Depression and Vitamin D_3 Supplementation in Women with Type 2 Diabetes

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Disclosures

- I have no relevant financial or nonfinancial relationships to disclose

Objectives

- The learner will describe the evidence regarding how low vitamin D levels impact diabetes and depression

- The learner will understand the impact that depression has on diabetes outcomes.

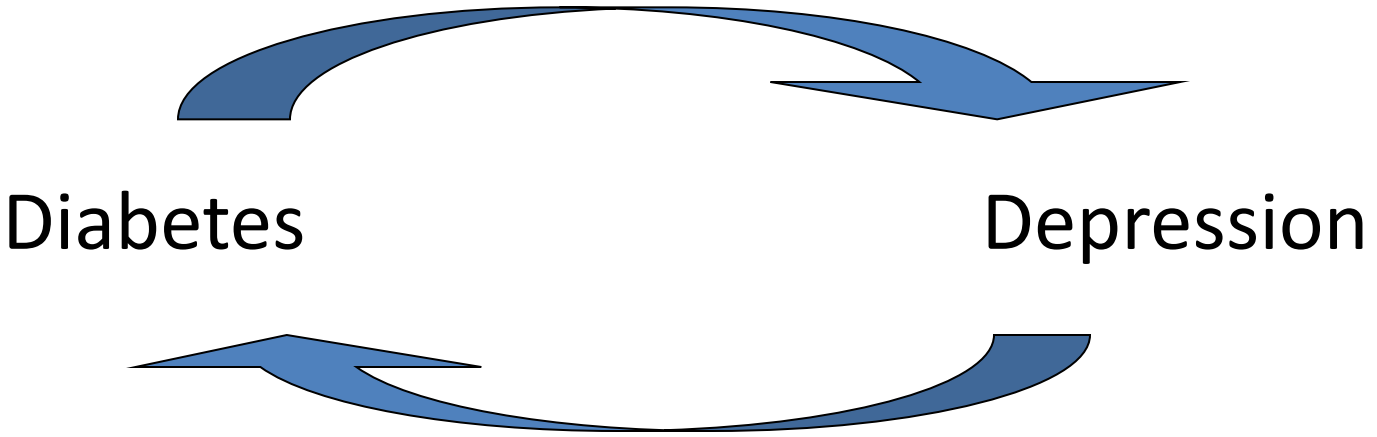
Diabetes and Depression

- About 20 to 25% of persons with diabetes have depression
- The rate of depression in women is twice that of men with diabetes
- Persons with diabetes and depression have:
  - 36% increased risk of microvascular complications (renal failure, blindness, amputation)
  - 25% increased risk of macrovascular complications (stroke, myocardial infarction)

van Dooren et al., PLOS One 2013; 8: e57058.

Diabetes & Depression Cycle

Diabetes can increase the risk and persistence of depression and depression can make it harder to manage your diabetes



Penckofer et al. Western Journal of Nursing Research 2014; 36: 1158-1182 .

Vitamin D and Depression

- Vitamin D receptors are located in the brain and may be important for mood regulation
- Depression is associated with isolation, thus persons may spend more time indoors (sun is main source of vitamin D)
- Depression is associated with poor dietary intake, thus persons may be deficient in foods containing vitamin D
- Depression is associated with obesity which decreases the bioavailability of vitamin D

Penckofer et al. Issues in Mental Health Nursing 2010; 31: 385-393.

Vitamin D and Diabetes

- Chronic illnesses like diabetes are associated with lower levels of vitamin D
- Reasons for this may be the same as those with depression such as less sun exposure, obesity, and food limited in vitamin D (e.g., eggs, salmon, dairy)
- Persons with diabetes may have impaired renal function and since the kidneys convert vitamin D to its active form, this may be a reason for lower vitamin D levels as well

Penckofer et al. Diabetes Educator 2008; 34: 939-954.

