28:1778-1783.

Additional publications of importance to the field or relevant to study design/experience (in chronological order)

11. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, **Dawson-Hughes B**. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. *N Engl J Med* 1989;32l:1777-83.
12. **Dawson-Hughes B**, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in post-menopausal women. *N Engl J Med*, 1990; 323:878-83.
13. Bischoff-Ferrari H, Orav JE, **Dawson-Hughes B**. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Int Med* 2006; 166: 424-430.
14. McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, Lo G, **Dawson-Hughes B**. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis. A randomized controlled trial. JAMA 2013;309(2):155-162.
15. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall, S, **Dawson-Hughes B**. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014: doi 10.1002/jbmr.2269.

D. Research Support (Federal or non-Federal)

Ongoing Research Support

1 R01 AR060261-01A1 Dawson-Hughes (PI) 09/01/2011 - 08/31/2015
NIA / NIAMS / ODS
Musculoskeletal benefits of bicarbonate in older adults – a dose-finding trial
Major goal: to identify the optimal dose of potassium bicarbonate for short-term effects on bone and muscle. In a subsequent study, this dose will then be tested for its long term effects.

U01DK098245 (Pittas) 01/31/2013 – 01/30/2018
NIDDK
Vitamin D and Type 2 Diabetes (D2d study)
Major goal: To evaluate the safety of oral daily vitamin D supplementation and its effect on the time to onset of clinical diabetes in participants with pre-diabetes (at risk for type 2 diabetes).
Role: Co-Investigator

R01 DK76092-06 (Pittas) 9/01/2012 - 7/31/2016
NIH/NIDDK
The Role of Vitamin D in Established Type 2 Diabetes
Major goal: To define the effects of vitamin D and calcium supplementation on glucose metabolism, including insulin sensitivity and insulin secretion, in individuals at high risk for type 2 diabetes.
Role: Co-Investigator

53-3K06-5-10 Dawson-Hughes (PI) 10/01/2009 - 09/30/2014
US Department of Agriculture
Studies of Nutrition and the Aging Skeleton
Major goal: To investigate the scientific basis for setting the calcium and vitamin D intake requirements of adults. It is renewed annually and Dr. Dawson-Hughes' effort level fluctuates as needed to complement her grant support.

HNRCA Pilot Study Dawson-Hughes (PI) 10/01/2011 - 9/30/2014
US Dept Agriculture
A pilot study of the effect of dietary fat type and amount on vitamin D_3 absorption
The goal of this project is to investigate the effects of the MUFA/PUFA ratio of the diet on the absorption of oral vitamin D supplements.

WS2105602 Dawson-Hughes (PI) 1/30/2012 - 9/30/2014
Pfizer, Inc.
A pilot study of the effect of dietary fat type and amount on vitamin D_3 absorption
The goal of this project is to investigate the effects of the MUFA/PUFA ratio of the diet on the absorption of oral vitamin D supplements. This grant co-funds the USDA funded pilot study listed immediately above.

Completed Research Support (last 3 years) *- most relevant to this application*

R01 AG02707087 Tucker (PI) 04/01/2007 - 02/28/2012
NIH / NIA
Nutrition, stress and bone in older Puerto Ricans
Major goal: A cross-sectional study to identify determinants of low bone mass in this understudied population.
Role: Co-investigator

R01 DK076092 Pittas (PI) 9/30/2006 - 7/31/2012
NIH / NIDDK / ODS
Vitamin D and Calcium Homeostasis in Relation to Type 2 Diabetes*: A randomized trial*
Major goal: A short-term trial to define the effects of vitamin D and calcium supplementation on glucose metabolism, including insulin sensitivity and insulin secretion, in individuals at high risk for type 2 diabetes.
Role: Co-Investigator

R01 DK79003 Pittas (PI) 9/30/2008 – 8/30/2011
NIH / NIDDK / ODS
Vitamin D Status in Relation to Incident Type 2 Diabetes and Cardiometabolic Risk
Major goal: To measure the association between vitamin D status and risk of developing type 2 diabetes and cardiometabolic disease in the Diabetes Prevention Program.
Role: Co-Investigator

RO1 AR051361 McAlindon (PI) 06/01/2005 - 04/30/2011
NIH / NIAMS
Role - Co-investigator
Trial of Vitamin D to Reduce Progression of Knee OA
Major goal: A randomized controlled trial to evaluate the effect of vitamin D (2000 IU per day) on the progression of knee osteoarthritis.
Role: Co-investigator

