

Vitamin D Testing

Effective: April 1, 2018

Next Review: October 2018

Last Review: March 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vitamin D is a fat-soluble vitamin that plays an essential role in mineral metabolism (e.g. calcium absorption) and is needed for normal bone growth and remodeling. In addition, the vitamin has several other roles, including but not limited to modulation of neuromuscular and immune functions.

MEDICAL POLICY CRITERIA

- I. 25-hydroxyvitamin D [25(OH)D], calcidiol, serum testing may be considered **medically necessary** in patients with a clinically documented underlying disease or condition which is specifically associated with vitamin D deficiency or decreased bone density as listed in Appendix I.
- II. 25(OH)D serum testing is considered **not medically necessary** unless there is clinical documentation of an underlying disease or condition specifically associated with vitamin D deficiency or decreased bone density as listed in Appendix I.
- III. 1,25-dihydroxyvitamin D [1,25(OH)₂D] calcitriol, serum testing may be **medically necessary** in the evaluation or treatment of conditions that may be associated with defects in vitamin D metabolism as listed in Appendix II.

- IV. 1,25(OH)₂D serum testing is considered **not medically necessary** unless there is clinical documentation of a condition specifically associated with defects in vitamin D metabolism as listed in Appendix II.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

It is critical that the History and Physical documenting serum testing and applicable treatment history of underlying disease or condition associated w/vitamin D deficiency, decreased bone density, or vitamin D metabolism defect is submitted for review to determine if the policy criteria are met. If not submitted, it could impact our review and decision outcome.

CROSS REFERENCES

None

BACKGROUND

Vitamin D, also known as calciferol, is a fat-soluble vitamin that has a variety of physiologic effects, most prominently in calcium homeostasis and bone metabolism. In addition to the role it plays in bone metabolism, other physiologic effects include inhibition of smooth muscle proliferation, regulation of the renin-angiotensin system, decrease in coagulation, and decrease in inflammatory markers.

Vitamin D intake (food and supplements) can be expressed in either International Units (IU) or micrograms (µg) (1 µg = 40 IU vitamin D).

Vitamin D is available from a limited number of dietary sources (fish liver oils, fatty fish, egg yolks, and fortified foods), supplementation, and from skin synthesis upon exposure to ultraviolet radiation from the sun.

There are 2 forms of activated vitamin D for which testing is performed:

- 25-hydroxyvitamin D [25(OH)D], calcidiol

This is the most abundant circulating form of vitamin D and is the most common measure of serum levels.

- 1,25-dihydroxyvitamin D [1,25(OH)₂D], calcitriol

Although the most metabolically active form, circulating 1,25(OH)₂D is generally not considered to be a reliable measurement of vitamin D as it has a very short half-life. Production in the kidney is closely regulated by a number of different factors, and a significant decrease is observed only when deficiency is severe. However, there may be a role for 1,25-dihydroxyvitamin D serum testing in the evaluation and treatment of a limited number of medical indications (see Appendix II).^[1-4] For these conditions, 1,25(OH)₂D serum testing is not a measure of vitamin D deficiency related to inadequate sunlight and/or nutritional exposure. Rather, the test is a measure of abnormal vitamin D metabolism and may be an indicator of disease.

Vitamin D testing to determine serum levels may be performed for two purposes:

- To assess serum levels in patients with signs and/or symptoms of toxicity or deficiency or with conditions strongly associated with vitamin D deficiency (see Appendices I & II); or
- To screen for potential deficiencies in:
 - Healthy individuals without signs or symptoms of an illness/disease (e.g., vitamin D screening as a part of routine health exams); or
 - Individuals with general symptoms which are not specific to or suggestive of vitamin D deficiency.

EVIDENCE SUMMARY

It is widely recognized that there are some disorders which are thought to be *caused* or *exacerbated* by vitamin D deficiency. In general, these disorders are related to bone health, such as rickets, osteomalacia, and osteoporosis. In addition, there are certain medical conditions which may *result* in vitamin D deficiency, such as chronic kidney disease, sarcoidosis and malabsorption disorders. There is strong medical consensus that vitamin D testing and treatment is appropriate when these specific conditions (see Appendices I and II) directly cause or result in vitamin deficiency. Specifically, for these patients, treatment of a detected vitamin D imbalance is thought to directly improve health outcomes. With the exception of testing for bone health disorders, the evidence regarding the causal relationship between vitamin D deficiency and these specific conditions is limited; however, assessment of serum levels in patients with these conditions is widely accepted and has become the standard of care.

Vitamin D testing has also been proposed as part of routine wellness check-ups in asymptomatic patients and in patients who present with a variety of conditions or symptoms not specifically associated with vitamin D deficiency. For many of these indications, evidence has accumulated which supports an association between vitamin D deficiency and the symptom or condition. However, there is limited evidence to establish a causal relationship or demonstrate that treatment based on vitamin D test results leads to an improvement in health outcomes associated with these indications.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of treating vitamin D deficiency is greater than the combined influence of all confounding factors for the given condition.^[5] This direct evidence could come from well-designed, randomized controlled trials. Evidence from non-randomized trials may also be considered when vitamin D supplementation results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible causes of the condition. Currently, evidence of this magnitude is limited with respect to vitamin D treatment in patients with or without a known condition. Therefore, in order to isolate the independent contribution of vitamin D testing on health outcomes, studies which control for confounding factors are essential. Large, well-designed, randomized controlled trials (RCTs) with adequate follow-up are needed.

METHODS OF EVIDENCE ASSESSMENT

Validation of the clinical use of any diagnostic test requires the demonstration of three key

components:

Analytic validity, including reproducibility and precision. For comparison among studies, a common standardized protocol for the new diagnostic technology is established.

Clinical validity (i.e., sensitivity, specificity, and positive and negative predictive value) which describes the ability of a test to accurately predict clinical outcomes in appropriate populations of patients. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive). The specificity is the ability to detect the absence of a disease or outcome when the disease is not present (true negative).

