Metformin, Vitamin D, and Depression in Polycystic Ovary Syndrome (PCOS) Trial

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PROJECT SUMMARY

The MINDD (Metformin, vitamIN D, and Depression) pilot study will include 20 reproductive-age women with polycystic ovary syndrome (PCOS), insulin resistance, low Vitamin D, and depression. Subjects will be randomly assigned in a 1:1 ratio to either Vitamin D or metformin for 12 weeks. We will use standardized, validated questionnaires to assess depression, anxiety and quality of life. At baseline, 6 weeks, and at the completion of the protocol, we will assess the following measures: 1) Depression Severity, 2) Serum 25-hydroxyvitamin D level, and 3) HOMA-IR (Homeostasis Model Assessment of Insulin Resistance), which is calculated from fasting insulin and glucose. The aim is to determine whether treatment of insulin resistance OR vitamin D deficiency in women with PCOS, insulin resistance, low Vitamin D, and depression, improves mood symptoms.

HYPOTHESIS

We hypothesize that treatment of metabolic abnormalities, specifically insulin resistance or Vitamin D deficiency, in women with PCOS and depression, will improve mood symptoms.

OBJECTIVES

Primary Aims
1- To collect pilot data that examines changes in depression symptoms among women with PCOS and depression taking metformin
2- To collect pilot data that examines changes in depression symptoms among women with PCOS and depression taking Vitamin D

Secondary Aims
1- To collect pilot data that examines changes in anxiety symptoms and PCOS-related quality of life among women with PCOS and depression taking metformin or Vitamin D
2- To investigate a potential correlation between change in serum25-hydroxy vitamin D and change in depression score, and HOMA-IR and change in depression score

DESIGN & METHODS

This is a single center, open-label, randomized, pilot clinical trial. Twenty-five subjects will be enrolled in order to have 20 subjects complete the study with roughly 10 subjects in each treatment regimen arm. Subjects will be randomly assigned in a 1:1 ratio to either Vitamin D3 (cholecalciferol) or metformin for 12 weeks. Evaluations will be completed at baseline, after 6 weeks, and after completing 12 weeks of treatment. Blood specimen collection and analysis will occur at baseline and after 12 weeks of treatment. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.
Total duration of subject participation will be 12 weeks. The following treatment regimens will be used:

- The Vitamin D group will receive 5,000 IU cholecalciferol (Vitamin D3) tabs once daily
- The Metformin group will receive 500 mg metformin once daily for the first week, 500 mg twice daily for the second week, and 1,000 mg twice daily for the duration of the 12-week trial.

Standard Survey Instruments

Beck Depression Inventory II (BDI-II),
State Trait Anxiety Inventory (STAI)
PCOS-related quality of life by the PCOS Quality of Life survey (PCOSQ)
International Physical Activity Questionnaire (IPAQ)

Blood specimen Assays

Blood specimens are assayed at Quest Diagnostics as part of routine clinical diagnostics, for participation in the UCSF PCOS Multidisciplinary clinic. This is a requirement for initial clinic intake, and the panel is

routinely repeated again after 3 months as part of clinical follow-up. These specimens are not stored but rather discarded after assay.
For those Clinic patients who did not have specimens assayed at Quest initially for these clinical baseline purposes, we will repeat the panel testing at Quest Diagnostics for consistency of assays for research purposes. Specimens are destroyed after assay and are not stored.