WS877392 Dawson-Hughes (PI) 10/15/2010 - 10/14/2013
Pfizer, Inc.
Meal effects on the $25OHD_3$ response to supplemental vitamin D_3
The goal of this study is to begin to explore the effect of meal conditions, specifically the presence or absence of a meal and the fat content of that meal, on the bioavailability of vitamin D.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Pittas, Anastassios, G	Professor of Medicine and Clinical and Translational Science Adjunct Professor of Nutrition, Science & Policy
eRA COMMONS USER NAME apittas	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Massachusetts Institute of Technology	B.S.	06/91	Biology
Cornell University Medical College	M.D.	06/95	Medicine
New York Presbyterian Hospital at Cornell	Post-Doctoral	06/98	Residency, Internal Medicine
Tufts Medical Center	Post-Doctoral	06/00	Fellowship, Endocrinology
Tufts Sch. of Graduate Biomedical Sciences	M.S.	02/06	Clinical Research

A. Personal Statement *(relevant to the proposed study)*

The purpose of the proposed study is to conduct an ancillary study to the multi-center, clinical trial, D2d (Vitamin **D** and type **2 d**iabetes) study, to define the relative importance of circulating D3, free 25OHD, and total 25OHD in beta cell function and in clinical measures of diabetes progression. I am delighted to participate as a co-Investigator on the proposed study. I have completed formal training in clinical research methodology and have acquired skills, knowledge and experience in clinical research related to type 2 diabetes during my K23 Career Development Award and my subsequent NIH-funded work in novel approaches to prevent type 2 diabetes, including on the potential role of vitamin D in diabetes risk. Based on my training and current position as the principal investigator of the parent D2d study and leader of the D2d Coordinating Center, I am qualified and well positioned to contribute as a co- Investigator. As a diabetes specialist and experienced clinical researcher in vitamin D and diabetes, I will contribute to overall project guidance, including facilitating coordination with the D2d coordinating center, central laboratory, and with study design, data analyses and interpretation of study findings.

⇒ The proposed study, which is a focused investigation on the value of vitamin D metabolites in predicting clinical outcomes, complements effectively the parent D2d study. The proposed ancillary study is very timely, given the current interest about the potential role of vitamin D metabolites and the controversy surrounding this topic. I look forward to contributing to the success of the proposed ancillary study to D2d.

B. Positions and Honors *(relevant to application)*

Positions and Employment

2000 -	Attending Physician, Division of Endocrinology, Tufts Medical Center, Boston MA
2000 - 2007	Assistant Professor of Medicine, Tufts U. School of Medicine, Boston MA
2002 -	Center Scientist, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts U.
2006 - 2007	Adjunct Assistant Professor, Friedman School of Nutrition, Science and Policy at Tufts U.
2007 -	Associate Director, Endocrinology Fellowship Program, Tufts Medical Center, Boston, MA
2007 - 2013	Associate Professor of Medicine, Tufts U. School of Medicine, Boston MA
2007 -	Adjunct Associate Professor, Friedman School of Nutrition, Science and Policy at Tufts U.
2011 -	Associate Professor, Sackler School of Biomedical Sciences, Tufts U., Boston, MA
2011 - 2012	Director, Tufts Clinical Translational Research Center (CTRC, a core component of the NIH-CTSA-supported Clinical Translational Science Institute at Tufts University)
2013 -	Professor of Medicine, Tufts U. School of Medicine, Boston MA

Other Experience and Professional Memberships

2000 -	Diplomat in Endocrinology and Metabolism (American Board of Internal Medicine)
2000 - 2009	Director, Pathophysiology Course - Endocrine Section, Tufts U. School of Medicine
2001 - 2007	Member, Curriculum Committee, Tufts U. School of Medicine
2001 -	Co-Director, The Gerald G. and Dorothy R. Friedman Program in Diabetes and Metabolism at Tufts Medical Center
2004 -	Consultant/Reviewer, Tufts Medical Center Evidence-based Practice Center
2004 -	Member as Investigator, Boston Obesity Nutrition Research Center
Various	Expert Reviewer (grant applications) [various dates] Canadian Institutes of Health Research; Diabetes United Kingdom; Children's Medical Research Foundation, Australia; Health Research Council of New Zealand; [2009] Boston Area Diabetes Endocrinology
Various	Member *(Ad Hoc),* NIH Study Section-Clinical & Integrative Diabetes and Obesity [Feb '08; Feb '09; Feb '10; Oct '10; Feb '11];
Various	Member (Ad Hoc), NIH Special Emphasis Panel-Pilot and Feasibility Clinical Research Grants in Diabetes, Endocrine and Metabolic Diseases [July '08; Oct '08; July '09; Nov '09; May '10; July '10]
2009 -	Member as Investigator, *Boston Area Diabetes Endocrinology Research Center*
2010.May	Member *(Ad Hoc),* NIH Special Emphasis Panel RC4 – Grants for NIH Director's Opportunity for Research in Five Thematic Areas
2010.July	Member *(Ad Hoc),* NIH Special Emphasis Panel ZDK1 GRB-9 02 – Obesity, Hypertension and Diabetes
2011.Sept	Chair, NIH Special Emphasis Panel – GRADE study collaborating sites
2011 - 2014	Member *(Standing),* NIH Study Section-Clinical & Integrative Diabetes and Obesity
2014 - 2015	Chair *(Standing),* NIH Study Section-Clinical & Integrative Diabetes and Obesity