In general, systematic reviews and evidence reports regarding the technical feasibility and diagnostic performance of vitamin D testing indicate there is uncertainty associated with this measurement.^[6-9] The appropriate testing method^[6,8] and cut-off values for optimal serum levels of vitamin D have not been defined.^[8-10]

After reviewing evidence from more than a thousand studies the Institutes of Medicine (IOM) 2010 report committee concluded that, “the measurements, or cut-points, of sufficiency and deficiency used by laboratories to report results have not been set based on rigorous scientific studies, and no central authority has determined which cut-points to use. A single individual might be deemed deficient or sufficient, depending on the laboratory where the blood is tested.”^[7] Without established cut-off values and reference standards, vitamin D tests may produce false results that in turn may mislead treatment decisions.

Despite uncertain evidence, the IOM report recommended an adequate intake (AI) of 600 IU for males and females 1-70 years of age and 800 IU for adults 71 years and older (recommended adequate intake is defined as average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people).^[7]

Clinical utility is a key aspect of evaluating clinical test performance, and it demonstrates how the results of a study can be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

The focus of the following literature review is on evidence related to the clinical utility of vitamin D testing for indications not otherwise listed in Appendices I and II. In order to establish clinical utility, evidence from randomized controlled trials is required to demonstrate the following:

1. How test results are used to guide treatment decisions that would not otherwise be made in the absence of testing, and
2. Whether those decisions result in improved primary health outcomes associated with the disease or condition being treated.

ALZHEIMER’S DISEASE

SYSTEMATIC REVIEWS

Several systematic reviews^[11-16] reported an association between Alzheimer’s disease and vitamin D deficiency when compared to healthy controls; however, the effect of vitamin D supplementation on patients with Alzheimer’s disease was not assessed. Therefore, the clinical utility of testing and treating for vitamin D deficiency was not established.

Additional reviews of published studies regarding vitamin D supplementation as a treatment for Alzheimer's disease have been published;^[17] however, these reviews are based upon non-randomized prospective studies, which are not considered reliable for establishing the clinical utility of testing.

RANDOMIZED CONTROLLED TRIALS

Stein evaluated vitamin D and nasal insulin treatment on memory and disability in 32 patients with mild-moderate Alzheimer's disease (AD).^[18] All patients took low-doses of vitamin D (1000 IU/day) throughout the study and were then randomized to additional high-doses of vitamin D for 8 weeks. After 8 weeks, patients were then randomized again to nasal insulin (60 IU qid) or placebo for 48 hours. Primary outcomes were measured with Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), Disability Assessment in Dementia (after high-dose D) and ADAS-cog and Wechsler Memory Scale-Revised Logical memory (WMS-R LM) for immediate and delayed recall (after nasal insulin). There were no reported differences in cognition or disability after high-dose vitamin D compared to the control group. In addition, this study is limited by small sample size, short-term follow-up and the addition of a confounding variable of the second medication (nasal insulin).

ASTHMA AND WHEEZING

SYSTEMATIC REVIEWS

A 2015 meta-analysis of the effect of vitamin D supplementation plus asthma controller medication on acute asthma exacerbation and lung function was published.^[19] Seven RCTs from seven countries (total N=903 patients) published up to July 2015 were selected. Three studies included children and four included adults. Doses as well as routes and lengths of administration of vitamin D varied by study, as did asthma severity. Mean baseline 25-OH(D) levels ranged from 19 to 21 ng/mL. The pooled relative risk (vitamin D vs control) of asthma exacerbation was 0.66 (95% CI, 0.32 to 1.37). There was no effect of vitamin D on asthma exacerbation, fractional exhaled nitric oxide, difference in mean in forced expiratory volume in one second, or Asthma Control Test score.

RANDOMIZED CONTROLLED TRIALS

Additional RCTs of vitamin D supplementation and asthma not already included in the above referenced review are summarized here.

An RCT of prenatal supplementation in 881 pregnant women at high risk of having children with asthma was published in 2016.^[20] Women between gestational ages of 10 and 18 weeks were randomized to daily vitamin D 4000 IU plus a multivitamin containing vitamin D 400 IU (4400 IU group) or daily placebo vitamin D plus a multivitamin containing vitamin D 400 IU (400 IU group). Coprimary outcomes were (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-OH(D) levels. Analysis of infant outcomes included 806 infants, 218 of whom developed asthma by age 3. The proportion of infants with asthma or recurrent wheeze was 24% in the 4400 IU group versus 30% in the 400 IU group (difference, -6%; 95% CI, -30% to 18%). There were no differences in the proportion of infants experiencing eczema or lower respiratory tract infections.

CANCER

SYSTEMATIC REVIEWS

In 2014, a Cochrane systematic review and meta-analysis assessed the benefits and harms of vitamin D supplementation on prevention of cancer in adults.^[21] Reviewers included 18 RCTs (50,623 participants) that compared vitamin D at any dose, duration, and route of administration to placebo or no intervention in healthy adults or diagnosed with a specific disease. Cancer occurred in 1927 (7.6%) of 25,275 participants assigned to receive vitamin D versus 1943 (7.7%) of 25,348 participants assigned to receive control interventions (RR=1.00; 95% CI, 0.94 to 1.06) based on GRADE moderate quality evidence. There was no substantial difference in the effect of vitamin D on cancer in subgroup analyses of trials only including participants with vitamin D levels less than 20 ng/mL at enrollment compared to trials including participants with vitamin D levels of 20 ng/mL or greater at enrollment. Vitamin D₃ combined with calcium was associated with increased nephrolithiasis (RR=1.17; 95% CI, 1.03 to 1.34).

A 2014 AHRQ report summarized the evidence on vitamin D supplementation and cancer outcomes.^[22] Based on a limited number of RCTs, the following conclusions were made:

- One RCT reported no effect of vitamin D on overall cancer mortality in healthy postmenopausal women.
- One RCT reported no effect of vitamin D on overall cancer mortality for elderly men or women.

The evidence on the association between vitamin D levels and cancer was reviewed by the Institute of Medicine in 2011, with the following conclusions:^[7]

- There are a small number of studies that address this question and they show a lack of consistency in associations between vitamin D intake, or levels, and all cancer mortality.
- Most available RCTs do not have cancer as a prespecified primary outcome, thus the validity of the data is less than optimal.
- Overall, the evidence is insufficient to form conclusions about the association of vitamin D with cancer.