Research Evidence

- Meta-analysis of cross-sectional cohort studies reported a significant reduced risk of depression with a 10 ng/ml increase in vitamin D levels (Ju, Lee, Jeong, 2013)
- Meta-analysis of cohort studies reported that non depressed individuals have an increased risk for their first diagnosis of depression when comparing lowest to highest categories of vitamin D (Anglin et al., 2013)
- Systematic review and meta-analysis using Cochrane guidelines examined seven RTCs of vitamin D for treatment of depression and found no effect on depression symptoms with supplementation, however for those who had significant depressive symptoms or depressive disorder, there was a moderate effect (Shaffer et al., 2014)

Research Evidence

- RCT conducted in Norway in persons (n=441) who did not have a diagnosis of depression showed a significant improvement in depression (using BDI) when taking 20,000 IUs or 40,000 IUs of D_3 vs. placebo for one year with a greater improvement in women who had more depressive symptoms (Jorde et al., 2008)

- Non RCT conducted in Iran in persons (n=120) with depression (using BDI) and vitamin D deficiency received a onetime injection of 300,000 IU, 150,000 IU or placebo (not RCT) with best response noted in those with higher dose after 3 months (Mozaffari-Khosravi et al., 2013)

- RCT conducted in Australia and New Zealand in persons (n=42) with diagnosis of major depressive disorder received daily 1500 IU vitamin D_3 plus fluoxetine (20 mg) or fluoxetine alone (20 mg) for eight weeks had better response with dual treatment (Khoraminya et al., 2013)

Sunshine 1 Study

- “Proof of Concept Study” (Funded NIH 5P60DK020595, University of Chicago) to establish whether there was evidence of a treatment effect following vitamin D supplementation on mood and other health outcomes.

- For the Sunshine Study women with type 2 diabetes who had significant depressive symptoms were given weekly vitamin D_2 (50,000 IUs Ergocalciferol capsules) for six months

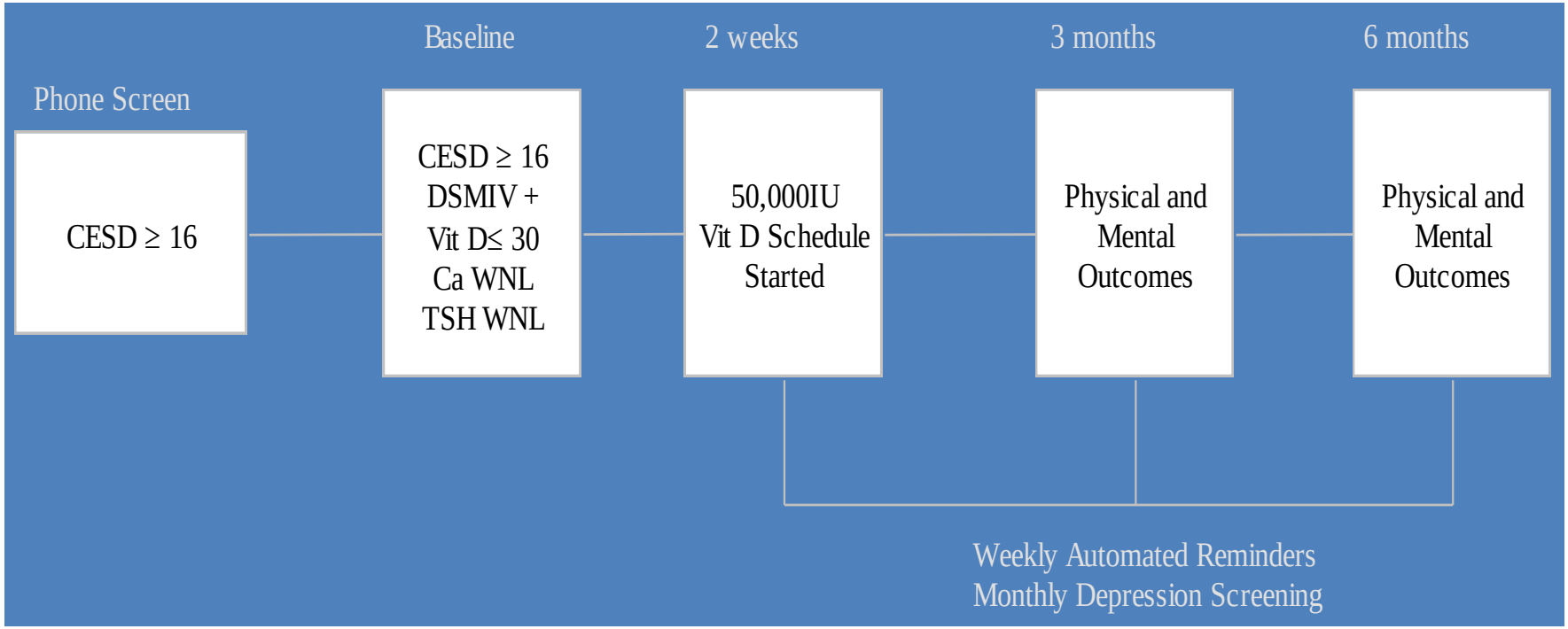
Penckofer et al. 2017, Paper Currently Under Review