Inclusion Criteria

1. Female age 18-45
2. Documentation of a Polycystic Ovary Syndrome diagnosis by Rotterdam Criteria
3. Insulin resistance as evidenced by HOMA-IR > 2.0, calculated from fasting glucose and insulin
4. Mild or greater severity depression as evidenced by BDI-II > 14
5. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

Exclusion Criteria

1. Currently receiving pharmacologic treatment for depression
2. Current metformin use of > 1gm daily
3. Current or recent (within prior month) Vitamin D supplementation, unless this preceded the lab confirming Vitamin D insufficiency
4. Insulin-dependent diabetes mellitus
5. Pregnancy or breastfeeding
6. Untreated hypothyroidism
7. Current active substance abuse
8. Other major medical comorbidity: renal or hepatic dysfunction, severe pulmonary disease
9. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

BACKGROUND

PCOS is the most common endocrinopathy in women, impacting 10-15%. Women with polycystic ovary syndrome (PCOS) are afflicted by depression at rates 4-8x that of their peers without PCOS, even when controlling for BMI (2, 3). Depression contributes to the burden of this disorder and impacts efforts at self-care. The cause of increased depression risk in PCOS is unknown, and there has been minimal investigation into underlying mechanisms. As a result, no targeted treatment strategies exist. Emerging evidence supports the paradigm that systemic metabolic disturbances act centrally to disturb mood. Metabolic derangements are common in PCOS, and hyperinsulinemic insulin resistance (IR) is core to the pathophysiology of the disorder. In addition, Vitamin D (Vit D) deficiency is prevalent and is associated with IR in PCOS. Indeed, in PCOS, we have shown that women with IR are at increased risk of depression compared to their non-IR peers, and similar findings have been suggested for Vit D deficiency, potentially due to a direct effect of Vit D on mood or due to its relationship with IR. However, it is not known if correcting either of these metabolic abnormalities will ameliorate depressive symptoms. We hypothesize that treatment of IR OR Vit D deficiency in depressed women with PCOS will improve mood. We propose to conduct a pilot open-label randomized trial to test our hypothesis.
We acknowledge potential concerns that delaying treatment for insulin resistance or Vitamin D insufficiency may negatively impact study participants. However, the primary well-established potential consequence of Vitamin D deficiency is reduced bone density with increased risk for osteoporosis with chronic deprivation over the course of many years. Thus, a 12-week delay in initiating Vitamin D treatment is not anticipated to negatively impact outcomes. Similarly, delay of 12 weeks for treatment of insulin resistance will not likely predispose to rapid development of diabetes mellitus, the primary indication for treatment. Further, we discuss diet and exercise interventions with all our patients; this is another established strategy for combatting insulin resistance. Because metformin and Vitamin D have not yet been shown to impact mood in PCOS, we cannot assume the short delay in initiating treatment with either medication will negative affect quality of life in our patients. Indeed, this is the objective of our study, to establish a new targeted therapeutic approach, which requires a randomized study design. Finally, we suspect that increased medical attention and counseling obtained through study participation will overall offset any risks inherent in a 12-week delay in initiating Vitamin D or metformin therapy.

PRELIMINARY STUDIES

Insulin resistance is strongly associated with depressed mood. Emerging evidence suggests the peripheral metabolic milieu impacts brain function. "Metabolic syndrome type II", and "type 3 diabetes mellitus" describe the respective mood and cognitive disorders associated with impaired insulin signaling at the level of the brain. Diabetes doubles depression risk. Insulin resistance is a proposed mediator, based on epidemiologic data, animal studies and clinical trials.

Vitamin D deficiency is also associated with depressed mood. Observations studies have linked Vitamin D deficiency with depression risk specifically in PCOS. Clinical trial data in the general population has demonstrated antidepressant efficacy of Vitamin D in deficient persons with major depression.

Standard Clinical Practices

In our UCSF Multidisciplinary PCOS Specialty Clinic, patients have a panel of laboratory work prior to seeing us in two separate weekly sessions each month. During their visits, they have sessions with: 1) Reproductive Endocrinologists, 2) a Genetic Counselor, 3) a Dermatologist, 4) a Psychologist, and 5) a Registered Dietician. All patients undergo rigorous diagnostic assessment to confirm or rule out a diagnosis of PCOS. All patients receive counseling about the implications of a PCOS diagnosis - including insulin resistance and metabolic dysfunction, the importance of endometrial protection, fertility concerns and hyperandrogenic stigmata. All patients receive counseling about lifestyle interventions to manage their PCOS risks, such as diet and exercise strategies. They also are counseled about options for medical management of symptoms which concern them. Medications are prescribed through insurance. Three months following our initial clinic visits, the patients repeat their laboratory testing and return for a follow-up
visit to check in on how they are doing.