Honors & Awards

2000 - 2002	The Dr. Gerald J. and Dorothy R. Friedman Foundation Scholar, Tufts Medical Center, Boston
2006	Nominated for the 2005-6 Milton O. M'30 and Natalie V. Zucker Clinical Teaching Prize for Innovation at Tufts U. School of Medicine
1999, 2007	Oliver Smith Award in recognition of excellence, compassion and extraordinary service and caring, Tufts Medical Center, Boston, MA
2009	The Blaise Widmer Distinguished Lectureship in Nephrology, "The Role of Vitamin D in Cardiometabolic Disease"
2012	Robert M. Russell Scientific Achievement Award, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

C. **Selected Peer-Reviewed Publications or Manuscripts *in press*** [Selected out of over 80]

PI and co-Investigators shown in **bold.**

Relevant to the current application (in chronological order).

1. **Pittas AG,** Dawson-Hughes B, Li T, Willett WC, Van Dam RV, Manson JE and Hu FB. Vitamin D and Calcium Intake in Relation to type 2 Diabetes. *Diabetes Care* 2006:29(3): 650-6. PMCID: PMC2085234

2. **Pittas AG**, Roberts SB, Das SK, Gilhooly CH, Golden J, Saltzman E, Stark PC and Greenberg AS. The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss. *Obesity* 2006: 14(12): 2200-2209.

3. **Pittas AG,** Dawson-Hughes B, Li T, Willett WC, Van Dam RV, Manson JE and Hu FB. Vitamin D and Calcium Intake in Relation to type 2 Diabetes. *Diabetes Care* 2006:29(3): 650-6.

4. **Pittas AG,** Harris S, Stark P and Dawson-Hughes B. The Effects of Calcium and Vitamin D Supplementation on Blood Glucose and Markers of Inflammation in Non-diabetic Adults. *Diabetes Care* 2007:30(4):980-986

5. Das SK, Gilhooly CH, Golden JK, **Pittas AG**, Fuss PJ, Dallal GE, McCrory MA, Saltzman E and Roberts SB. Long-term effects of energy-restricted diets differing in glycemic load on metabolic adaptation and body composition. *The Open Nutr J* 2008 (2) 76-85. PMCID: PMC2920502

6. Das SK, Saltzman E, Gilhooly CH, Delany JP, Golden JK, **Pittas AG**, Dallal GE, Bhapkar MV, Fuss PJ, Dutta C, McCrory MA, Roberts SB. Low or Moderate Dietary Energy Restriction for Long-term Weight Loss: What Works Best? *Obesity* 2009:17 (11): 2019-24 PMCID: PMC2869203

7. **Pittas AG**, Chung M, Trikalinos TA, et al. Vitamin D and Cardiometabolic Outcomes: A Systematic Review. *Ann Intern Med* 2010:152:307-314. PMCID: PMC3211092

8. **Pittas AG**, Harris SS, Eliades M, Stark P and Dawson-Hughes B. Association between serum osteocalcin and markers of metabolic phenotype. *J Clin Endocrinol Metab* 2009:94(3):827-832. PMCID: PMC2681283

9. **Pittas AG,** Qi S, Manson JE, Dawson-Hughes B and Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care* 2010:33(9):2021-3 [PMC2928356 / Available on 2011/9/1] [Free Article] PMCID: PMC3322702

10. Liu, E., N. M. McKeown, **Pittas AG**, Meigs JB, Economos CD, Booth and Jacques PF. Predicted 25-hydroxyvitamin D score and change in fasting plasma glucose in the Framingham offspring study. *EJCN* 2012:66(1):139-41 PMCID: PMC3796766