Vitamin D Status

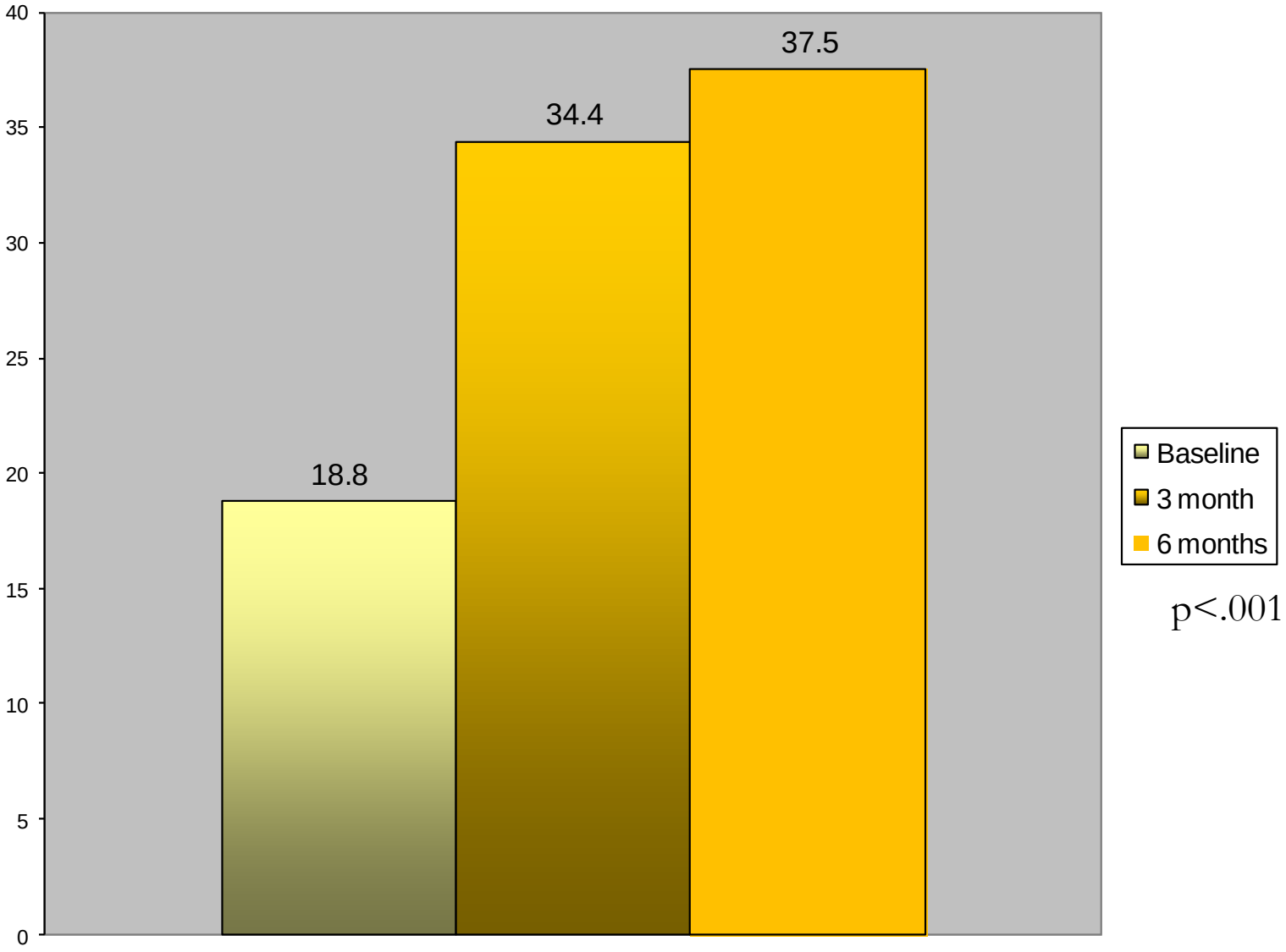
Serum 25-Hydroxyvitamin D= 25 (OH) D (ng/ml)	Vitamin D Status
≤ 10	Severe deficiency
10-20	Deficiency
21-29	Insufficiency
≥ 30 (40 to 50 Ideal Range)	Sufficiency
>100	Possibly Unsafe
>150	Toxicity