RANDOMIZED CONTROLLED TRIALS

Additional RCTs of vitamin D supplementation and cancer not already included in the above referenced Cochrane review are summarized here.

In 2017, Ammann reported results of a secondary analysis from the Women's Health Initiative (WHI) Calcium/Vitamin D (CaD) trial.^[23] Participants were offered to participate in the CaD at their first follow-up visit for the large WHI trials between 1995 and 2000. A total of 36,282 women were stratified by treatment location and age, and randomized to calcium (1000 mg of elemental calcium carbonate) and vitamin D (400 IU of D₃) or placebo in a 1:1 allocation. Daily non-study calcium and vitamin D supplements were also allowed. Data not included in analysis did not differ between arms (data were excluded for missingness or diagnosis of a hematopoietic malignancy prior to the start of the CaD trial), nor did length of follow-up. Total participant data included in final analysis included 17,411 in active treatment, and 17,352 in the control arm (total N = 34,763). Primary endpoints were 1) incident hematologic malignancy (HM) (all types), and 2) hematologic cancer-specific mortality. Median follow-up was 7 years; median age (range) was 63 (58-69) for both arms. Overall risk of HM was found to be statistically lower in the intervention arm compared to the control arm (Cox hazard ratio [HR], 0.80; 95% confidence interval [95% CI], 0.65-0.99 [*P* = 0.04]). However, no significant association was found between CaD supplementation and HM-cancer specific mortality (HR,

0.77; 95% CI, 0.53-1.11 [$P = 0.16$]). Following the results of this large, well designed RCT, authors concluded additional research regarding the association between vitamin D supplementation and HM is warranted.

In 2015, Baron published results of a randomized, double-blind, placebo-controlled trial of supplementation with vitamin D, calcium, or both for the prevention of recurrent colorectal adenomas.^[24] The trial assigned treatment to 2259 patients with recently diagnosed adenomas and no known colorectal polyps remaining after complete colonoscopy. Patients received treatment and continued follow-up for 3 to 5 years and the primary outcome was adenomas diagnosed through colonoscopy. Overall, 1301 (43%) of patients had one or more newly diagnosed adenomas during follow-up. Relative risks for recurrent adenomas were adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), sex, type of randomization, and number of baseline adenomas. The adjusted relative risk for recurrent adenomas was 0.99 (95% CI, 0.89 to 1.09) with vitamin D versus no vitamin D. The findings for advanced adenomas were similar. There were few serious adverse events, and hypercalcemia did not differ between vitamin D and no vitamin D.

DEPRESSION

SYSTEMATIC REVIEWS

In 2015, Gowda published a meta-analysis of randomized controlled trials evaluating the effect of vitamin D supplementation in reducing depressive symptoms.^[25] A total of 9 trials were included in the review with a total of 4923 patients who were diagnosed with depressive disorder based upon the Diagnostic and Statistical Manual of Mental Disorders or other symptom checklist for depression. No significant reduction in depression related symptoms was observed with vitamin D supplementation compared to no supplementation. The study was limited by inclusion of patients with adequate vitamin D serum levels at baseline. In addition, vitamin D doses and intervention duration varied among included studies.

Authors of the IOM report conducted an extensive systematic review to clarify the benefits of vitamin D supplementation for a variety of indications.^[7] For depression, five randomized controlled trials (RCTs) on general depression and seasonal affective disorder were identified. The shorter, smaller studies^[26-28] reported some improvement in mood with increased vitamin D supplementation, while the longer, larger studies^[29] showed no improvements. The IOM committee concluded the findings were inconsistent, “and few or no clinical trials were identified to support biological plausibility. As a result of the many shortcomings in study design and quality of observational evidence and the paucity of high quality evidence from RCTs identified by the committee, the findings for neuropsychological indicators are inconclusive.”

In 2013, Li evaluated the efficacy of oral vitamin D supplementation on depression.^[30] A total of six RCTs containing 1203 patients (72% female, 71 depressed patients) were selected for inclusion. Five of the studies evaluated adults at risk for depression while one study evaluated the effects of vitamin D on patients with depression. Authors noted that the quality of evidence was low. A classic and Bayesian meta-analysis demonstrated no significant effect of vitamin D supplementation on postintervention depression scores compared to the placebo group. In addition, no differences were demonstrated in subgroup or sensitivity analyses.

The 2012 Washington State Health Care Authority Health Technology Assessment (WA TEC)^[9] concluded that although current evidence suggested an association between vitamin D

deficiency and mood disorders, including depression, there were no studies which provided support for a causal relationship between vitamin D and mood disorders.

Additional systematic reviews^[31] reported an association between depression symptoms and vitamin D deficiency when compared to healthy controls; however, the effect of vitamin D supplementation on patients with depression was not assessed. Therefore, the clinical utility of testing and treating for vitamin D deficiency was not established. Also, reviews of published studies regarding vitamin D treatment to prevent or treat depression have been published;^[32] however, these reviews are based upon nonrandomized trials and are therefore are not considered reliable for establishing the clinical utility of vitamin D testing or treatment for depression.

RANDOMIZED CONTROLLED TRIALS

Small, short term randomized controlled trials exist in the literature,^[33] although larger studies with longer-term outcomes are reported here.

In 2012, Kjaergaard assessed the effect of vitamin D treatment on depression scores in participants with both low and high 25-hydroxyvitamin D (25-D) levels.^[34] Participants with low 25-D levels (n=230) were randomized to either placebo or 40,000 IU of vitamin D/week for 6 months. Those with high 25-D levels (n=114) were used as nested controls. The Beck Depression Inventory, Hospital Anxiety and Depression Scale, Seasonal Pattern Assessment Scale and Montgomery-Åsberg Depression Rating Scale were all used to evaluate depressive symptoms. Although depression was found to be associated with lower vitamin D levels, no differences were observed in depressive symptoms with vitamin D treatment compared to placebo.