11. **Pittas AG,** Nelson J, Mitri J, Hillmann W, Garganta C, Nathan DM, Hu FB and Dawson-Hughes B. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care* 2012:35(3):565-573 PMCID: PMC3322702 ***

12. Mitri J, Nelson J, Ruthazer R, Garganta C, Nathan DM, Hu FB, Dawson-Hughes B and **Pittas AG**. Plasma 25-hydroxyvitamin D and risk of metabolic syndrome: an ancillary analysis in the Diabetes Prevention Program. *EJCN* 2014:1 PMCID: PMC3322702

Additional publications of importance to the field of type 2 diabetes (in chronological order)

13. Ceglia L, Lau J and **Pittas AG**. Efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. A systematic review. *Ann Intern Med* 2006:145:665-675.

14. **Pittas AG,** Harris S, Stark P and Dawson-Hughes B. The Effects of Calcium and Vitamin D Supplementation on Blood Glucose and Markers of Inflammation in Non-diabetic Adults. *Diabetes Care* 2007:30(4):980-986

15. Amori R, Lau J and **Pittas AG.** Incretin Therapy in Type 2 Diabetes. A meta-analysis of randomized trials *JAMA* 2007:298(2):194-206

D. Research Support (Federal or non-Federal)

Ongoing Research Support *– in chronological order, by start date*

R01 DK07609206-07 Pittas (PI) 9/30/2006 - 7/31/2016
NIDDK / ODS
The role of vitamin D in established type 2 diabetes.
Major goal: A randomized, double-masked, placebo-controlled trial to test the safety and efficacy of vitamin D3 supplementation in persons with established t2DM of mild/moderate severity.
Role: Principal Investigator

Contract No. 200-2012-53787 Balk/Uhlig (PI) 9/28/2012 – 9/27/2014
Centers for Disease Control and Prevention (CDC)

PPHF-2012-Community Guide-Update of Community Guide Reviews on the Effectiveness of Interventions financed solely by 2012 Prevention and Public Health Funds. Component A (Diabetes) Updates to Existing Systematic Reviews on Diabetes Prevention and Control for the Guide to Community Preventive Services
Role: Co-Investigator

U01 DK98245-01 Pittas (PI) 6/1/2013 – 5/31/2018
NIH/NIDDK/ODS
Vitamin D and Type 2 Diabetes (D2d study)
Major goal: To conduct a multi-center (20 sites) randomized trial to test the safety of vitamin D supplementation and its efficacy in prevention of diabetes is participants at high risk for diabetes.
Role: Principal Investigator

1-14-D2d-01 Pittas (PI) 1/1/2014 – 12/31/2014
American Diabetes Association
D2d Co-Support
Major goals: (1) To enhance the science of D2d, thereby increasing the scientific and clinical return on its investment and (2) to bolster recruitment efforts of D2d.
Role: Principal Investigator

D43TW009377 Wanke (PI) 8/31/2014- 8/31/2018
Fogarty International Center
Tufts-CMC Framework Program for Global Health Innovation
Major goal: A randomized, double-masked, placebo-controlled trial to test the safety and efficacy of vitamin D3 supplementation in persons with established t2DM of mild/moderate severity.
Role: Mentor **(no support)**

Completed Research Support (last 3 years) *– in chronological order, by end date*

R01 DK79003 Pittas (PI) 9/25/2008 - 8/31/2012
NIH / NIDDK / ODS [no cost extension]
Vitamin D Status in Relation to Incident Type 2 Diabetes and Cardiometabolic Risk
Major goal: To measure the association between vitamin D status and risk of developing type 2 diabetes and cardiometabolic disease in the Diabetes Prevention Program.
Role: Principal Investigator

7-08-CR-27 Harris (PI) 7/1/2008 - 6/30/2011
American Diabetes Association
Vitamin D, glucose control and insulin sensitivity in African-Americans
Major goal: a 12-week randomized placebo-controlled trial to examine the effect of vitamin D supplementation on glucose control and insulin sensitivity in overweight, pre-diabetic African American adults.
Role: Co-Investigator

Marilyn Fishman Grant for Diabetes Research Mitri (PI) 11/1/2009 - 12/31/2011
Endocrine Fellows Foundation
The effects of vitamin D supplementation on inflammation, lipid profile and endothelial dysfunction
Major goal: Ancillary study to the CADDM trial (R01 DK076092) to determine the effects of vitamin D supplementation on systemic inflammation, lipid profile and endothelial dysfunction.
Role: Mentor ***(no support)***