To convert 25- hydroxyvitamin D to nanomoles/L multiply by 2.496

Sunshine 1 Study: One Arm Study

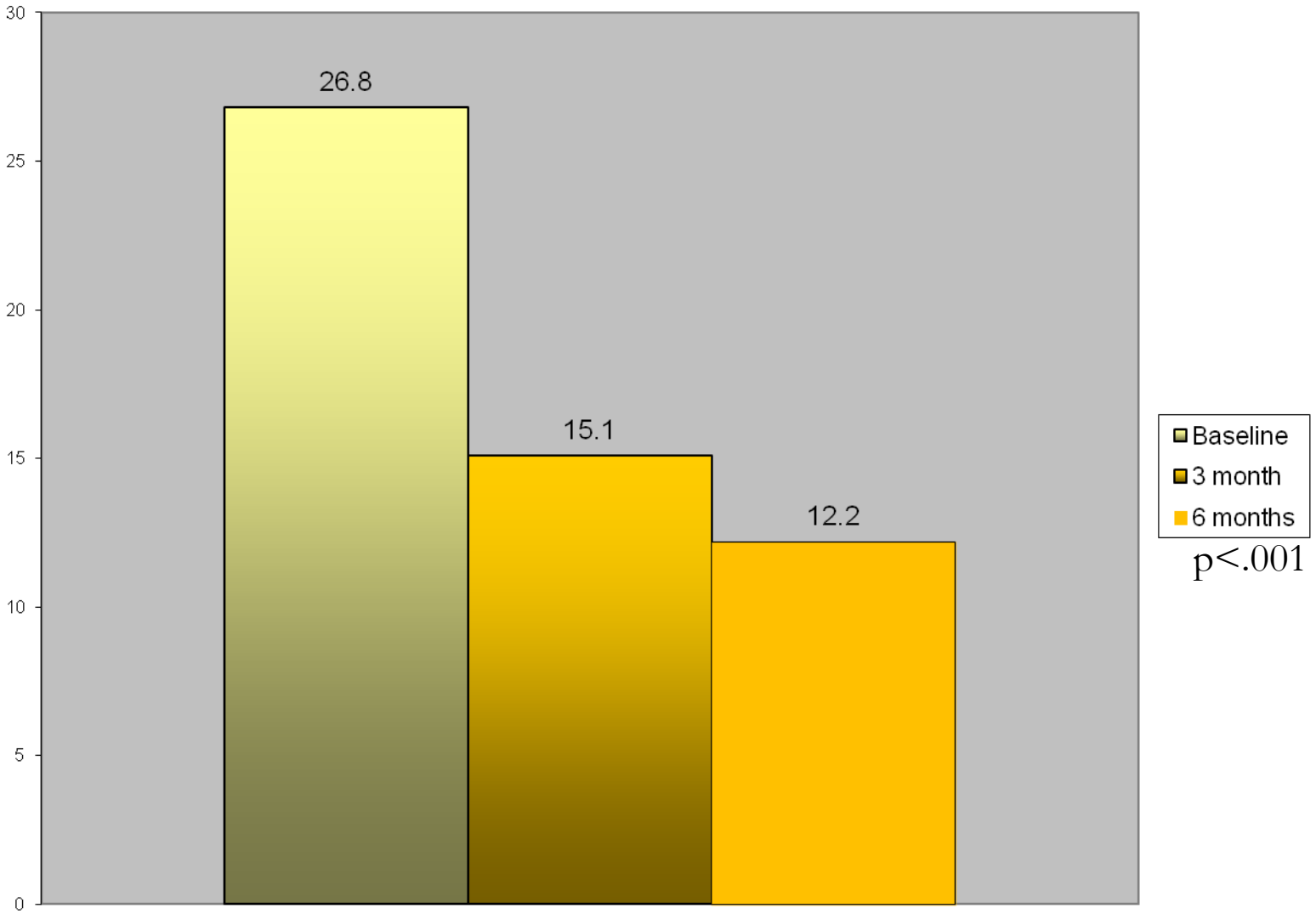


Vitamin D Levels



$p<.001$

Depression: CES-D