The Women's Health Initiative (WHI) Calcium and Vitamin D (CaD) trial included postmenopausal women aged 50-79 in a large, randomized trial evaluating the effect of vitamin D treatment on depression symptoms.^[35] Exclusion criteria did not include recent history of vitamin D supplementation and women were allowed to continue personal use of vitamin D and calcium supplementation throughout the study. Participants in the treatment group (n=18,176, total 36,282) received 1,000 mg of calcium and 400 IU of vitamin D daily for three years. The Burnam scale was used to assess depressive symptoms at baseline and annually. Ultimately, authors reported no significant differences in the risk for depression between groups. This study was limited by a 63% adherence rate reported at the three year follow-up. In addition, mean baseline depression scores were low, suggesting most participants were not experiencing clinically relevant depression at the start of the study.

Sanders conducted a double-blind, randomized, placebo-controlled trial to examine the effects of high-dose vitamin D on mood in women aged 70 or older.^[36] Participants who were taking vitamin D supplementation were excluded leaving approximately 2260 to be randomized. Active control groups were instructed to take a single dose of 500,000 IU vitamin D3/annually during the autumn/winter months for 3-5 years. Participants were asked to complete the General Health Questionnaire (GHQ) at three time points during the study (baseline, 12 & 15 months post-dose). In addition, a subset of 150 participants, randomly chosen from both groups, completed additional questionnaires and blood sampling to determine serum 25D levels at baseline and post-dose time points. Serum samples were not otherwise collected in the general study participants. Ultimately no differences were observed in either the general or nested studies. Despite a measured increase in 25D levels from low to normal in the nested treatment group, no changes in mood or depression status were observed compared to the

control group.

In another large randomized study of older women (70 years or older), Dumville evaluated the effects of vitamin D supplementation as a prevention of seasonal affective disorder (SAD), a sub-type of depression.^[37] A total of 2117 women were randomized to receive 800 IU of vitamin D daily with calcium or placebo between the months of May-October. Only 1621 (77%) participants completed both baseline and six-month SF-12 questionnaires. At the six-month follow-up, no significant difference was observed between groups in mental health scores. Serum measures and pre-study vitamin D levels and supplementation were not reported.

In a randomized study by Jorde, the effect of vitamin D supplementation was evaluated on symptoms of depression in 441 overweight subjects.^[38] Subjects were randomized to one of three groups: group DD received 40,000 IU of vitamin D, group DP received 20,000 IU of vitamin D and group DD received a placebo per week, over the course of one year. Participant depression scores were measured by the Beck Depression Inventory (BDI) questionnaire at baseline and 12 months. Serum blood samples were drawn at baseline and every three months during the study. During the course of the study, no significant changes or differences were observed regarding weight and physical activity in either group. A significant improvement in BDI scores was reported in both treatment groups; however, authors were unable to control for confounding factors which may have influenced these findings such as age, sex, smoking, and other medications or medical conditions. For example, the placebo group had a higher number of non-smoking males with higher BMIs. In addition, there was a high (over 22%) drop-out rate which calls into question conclusions reached by this study.

DIABETES

SYSTEMATIC REVIEWS

In 2017, Thompson published an evidence-based review to serve as a resource for the management of comorbidities associated with childhood overweight and obesity.^[39] Authors conducted a narrative review of 35 studies published between January 2010 and January 2015, and vitamin D deficiency recommendations were based on Level II evidence ([a] randomized controlled and [b] nonrandomized trials). The care algorithm included serum 25(OH)D testing for children aged 2-18 years with BMI \geq 85th percentile. However, treatment was recommended as either brief daily unprotected sun exposure, or a combination of sun exposure and vitamin D₂ or D₃ supplementation depending on serum testing results. Limitations have previously been described (see Background, above) regarding uncertainty for optimal cutoff values in testing, and performance of the testing diagnostic. Overall, this resource statement was limited by availability of high-quality evidence as stated by the authors.

In the 2010 Institute of Medicine (IOM) summary regarding vitamin D treatment in patients with diabetes, the committee found that studies associating type 2 diabetes with vitamin D deficiency were unable to control for confounding factors such as weight and obesity, which predispose individuals to lower vitamin D levels.^[7] The committee found no randomized controlled trials regarding vitamin D treatment and type 1 diabetes. Overall, the IOM report concluded that, “(e)vidence from RCTs on the effect of vitamin D supplements on incident diabetes or markers of glucose homeostasis is variable, and few RCTs showing significant results were identified.” The review committee concluded that there was insufficient evidence to support a role for vitamin D in the production of insulin and as a modulator of pancreatic endocrine function.

The WA TEC report concluded that evidence considered from three RCTs found no evidence to suggest that vitamin D treatment had a positive effect on the incidence of diabetes or diabetes markers in adults.^[9]

In 2015, Haroon published results of a meta-analysis of seventeen RCTs and seven nonrandomized trials assessing the effect of vitamin D supplementation upon glycemic control in patients type 2 diabetes.^[40] Authors concluded the current evidence did not demonstrate any long-term symptom improvement upon hyperglycemia with vitamin D supplementation.

In 2012, George conducted a systematic review and meta-analysis which evaluated the effect of vitamin D supplementation on fasting glucose, glycemic control, insulin resistance, insulin/C-peptide levels, micro- and macrovascular outcomes and progression from non-diabetes to diabetes.^[41] Data was pooled from 15 RCTs and authors reported no significant difference in fasting glucose, HbA1C or insulin resistance in the treatment group compared to the placebo group. There was insufficient data to draw conclusions regarding micro- and macrovascular events. Authors concluded that there is, “currently insufficient evidence of beneficial effect to recommend vitamin D supplementation as a means of improving glycaemia or insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance.”

Additional reviews of published studies regarding vitamin D supplementation to prevent or treat type 2 diabetes have been published;^[42-48] however, these reviews are based upon non-randomized prospective studies and are therefore not considered reliable for establishing the clinical utility of vitamin D testing or treatment in these patients.

RANDOMIZED CONTROLLED TRIALS

Several RCTs, which primarily focused on type 2 diabetes patients, were identified since the publication of the IOM summary and are reviewed below. A single RCT was identified regarding vitamin D treatment in patients with type-1 diabetes.

