D2d Ancillary Study Letter of Intent

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Ancillary Study Number AS14-06 Date Submitted (MM/DD/YYYY) 10/31/2014

To: D2d Ancillary Studies Subcommittee

Re: D2d Ancillary Study Preliminary Concept Proposal

Title of Proposal *(81 character limit)*: Vitamin D, Depression and Cardiovascular Risk in Pre-diabetes

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

Significance, Brief Background, Proposed Central Hypothesis and Specific Aims

One in three adults in the US has pre-diabetes, which is strongly associated with premature cardiovascular disease (CVD) risk and mortality. There is increasing evidence from epidemiological studies that vitamin D may play a substantial role in mediating several CVD risk factors including hypertension, inflammation and hypertrophy of smooth muscle cells in the vascular tree. At the same time, vitamin D deficiency may also predispose to depressive symptoms, and depression is well recognized as a CVD risk factor in both healthy, type 2 diabetes and in those with existing CVD, independent of established CVD risk factors. Although patients with pre-diabetes are at increased risk for CVD, the role of vitamin D deficiency in promoting inflammation and vascular dysfunction is not clear. We hypothesize that vitamin D deficiency predisposes to depressed mood and mediates increased cardiovascular risk characterized by inflammation and vascular dysfunction in patients with prediabetes. Furthermore, supplementation with vitamin D will lower cardiovascular risk by reducing depressive symptoms. Therefore, in this study we will investigate the relationship between vitamin D levels, depression and cardiovascular risk at baseline and following supplementation.
Aim 1. Determine if vitamin D status is related to depressive symptoms in patients with pre-diabetes at baseline.
Aim 2. Determine if severity of depressive symptoms in pre-diabetes are related to metabolic syndrome components and cardiovascular risk factors (inflammation and endothelial function)
Aim 3. Determine if vitamin D supplementation mitigates cardiovascular risk by improving depressive symptoms independent physical activity.

The significance of this research will highlight the impact of depression to mediate inflammation and cardiovascular risk in an at risk population. Furthermore, we will determine if vitamin D supplementation may reduce cardiovascular risk by enhancing mood and it's associated impact on inflammation and endothelial dysfunction.

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Is that ethical if a person has worsening symptoms?

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).

Study overview: The proposed observational study would prospectively examine depression and CVD risk in D2d participants. Participants will be enrolled for two groups: 1) D2d participants that receive vitamin D supplementation (N = 200); and 2) D2d participants that receive placebo (N = 200). All participants will undergo assessment of depression (Beck Depression Inventory) and CVD risk measures (CRP levels and endothelial function of brachial artery flow mediated dilation) at Randomization and then at 12 and 24 months.

Study type: Observational examination of depression and CVD risk assessment in D2d participants before and after established intervention.

Population and setting: In addition to those criteria established for the parent D2d study, participants will be required to consent to this ancillary study. Persons will be excluded for history of active suicidal ideation or history of suicide attempt, lifetime history of bipolar depression, psychotic disorder (ie. schizophrenia), and current substance abuse of dependence disorder. Participants currently prescribed anti-depressant medication will be enrolled if on stable doses of medication for 6 weeks and will be asked to refrain from making changes to their anti-depressant medication once enrolled into the study. Additional demographic variables of interest in this analysis include work status, marital and divorce status, education and income status

Innovation and Impact

Depressive symptoms occur commonly as a comorbid condition in people with prediabetes and type 2 diabetes and are associated with increased CVD risk, however the relationship between vitamin D levels, depression and CVD risk is unclear. This research will determine if vitamin D supplementation may reduce CVD risk by enhancing mood.

The Committee has raised concerns about using any inventor that may detect suicidal thoughts and the responsibility of the investigative site to respond and act on the reports.

How many participating sites are needed and will they all be required to have this model of device?

Please address parts 2 and 3 and detail participant time commitment.

D2

Su

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

Beck Depression Inventory: A 21 item questionnaire self-report questionnaire used to assess symptoms of depression that correspond to DSM-IV-TR diagnostic criteria. The measure will be administered at baseline and at 12 and 24 month post randomization. The BDI-II has been shown to have excellent test-retest reliability (r = 0.93) and inter-item correlations (ranging from r = 0.91-0.95) when used in general populations and diabetes samples.
Vascular functional assessment. The brachial artery will be imaged above the antecubital fossa using high-resolution B model ultrasound (Seimens Sequoia, 8L/8MHz linear array transducer) with optimization of near and far wall intima. After a rest period of 10 minutes, baseline images of the brachial artery were obtained gated to the R-wave on ECG. To assess endothelial-dependent flow mediated vasodilation in response to ischemia and reactive hyperemia, a blood pressure cuff is positioned on the upper arm and was inflated to 200 mm Hg (or at least 40 mm Hg above baseline systolic blood pressure) for a period of 5 minutes. After rapid release of the cuff, R-wave gated images of the brachial artery were acquired from to 55-65 seconds after cuff release. Pulse Doppler spectra were obtained at baseline and within 10 seconds after cuff release to assess the adequacy of reactive hyperemia. After a rest period of 15 minutes, repeat baseline images are obtained. To assess endothelial-independent vasodilation , one 0.4 mg dose of nitroglycerin spray is administered. Repeat gated brachial artery images were obtained 3 minutes after nitroglycerin administration. Mean brachial artery diameter at baseline, after reactive hyperemia, at second baseline, and after nitroglycerin are measured by a a single investigator blinded to treatment allocation using specialized edge-detection software.
Inflammatory CVD maker- ultrasensitive CRP will be measured by ELISA

If done at the annual visits, it will add time to an already lengthy visit. Could they be done at semi-annual visits?

Use of Stored Specimens

Please select all specimens required for the ancillary study.

☐	DNA				
☑	Plasma	Amount needed:	100.0 mL	Time point(s):	
☐	Serum	Amount needed:	mL	Time point(s):	
☐	Urine	Amount needed:	mL	Time point(s):	

Please clarify amount. We are looking for what volume per participant per timepoint is required. 100 mL does not make sense.

Funding

Anticipated Funding Source _____

Anticipated Date of Submission to Funding Agency _____

Please complete questions on funding.

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 Sangeeta Kashyap Digitally signed by Sangeeta Kashyap DN: cn=Sangeeta Kashyap, o, ou, email=kashyas@ccf.org, c=US Date: 2014.10.31 13:41:11 -04'00' Date 10/31/2014
(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