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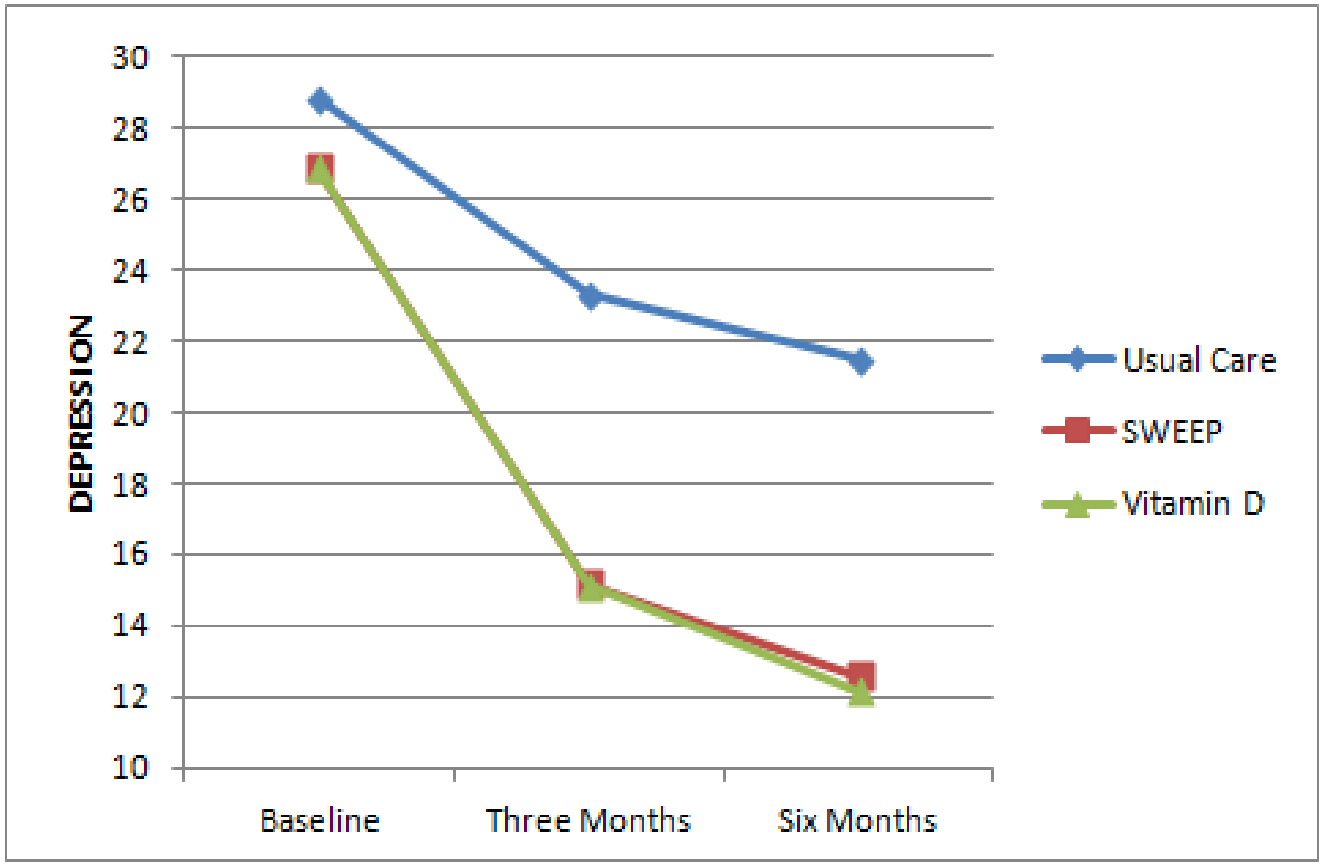
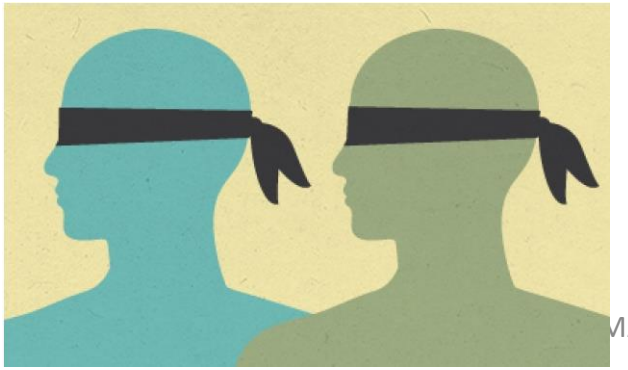
Can CBT provide same outcome as Vitamin D?