For women with PCOS and Vitamin D below 30 ng/mL, it is standard clinical practice to recommend Vitamin D supplementation. Provider practice varied historically with serum levels ranging from 20-30; however, the Endocrine Society does recommend supplementation at these levels and we are in agreement. Notably, in our PCOS clinic, which has been functioning for more than a decade, we only starting testing Vitamin D levels this year, as additional research implicates this Vitamin in a variety of potential health issues, although the primary indication for supplementation is bone health, a chronic process. Recent literature suggests that at least 2 in 3 women with PCOS are Vitamin D insufficient. The vitamin D dosing outside the context of this research trial may differ (i.e. weekly dosing rather than daily dosing). We selected daily dosing to more closely match the daily requirement of the Metformin group to take a medication, and the psychological outcome of interest which, which might benefit from a more closely matched daily reminder of intention. We would not routinely assess adverse side effects as we plan in this trial.

For women with impaired fasting glucose (i.e. fasting glucose > 100 mg/dL) or impaired glucose tolerance (i.e. 2-hour glucose level >140 mg/dL), standard clinical practice is to recommend insulin sensitizing interventions. Options include lifestyle interventions and metformin, which is the first line medication. For patients with insulin resistance as indicated by HOMA-IR, believed to be an early stage of impaired glucose tolerance, metformin is another option we discuss. The threshold HOMA cut-off varies; ours was selected given our prior research on the association between insulin resistance and depression risk. Recent evidence suggests that Vitamin D may have an insulin sensitizing role in diabetics; however, this is not definitive.

Thus, standard clinical practice in patients participating in our trial, who are insulin resistant, would be a combination of Vitamin D repletion and insulin sensitizing measures which can include a variety of lifestyle and metformin. All patients are thoroughly counseled about the importance of diet and exercise and thus all patients will have an intervention to improve insulin resistance. A possible 12-week delay in initiating Vitamin D treatment (if recommended), while outside of standard clinical practice, is not an urgent intervention. At the 3-month follow-up visit we check the status of IR and Vitamin D and prescribe treatments on that basis, ensuring close follow-up and addressing metabolic needs. Notably, the prevalence of Vitamin D insufficiency and IR is estimated at over 2 in 3 women with PCOS, most of whom are likely unaware of these conditions. Our close clinical attention and diagnostics overall with help offset risks imposed by these conditions if they exist chronically over years, primarily concerns regarding bone health and progression to pre-diabetes or diabetes.

STATISTICAL ANALYSIS PLAN

Sample Size Calculations: In our study, the primary outcome is change in BDI-II score (depression symptoms). A 3-point difference in BDI-II change is considered clinically significant (38). We determined expected change in BDI-II scores and standard deviations from prior studies of Vitamin D (14) and metformin (39). Using an alpha=0.05, power=0.80, and a 1:1 randomization scheme, we calculated a sample size of 8 per group, for a total of 16. Given a level of uncertainty with our assumptions on the basis of limited prior research, we aim to have 10 subjects per group complete the trial, for a total of 20. Assuming 20% attrition, we will recruit 25 subjects to result with 20 in total.

Statistical Analysis Plan: The primary endpoint is to investigate the effectiveness of the treatments on the BDI depression scores. The secondary endpoints are the change in HOMA-IR and 25(OH)D. These models will be adjusted for important covariates as needed such as BMI, age and baseline BDI-II as appropriate. Summary statistics will be provided and all testing will be performed at the 0.05 level of significance. Exploratory analyses will test for a relationship between change in HOMA-IR and 25(OH)D and depression scores.