D2d Ancillary Study Letter of Intent

Office Use
Ancillary Study Number AS14-02 Date Submitted (MM/DD/YYYY) 04/08/2014

To: D2d Ancillary Studies Subcommittee

Re: D2d Ancillary Study Preliminary Concept Proposal

Title of Proposal *(81 character limit)*: Effect of Vitamin D on Androgen Levels in Prediabetic Women

Principal Investigator: Anindita Nandi, MD
Institutional Affiliation: Beth Israel Mount Sinai - Mount Sinai Icahn School of Medicine
Street Address 1: 317 East 17th Street, 7th Floor
Street Address 2:
City: New York State: NY Zip Code: 10003
Phone: (212) 844-5037 Fax: (212) 450-2224 Email: anandi@chpnet.org

If Principal Investigator is not a member of the D2d study group, please specify:
D2d Co-Investigator: Leonid Poretsky, MD
Institutional Affiliation: Beth Israel Mount Sinai - Mount Sinai Icahn School of Medicine

Significance, Brief Background, Proposed Central Hypothesis and Specific Aims

The D2d study is designed to evaluate whether vitamin D supplementation prevents development of diabetes in patients with prediabetes. Prediabetes and insulin resistance have been associated with increased incidence of hyperandrogenism and polycystic ovary syndrome. Observational studies indicate a high prevalence of vitamin D deficiency in patients with polycystic ovary syndrome. A number of small studies have shown conflicting results in improvement in insulin resistance, androgenic markers, and ovarian function in this population with vitamin D supplementation. In this ancillary study, we propose to evaluate whether vitamin D supplementation in women with prediabetes decrease hyperandrogenemia.

We propose to evaluate women with prediabetes between the ages of 30 and 45. We will follow androgen indices in these women thorough measurement of total and free testosterone and SHBG levels at 6,12, 18, and 24 months after replacement with either vitamin D supplementation or placebo pill. We further aim to correlate changes in these parameters with changes in metabolic markers including insulin resistance (HOMA-IR) and inflammation (CRP). It has been debated whether vitamin D exerts its metabolic effects by directly affecting insulin sensitivity or rather by affecting the pro-inflammatory state associated with insulin resistance. Correlation of HOMA-IR and pro-inflammatory cytokines with androgenic markers will help us to assess whether changes in gonadal function, if any with vitamin D supplementation, may be mediated through improvement in metabolic status either directly or by affecting inflammatory markers.

D2d Ancillary Study Letter of Intent

Study Design

Please address study type (e.g. intervention or observational); population and setting (inclusion/exclusion); study design (e.g. study procedures, outcomes assessment and time-points, confounders); analytical methods (e.g. preliminary sample size/power calculations and assumptions).

The proposed ancillary study will be an interventional study, evaluating the effects of vitamin D supplementation versus placebo on androgenic parameters in women with prediabetes and insulin resistance. Inclusion criteria: prediabetes as defined for the D2d study, female gender, and age between 30 and 45. Exclusion criteria: abnormal thyroid function, elevated 17-hydroxyprogesterone, or prolactin. As the study progresses, any woman who develops diabetes or becomes pregnant will no longer be considered eligible to continue in the study. Baseline evaluations will include a laboratory assessment of prolactin, 17-hydroxyprogesterone, TSH, total and free testosterone, SHBG, CRP, glucose and insulin. Women with 17-hydroxyprogesterone greater than 200 ng/dl, TSH less than 0.5mIU/L or greater than 45mIU/ml, and prolactin level greater than 20ng/ml will be excluded from the study. Patients will be reassessed at 6 months, 12 months, 18 months, and 24 months. At each visit, laboratory test for total and free testosterone level, SHBG, CRP, fasting glucose and insulin will be obtained.