Penckofer et al. A psychoeducational intervention (SWEEP) for depressed women with diabetes. *Annals of Behavioral Medicine* 2012; 44: 192-206. Funded by NINR, NIH: K-23 NR009240-A1.

Randomized Controlled Trial

- Same schemata as Sunshine 1 but RCT with use of vitamin D3 supplementation (50,000 vs. 5,000 IUs weekly)
- Women stratified using Center for Epidemiologic Studies Depression Tool (CES-D) where (low= 16-26 and high = 27-60)
- Patients, staff, and physicians are blinded
- Only pharmacist filling script is unblinded
- Obtained FDA-IND for evaluating use for treating depression
- Data safety monitoring board every 6 months with reports on enrollments and adverse events (NIH officials)



Can the Sunshine Vitamin Improve Mood and Self-Management : **Sunshine 2 Study** (NIH, NINR 1R01NR013906-01A1)

Aim 1: To determine the effect of 50,000 IUs of vitamin D_3 supplementation on depressive symptoms (primary outcome), self-management (secondary outcome), and systolic BP (exploratory outcome) compared to 5000 IUs.

Hypothesis: Women receiving 50,000 IUs of vitamin D_3 supplementation will report fewer depressive symptoms, increased diabetes self-management mediated by depression improvement, and have a lower systolic BP compared to those taking 5000 IUs at three and six months follow-up.

Enrollment Criteria

Inclusion Criteria

- Women aged 21 and older
- Diagnosis of diabetes and being treated by a healthcare provider
- Depressive symptoms as measured by the Center for Epidemiologic Studies Depression Tool (CES-D) $\geq$ 16
- Vitamin D levels < 32 ng/dl

Exclusion Criteria

- Active suicidal ideation, bipolar depression, psychotic disorders, alcohol or substance disorders (assessed by Diagnostic Interview Schedule)
- Persons with significant complications of diabetes (e.g., amputation) that could impact on health-related quality of life
- Other Conditions: Malabsorption disorders for vitamin D, Hypercalcemia, Hypertension (BP>160/100), Impaired renal function

Subject Recruitment

- Over 1400 women were phone screened
- 265 were enrolled for baseline visit
- 134 women were not eligible to participate
- 131 were eligible, 2 not randomized, N=129