Bizzarri evaluated whether calcitriol, the active form of vitamin D, supplementation had any effect on beta-cell function and glycemic control in recently diagnosed type 1 diabetes patients.^[49] A total of 34 patients were randomized to receive 0.25 microg/daily calcitriol or placebo for 24 months. No significant differences were observed in A1C or c-peptide levels between groups. Although the study follow-up period was sufficient, the number of subjects recruited was small which may limit any conclusions reached in this study. Ultimately, authors concluded that the doses of calcitriol used were ineffective in effecting glycemic control or beta-cell function.

de Zeeuw conducted the VITAL study, a multi-national study regarding the effect of paricalcitol supplement (the active form of vitamin D) on albuminuria in type 2 diabetic patients with nephropathy.^[50] A total of 281 patients were randomized into one of three groups: 1 ug/daily paricalcitol, 2 ug/daily paricalcitol or placebo for 24 weeks. Authors reported that patients on 2 ug paricalcitol showed a nearly sustained reduction in urinary albumin-to-creatinine ratio (UACR), ranging from -18% to -28% ($p=0.014$ vs placebo). However, UACR reduction levels did not reach a significant change from baseline ($p=0.053$) and the 2 ug group had a significantly higher drop-out rate compared to the 1 ug and placebo groups. Ultimately, authors did not demonstrate that these effects prevented progression of renal failure in this patient population, and several additional authors recommended longer follow-up and evaluation of additional study end-points.^[51-54]

Yiu studied the effect of vitamin D supplementation on endothelial dysfunction and cardiovascular disease in 100 type 2 diabetes patients^[55] for 12 weeks. Although significant increases in serum 25-D levels were observed in the treatment group, no difference was observed in vascular function or inflammation between groups.

Harris examined the effects of vitamin D treatment on insulin sensitivity and glycemia in 89 overweight African Americans for 12 weeks.^[56] Again, a significant increase in 25-D levels was observed; however, this change did not impact post-load glucose or other measures of glycemia compared to the placebo group.

Shab-Bidar evaluated the effects of a vitamin D-fortified yoghurt drink (doogh) on systematic inflammation biomarkers in 100 patients with type 2 diabetes^[57] for 12 weeks. Significant improvements in inflammatory biomarkers were observed in the treatment group compared to those receiving the placebo; however, authors did not demonstrate how these changes translated into an improvement in symptoms or resolution of diabetes.

Mitri examined the effects of vitamin D supplementation on glucose homeostasis in 92 adults at high risk for diabetes.^[58] Patients randomized to the treatment group received 2000 IU/ of vitamin D daily for 16 weeks. A significant improvement in pancreatic β cell function was observed in the treatment group compared to the placebo group; however, there was no significant improvement in HbA1C levels between groups.

Additional studies were identified which indicated some improvement in various serum levels associated with type 2 diabetes;^[59-67] however, similar to the previously reviewed RCTs, these studies were limited by small sample size ($n < 100$), short-term follow-up and/or potential confounding factors which could have influenced outcomes. In addition, the doses of vitamin D administered to the treatment groups varied among studies, calling into question the optimal level of supplementation required for this population. Additional studies which found no improvement in diabetes symptoms with vitamin D supplementation were also identified.^[68-70]

FATIGUE AND PAIN

The principal outcomes associated with treatment of fatigue or pain due to any cause may include: relief of fatigue or pain, improved functional level, and return to work. Relief of these indications is a subjective outcome that is typically associated with a placebo effect. Therefore, data from adequately powered, blinded, RCTs are required to control for the placebo effect, determine its magnitude, and determine whether any treatment effect from vitamin D supplementation provides a significant advantage over the placebo.

SYSTEMATIC REVIEWS

No evidence-based systematic review or meta-analysis of randomized controlled trials regarding vitamin D supplementation for either generalized pain, myofascial pain, bone pain, chronic pain or fatigue were identified.

RANDOMIZED CONTROLLED TRIALS

Schreuder evaluated vitamin D supplementation on non-specific musculoskeletal complaints in 84 vitamin D-deficient (defined as a 25-hydroxyvitamin D level of less than 50 nmol/L) non-Western immigrants in a semi-crossover randomized trial.^[71] Patients randomized to the treatment group received 150,000 IU vitamin D at baseline; at six weeks participants in this group were then randomized again to receive a second dose or placebo. Patients in the

placebo group all received vitamin D treatment at six weeks. Pain was assessed using a visual analogue scale (VAS) and by marking pain sites on a mannequin. Pain medication and physical therapy were reported to be similar between groups. At six weeks, a significant difference in pain reduction was reported in patients receiving vitamin D treatment (34.9% vs. 19.5%, $P = .04$). In order to assess the durability of any treatment effects, larger, long-term studies are needed that control for the sample heterogeneity, continued use of pain medication and physical therapy. In addition, this study is limited by a relatively small sample size given the prevalence and causes of non-specific musculoskeletal pain.

Björkman conducted a RCT of 216 elderly, long-term care patients to evaluate the treatment of vitamin D on reported symptoms of pain.^[72] Patients were randomized to receive 0, 400, or 1200 IU cholecalciferol/day for six months. Pain was measured by the Resident Assessment Instrument (RAI), Discomfort, Behavior Scale, and Pain Assessment in Advanced Dementia Scale. Although a marked increase in 25-OHD levels was observed in the treatment groups, no significant difference were reported in pain levels compared to the placebo group. Authors concluded that, “vitamin D deficiency was not associated with pain or pain behavior.”

Additional studies reported on the use of vitamin D supplementation as a treatment for pain or fatigue in patients with a variety of conditions such as: nonspecific low back pain, cancer, multiple sclerosis, menopause and fibromyalgia. In many of these studies, no significant difference between groups was observed.^[73-80] In addition, these and other studies suffered from methodological limitation such as: small sample size^[73,75,81-84] ($n < 100$), short-term follow-up (< 1 year)^[75,81-84], or inclusion of participants who did not have vitamin D deficiency at the start of the study.^[74,75,82,84,85] It is also worth noting that dose levels and frequency of dosing varied drastically across all studies, calling into question any conclusions regarding optimal dosing strategies in patients with pain or fatigue.