The primary outcome in the study will be a reduction in free testosterone level. Secondary outcomes will include improvement in total testosterone and increase in SHBG. We will further correlate our findings with changes in HOMA-IR and CRP. We will thus attempt to dissect whether the effect of vitamin D supplementation on androgen levels is temporally associated with changes in matabolic or inflammatory indices.

The design of this study is a 1-within factor (patient/time) and 1-between factor (vitamin D group) analysis of variance (ANOVA). As discussed above, patients in the treatment and control groups will be evaluated at baseline and 6, 12, 18, and 24 months. Observed variability in the primary outcome parameter of free testosterone will be utilized in determining sample size for the study. The number of patients required to achieve a power of 0.80 at an alpha level of 0.05 across values of the assumed correlation between measure on the same individual (r=0.50) is 33 in each group. However, we will take into account a 10% possibility each of loss to follow up and development of diabetes, and 5% possibility of pregnancy. The total number therefore to be recruited will be approximately 42 patients in each arm of the study.

Innovation and Impact

Several small studies suggest a beneficial effect of vitamin D supplementation in improvement of ovulatory function and insulin resistance in women with PCOS. However, these studies are limited by cohort size and lack of a placebo control arm. The D2d study is a rare opportunity to address this question. We hope through this ancillary study to determine whether vitamin D supplementation affects androgen levels in women with prediabetes. We will also correlate these findings with changes in metabolic function, especially insulin resistance and inflammation.

D2d Ancillary Study Letter of Intent

Subject Burden and Potential Risks

Please describe (1) additional procedures that will be required of participants; (2) risks to participants from the proposed procedures; (3) ways to minimize burden and risk

This ancillary study requires minimal extra burden for study participants. The laboratory evaluations will be performed on stored samples that have already been drawn for the greater D2d study at baseline, 6 month, 12 month, 18 month, and 24 month time points. This procedure is part of the D2d protocol.

Use of Stored Specimens

Please select all specimens required for the ancillary study.

- ☐ DNA
- ☐ Plasma — Amount needed: _____ mL — Time point(s): _____
- ☑ Serum — Amount needed: 1.2 mL — Time point(s): 0, 6, 12, 18, 24 months
- ☐ Urine — Amount needed: _____ mL — Time point(s): _____

Funding

Anticipated Funding Source: D2d ancillary study funds

Anticipated Date of Submission to Funding Agency: _____

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)

D2d Co-Investigator Signature _____ Date _____
(e-signature accepted)

Final steps to submission:
Save a copy of this form to your computer.
Click on the "Submit" button and follow the directions to submit electronically. Alternatively, you may attach the file manually to an email and send to: D2d@TuftsMedicalCenter.org.

Submit

D2d Ancillary Study Letter of Intent

Subject Burden and Potential Risks

Please describe (1) additional procedures that will be required of participants; (2) risks to participants from the proposed procedures; (3) ways to minimize burden and risk

This ancillary study requires minimal extra burden for study participants. The laboratory evaluations will be performed on stored samples that have already been drawn for the greater D2d study at the baseline, 6 month, 12 month, 18 month, and 24 month time points. This procedure is part of the D2d protocol.

Use of Stored Specimens

Please select all specimens required for the ancillary study.

☐ DNA					
☐ Plasma	Amount needed:	____	mL	Time point(s):	____
☑ Serum	Amount needed:	1.2	mL	Time point(s):	0, 6, 12, 18, 24 months
☐ Urine	Amount needed:	____	mL	Time point(s):	____

Funding

Anticipated Funding Source: D2d ancillary study funds

Anticipated Date of Submission to Funding Agency: ____

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 *(e-signature accepted)*: Amrita Sarkar Date: 4/7/14.

D2d Co-Investigator Signature *(e-signature accepted)*: Sal Raffy Date: 4/7/14

Final steps to submission:
Save a copy of this form to your computer.
Click on the "Submit" button and follow the directions to submit electronically. Alternatively, you may attach the file manually to an email and send to: D2d@TuftsMedicalCenter.org.

Submit