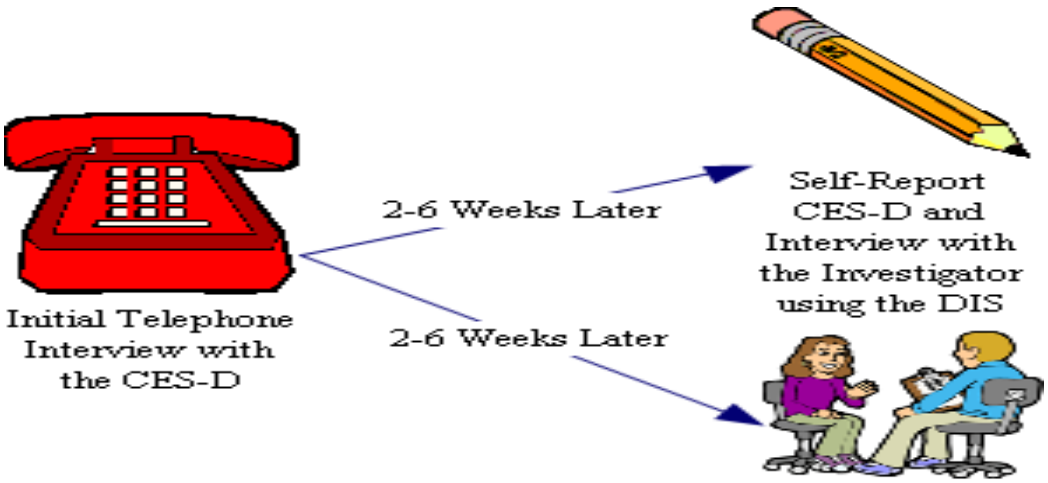
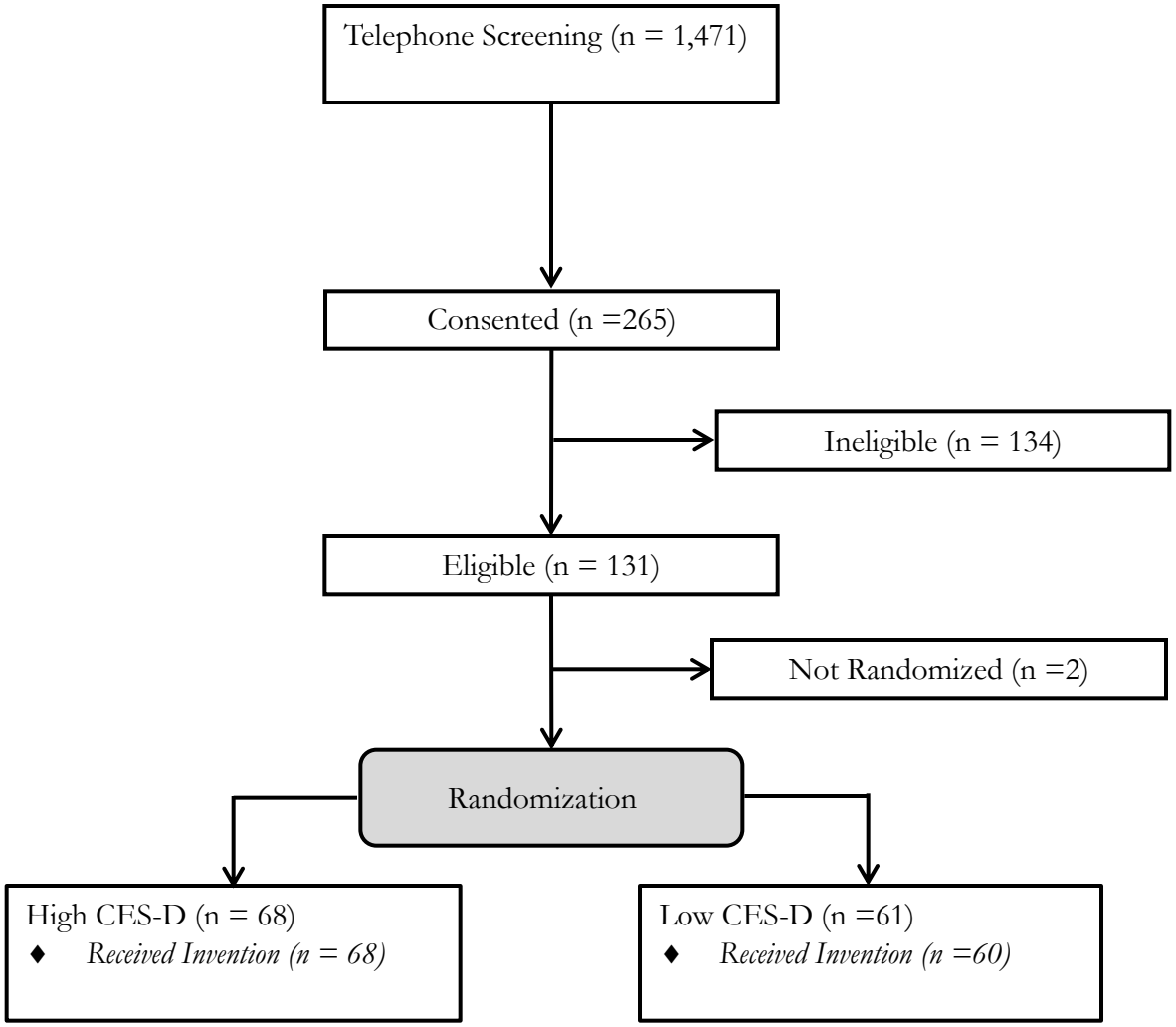