FIBROMYALGIA

SYSTEMATIC REVIEWS

In a review by Daniel, evidence regarding and association between vitamin D deficiency and fibromyalgia was assessed to determine whether vitamin D testing and subsequent treatment is warranted.^[81] Ultimately authors concluded that evidence establishing an association between vitamin D deficiency and fibromyalgia is inconclusive. The identified RCTs demonstrated no association between vitamin D and relief of pain associated with fibromyalgia; nonrandomized trials were inconclusive regarding an association. The single adequately powered RCT identified, suggested supplementation did not improve pain related to fibromyalgia.

RANDOMIZED CONTROLLED TRIALS

Other than the randomized controlled trial noted in the systematic review by Daniel above, no other RCTs regarding vitamin D treatment and fibromyalgia were identified.

HYPERLIPIDEMIA

SYSTEMATIC REVIEWS

In 2012, conducted a meta-analysis of RCTs evaluating the effects of vitamin D treatment on blood lipids.^[86] A total of 12 RCTs were identified and data from 1346 participants were pooled.

The primary outcome measures were changes in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) from baseline. No significant differences were observed in any of the study measurements. The authors of this study called for additional, large-scale trials with adequate doses and appropriate population selection to help determine the efficacy of vitamin D treatment on lipid profiles.

Elamin conducted a systematic review and meta-analysis of the effect of vitamin D supplementation on the following cardiovascular outcomes: hypertension, coronary artery disease and heart disease.^[87] Authors identified 51 RCTs which were rated moderate in quality. Baseline vitamin D deficiency was determined using a variety of methods; such as, 25-hydroxyvitamin D level <20ng/ml, age of study population, winter months, obesity, etc. In a pooled analysis of over 1000 patients, no significant differences were observed between treatment and control groups for cholesterol, triglycerides, LDL, and HDL levels.

RANDOMIZED CONTROLLED TRIALS

Ponda examined whether oral vitamin D supplementation improved the lipid profile of 150 vitamin D deficient (defined as 25-hydroxyvitamin D <20 ng/mL) adults with cardiovascular disease.^[88] Patients were randomized into either the treatment group which received 50,000 IU of vitamin D3 weekly for 8 weeks or placebo. No changes to the lipid profile were observed in the treatment group compared to the placebo group. Authors concluded that short-term correction of a 25-hydroxyvitmain D deficiency did not improve lipid profiles.

Wood evaluated vitamin D treatment on conventional cardiovascular disease (CVD) markers in 305 healthy post-menopausal women.^[89] Patients were randomized to receive 400 or 1000 IU vitamin D3 daily or placebo for one year. Primary outcomes were serum lipid profile [total, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides; and apolipoproteins A-1 and B100], insulin resistance (homeostatic model assessment), inflammatory biomarkers (high-sensitivity C-reactive protein, IL-6, soluble intracellular adhesion molecule-1), and blood pressure. A total of 265 (87%) of patients completed the study and no difference in any lipid marker in the treatment group compared to the placebo group was observed. Authors concluded that improvements in vitamin D status were unlikely to reduce markers related to CVD.

Muldowney examined the effects of cholecalciferol on a variety of biomarkers for cardiovascular disease, including: serum 25-hydroxyvitamin D [s25(OH)D], intact parathyroid hormone, systolic and diastolic blood pressure, fasting lipids, glucose and insulin, HOMA-IR, high-sensitivity CRP, matrix metalloproteinase-9, and its inhibitor (tissue inhibitor metalloproteinase-1).^[90] Patients from two studies; one with patients aged 20-40 y. (n=202) and the other with patients ≥64 y (n = 192) were randomized to receive 0 (P), 5 (D3-5), 10 (D3-10), or 15 (D3-15) µg/d (0-600 IU) doses of cholecalciferol during wintertime. Measurements were taken at baseline and then again at 22 weeks. There were no reported differences in either age group between the treatment and control group.

Heikkinen evaluated the effects of vitamin D supplementation and hormone replacement therapy on serum lipids in 464 postmenopausal women.^[91] Subjects were randomized into one of four groups: HRT (sequential combination of 2 mg estradiol valerate and 1 mg cyproterone acetate), Vit D3 (vitamin D3 300 IU/day), HRT+Vit D3 (both as above), or placebo (calcium lactate 500 mg/day) for 3 years. Concentrations of serum cholesterol, LDL, HDL and TG were measured at baseline, 12, 24 and 36 months. Over the course of the study 76 (16.4%) women

dropped out; with 57 of them dropping out of the HRT and HRT+Vit D3 groups. Data from the 320 women who completed the study indicated that serum concentrations of low density lipoprotein (LDL) cholesterol decreased in the HRT group (10.1%, $P<0.001$) and the HRT+Vit D3 group (5.9%, $P=0.005$), increased in the Vit D3 group (4.1%, $P=0.035$) but remained unchanged in the placebo group. Total cholesterol decreased slightly in both the HRT and HRT+Vit D3 groups, but not in the other two groups. The HDL:LDL ratio decreased in the vitamin D3 group (10.5%, $P<0.001$) and triglycerides increased slightly in all groups. These results suggest that pure vitamin D3 treatment may have a negative effect on lipids in postmenopausal women taking HRT; however, the loss-to-follow-up rate was high, limiting conclusions reached in this study.

Major conducted a 15-week placebo controlled trial to evaluate the effects of vitamin D and calcium supplementation on blood pressure, plasma lipids and lipoprotein concentrations of 63 overweight women participating in weight-loss intervention program.^[92] Treatment groups were given 600 mg elemental calcium and 200 IU vitamin D daily and all patients participated in a weight-loss program. Authors reported a significant reduction of total LDL, HDL ($P<0.01$) and LDL cholesterol ($P<0.05$) in the treatment group compared to the placebo group. However, not all of these changes were reported to be independent of weight loss or waist circumference and the effects of calcium supplementation on these findings is unclear. Overall, the study sample size and follow-up period were limited precluding conclusions from this study.