Figure 1

Summary of enrollment



Retention in Sunshine Study

	Consented	Randomized	Started TX	3 Months	6 Months
Completed (%)	265	129/265 (49%)	128/129 (99%)	113/118 (96%)	99/107 (93%)

CHARACTERISTICS OF PARTICIPANTS

	Ineligible (n = 134)	Eligible (n = 131)
Mean Age (SD)	**54.86 (10.32)**	**50.48 (11.09)**
Race/Ethnicity (%)		
White, Non-Hispanic	39 (29%)	43 (33%)
White, Hispanic	15 (11%)	21 (16%)
Black, Non-Hispanic	71 (53%)	61 (46.5%)
Black, Hispanic	2 (1.5%)	2 (1.5%)
Other, Non-Hispanic	6 (4.5%)	4 (3%)
Other, Hispanic	1 (1%)	0
Mean Years with Diabetes (SD)	9.19 (7.99)	8.87 (6.79)
Mean HBA1c (SD)	7.83 (1.97)	7.77 (1.82)
Mean CES-D (SD)	26.68 (10.51)	28.64 (8.59)
Mean Blood Pressure (SD)		
Systolic	136.63 (21.41)	132.05 (15.41)
Diastolic	74.57 (9.95)	73.30 (9.80)

Among the 131 eligible participants, the average CES-D is 28.64 (SD = 8.68), and there are 62 (47%) in low depression group and 69 (53%) in high depression group

CHARACTERISTICS OF PARTICIPANTS

	Ineligible (n = 134)	Eligible (n = 131)
Vitamin D Level		
Mean Vitamin D, 25-OH, TOTAL (SD)	29.94 (11.50)	20.90 (6.44)
Mean Vitamin D, 25-OH, D3 (SD)	26.87 (11.63)	19.65 (6.64)
Mean Vitamin D, 25-OH, D2 (SD)	6.10 (6.32)	4.61 (2.27)
Mean CMP Calcium (SD)	9.59 (0.38)	9.44 (0.31)
Mean PTH (SD)	--	51.41 (20.23)
Mean PTH Calcium (SD)	--	9.43 (0.30)
Mean BUN (SD)	15.80 (8.05)	13.50 (3.74)
Mean Creatinine (SD)	0.86 (0.37)	0.74 (0.14)
Mean Body Mass Index (SD)	36.78 (8.58)	38.48 (8.14)

Among the 131 eligible participants, at baseline there was no difference in vitamin D levels for those in the low depression group (M = 20.94, SD = 7.15) and high depression group (M = 20.87, SD = 5.77).

Implications

If study demonstrates significant results:

- Vitamin D could be used as a cost-effective treatment for depressive symptoms and/or as an adjunct to current depression treatment
- Improvement in depression could enhance diabetes self-management and improve overall glycemic control
- Improvement in depression would decrease cardiovascular morbidity and mortality

Forthcoming trials results in 2018 include the Sunshine 2 study and the Vitamin D and Omega 3 Trial (VITAL DEP Sub study) examining onset of depressive symptoms and depression in older adults (Okereke & Singh, 2016).

Acknowledgements

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