Additional, short-term randomized trials which include varying dose levels of administered vitamin D were identified which showed no difference between treatment and placebo groups for multiple cardiovascular disease risk markers.^[93-104]

HYPERTENSION

SYSTEMATIC REVIEWS

The WA TEC report concluded that evidence from a single meta-analysis of seven small RCTs may suggest some small clinically meaningful reduction in systolic blood pressure with vitamin D treatment and an uncertain effect on diastolic blood pressure.^[9]

Wu conducted a meta-analysis to evaluate the use of vitamin D supplements on blood pressure reviewing only double-blind randomized controlled trials of oral vitamin D in normotensive or hypertensive patients.^[105] Of the 244 studies reviewed, only four met inclusion criteria. Data from 429 patients were pooled. A statistically significant reduction in systolic blood pressure (SBP) was observed in patients treated with vitamin D compared to placebo 2.44 mm Hg (weighted mean difference [WMD]: -2.44, 95% confidence interval [CI]: -4.86, -0.02). No reduction was observed in diastolic blood pressure compared to placebo. Study authors note the need for additional RCTs in order to determine the effects of vitamin D supplementation on patients with hypertension.

Witham conducted a systematic review and meta-analysis to determine the effects of vitamin D supplementation on blood pressure in patients with hypertension.^[106] A total of 11 small RCTs with variable methodological quality were included in the review. A meta-analysis was performed on eight studies where patient baseline blood pressure was more than 140/90 mmHg. From that meta-analysis a small statistically significant reduction in diastolic blood pressure of -3.1 mmHg was reported in the treatment group. No other significant differences were observed between groups.

In the previously mentioned Elamin review of vitamin D treatment on cardiovascular outcomes, pooled analysis of RCTs included data on systolic or diastolic blood pressure from 767 patients.^[87] No significant difference between treatment and control groups was reported.

Kunutsor evaluated the effects of vitamin D supplementation on SBP and diastolic blood pressure (DBP).^[107] Sixteen randomized trials were included in the analysis which showed no significant reduction in SBP (-0.94, 95% CI -2.98, 1.10 mmHg) and DBP (-0.52, 95% CI -1.18, 0.14 mmHg). In addition, authors noted there was significant heterogeneity and publication bias among SBP trials.

Additional reviews of published studies regarding vitamin D supplementation to prevent or treat hypertension have been published;^[108-113] however, these reviews either showed no benefit with supplementation^[114] or were based upon non-randomized prospective studies and are therefore not considered reliable for establishing the clinical utility of testing and treatment in patients with hypertension.

RANDOMIZED CONTROLLED TRIALS

Larsen evaluated the effects of vitamin D treatment on ambulatory blood pressure (BP) and arterial stiffness in 112 hypertensive patients between the months of October and March.^[115] Patients were randomized to receive 75 ug cholecalciferol daily or placebo for 20 weeks. Although vitamin D levels were increased in the treatment group, no reduction in 24-h BP or arterial stiffness was observed compared to the placebo group. In a secondary subgroup analysis of 92 subjects deemed to be vitamin D deficient (defined as 25D levels < 32 ng/ml) at the start of the study, a significant decrease in 24-h blood pressure was observed in the treatment group compared with placebo.

In the previously mentioned Women's Health Initiative (WHI) Calcium and Vitamin D (CaD) trial, data were analyzed to determine the effect of vitamin D treatment on blood pressure and the incidence of hypertension in postmenopausal women.^[116] Over 17,122 hypertensive women were randomized and to either vitamin D treatment or placebo and followed for seven years. Data from this study found no reduction in either blood pressure or the risk of developing hypertension in patients taking vitamin D compared to those taking placebo.

In a follow-up analysis from the previously mentioned study by Jorde, data were evaluated to determine the effect of vitamin D supplementation on cardiovascular risk markers in 330 overweight and obese patients.^[97] A slight increase in systolic blood pressure was observed in the treatment group receiving 20,000 IU per week of vitamin D compared to placebo. Otherwise, no significant differences were observed in blood pressure measures between the treatment and placebo groups.

Additional trials were identified which showed no difference between treatment and placebo groups for vascular health disease risk markers.^[101,104,117-120]

HYPOTHYROIDISM

There were no systematic reviews, RCTs, or clinical practice guidelines identified which evaluated vitamin D treatment in patients with hypothyroidism.

MORTALITY

SYSTEMATIC REVIEWS

Avenell published a 2016 update of a 2010 Cochrane Systematic Review regarding nutritional supplementation for hip fracture aftercare in older people.^[121] Reviewing 41 trials through November 2015 (including 3,881 participants, total), the authors pooled outcome data when possible. Interventions included multinutrient supplements (providing non-protein energy, protein, vitamins and minerals) given orally, enterally or intravenously, compared with supplements containing less or none of these components, or no treatment. Placebo controlled trials, and trials comparing various doses, or comparison to no treatment were included. Only one study of vitamin D was included, though not part of the primary outcome analysis. The study compared use of D3 (1000 IU/d) and calcium carbonate (600 mg/d) to vitamin D2 (1000 IU/d) and an equivalent dose of calcium carbonate over three months; however, incomplete outcome data were available. The authors found low-quality evidence that oral multinutrient supplements (all supplements) started before or soon after surgery may prevent complications within the first 12 months after hip fracture, but that they have no clear effect on mortality.

In 2015, Zheng published a meta-analysis assessing high-dose intermittent vitamin D supplementation on falls, fractures and mortality among older adults.^[122] Nine randomized trials were included in the analysis. Intermittent, high-dose vitamin D supplementation did not reduce all-cause mortality or prevent falls or fractures.

In 2014, Schottker assessed the association of serum 25-hydroxyvitamin D concentrations (25(OH)D) in all-cause, cardiovascular and cancer related mortality.^[123] Large consortium cohort studies were utilized and 26,018 patients, ages 50-79, were included. Serum concentrations from the highest quintile were compared to the lowest quintile. Low serum concentrations were associated with increased risk for all-cause mortality (risk ratio, 1.57) and for cardiovascular mortality in patients with (risk ratio, 1.70) and without a history of cardiovascular disease (risk ratio, 1.41). In addition, low serum levels were associated with an increased risk for cancer-related mortality in patients who had previously had cancer (risk ratio 1.70).

In a similar study, Chowdhury evaluated the association of vitamin D and all-cause, cardiovascular and cancer related mortality.^[124] Authors included data from 73 nonrandomized (849,412 participants) and 22 randomized controlled trials (vitamin D given alone versus placebo or no treatment; 30,716 participants). Baseline bottom versus top third vitamin D levels were compared and lower third vitamin D levels were associated with cardiovascular mortality (relative risk [RR] 1.35), cancer mortality (RR 1.14) and all-cause mortality (RR 1.35) when compared to the top third. However this study did not evaluate whether vitamin D supplementation had any impact upon mortality risks in patients with low serum levels.

Additional reviews were identified which demonstrated an association between vitamin D levels and mortality risk;^[125-128] however, the analysis included nonrandomized studies and included studies which were heterogenous in nature, contained significant outcome reporting bias and did not evaluate the impact of supplementation upon improved health outcomes.

RANDOMIZED CONTROLLED TRIALS

There were no RCTs identified which evaluated vitamin D impacts on mortality.

MULTIPLE SCLEROSIS

SYSTEMATIC REVIEWS

At least four systematic reviews have examined the effect of vitamin D supplementation in patients with multiple sclerosis (MS).^[129-132] Authors described six RCTs, all of which were small (n<100). Patient follow-up ranged from 6 months to 2 years, and dosing and administration of vitamin D varied. None of the trials reported improvement in MS relapse rates; most trials showed no effect of vitamin D on any of the surrogate or clinical outcomes. Only one trial reported improvement in magnetic resonance imaging of lesions in the vitamin D supplementation group.

The 2007 Agency for Healthcare Research and Quality (AHRQ) report, evaluated the evidence related to multiple sclerosis (MS) and vitamin D and found only case-controlled, non-randomized trials.^[6] In many of these studies an association was found between MS and lower levels of vitamin D; however, no study was identified which demonstrated the effect of vitamin D treatment on symptoms of MS or overall improvement of the condition.

The IOM report found only observational non-randomized studies with conflicting conclusions regarding an association between vitamin D deficiency and MS. The IOM report concluded that, “The lack of causal evidence further diminishes the likelihood for a relationship between vitamin D and MS.”^[7]

The WTA TEC report reviewed evidence from three RCTs and concluded, “There was insufficient evidence regarding a link with the risk of obesity, gestational diabetes, multiple sclerosis (MS), or depression and mood disorders; for these outcomes, there was no evidence from longitudinal studies or very sparse evidence.”^[9]

RANDOMIZED CONTROLLED TRIALS

Other than the randomized controlled trials reviewed in the systematic reviews above, no additional RCTs regarding vitamin D treatment and multiple sclerosis were identified.

PREGNANCY

SYSTEMATIC REVIEWS

Roth (2017) reported results from a systematic review of randomized controlled trials implementing prenatal vitamin D (vitamin D2 or D3, any dose) administration.^[133] Trials used placebo, no vitamin D, or vitamin D ≤ 600 IU/day. Using transparent study inclusion and evaluation criteria, 43 trials from 77 publications (totalling 8406 enrolled women) were included for meta-analysis, and were graded for risk of bias according to the Cochrane Collaboration tool. Pooled risk ratios (dichotomous outcomes) and weighted mean differences (continuous outcomes) were calculated with 95% confidence intervals; missingness was appropriately accounted for, and sensitivity analyses were conducted. Both maternal, and infant/childhood outcomes were analyzed. Vitamin D increased maternal/cord serum concentration of 25-hydroxyvitamin D, but the dose-response effect was weak; maternal clinical outcomes were rarely ascertained or reported, and the available data did not provide evidence of benefit. Authors found strong evidence that prenatal vitamin D reduced the risk of offspring wheeze by age 3 years (0.81, 95% confidence interval 0.67 to 0.98; two comparisons). Additionally, vitamin D supplementation contributed to increased mean birth weight 58.33 g (95% confidence interval, 18.88 g to 97.78 g; 37 comparisons), reduced risk of small for gestational age risk ratio 0.60, 95% confidence interval 0.40 to 0.90; seven comparisons, and increased infant length at one year (weighted mean difference 1.30, 95% confidence interval 0.54 to 2.06). These outcomes were not robust in sensitivity and subgroup analysis. Only 8 of 43 trials

were found to have low risk of bias; overall the studies were small and of low quality. The authors concluded that additional trials are needed to inform clinical or policy recommendations, particularly with well-designed endpoint data collection.

RANDOMIZED CONTROLLED TRIALS

Other than the randomized controlled trials reviewed in the systematic review above, and the RCT of prenatal supplementation in 881 pregnant women at high risk of having children with asthma (2016) summarized in the Asthma and Wheezing section above^[20], no additional RCTs regarding vitamin D treatment and pregnancy were identified.

PSORIASIS

The majority of published evidence regarding vitamin D treatment for skin diseases is focused on first-line topical treatment options for psoriasis.^[134-138] There is a vast body of both randomized controlled trials and systematic reviews evaluating vitamin D analogue therapy for psoriasis. In addition, the American Academy of Dermatology lists vitamin D analogues as a topical treatment option for patients with psoriasis.^[139] However, recent meta-analyses do not demonstrate that vitamin D analogue therapy is superior to topical corticosteroid treatment. Many of the randomized studies combine the two therapies, which limit conclusions regarding the effect of vitamin D-based topical treatment. Despite this evidence, vitamin D analogue therapy has become an established treatment for psoriasis; however, it is not established that vitamin D testing is required or routinely performed when choosing this therapy. No published, peer-reviewed evidence was identified which evaluated vitamin D analogue therapy in patients with vitamin D deficiency. In addition, no studies were identified which included vitamin D testing as part of the study design, suggesting an evaluation of vitamin D levels is not an essential component of treatment decision-making or treatment success in patients with psoriasis.

STEROID USE

The use of systemic steroids have been associated with long-term side effects and include compromise of the immune system causing a number of health conditions, including but not limited to infections, osteoporosis, peptic ulcers, hypertension, myopathy, ocular effects, impaired healing and avascular necrosis. Vitamin D deficiency has been associated with long-term steroid use,^[140] however evidence is limited regarding the benefit of vitamin D supplementation in patients with extended steroid use.

SYSTEMATIC REVIEWS

Davidson conducted a review of the relationship between glucocorticosteroid (GCS) use and serum 25-hydroxyvitamin D 25-OHD.^[141] A literature search was conducted between 1970-2011 and studies were excluded if patients were consuming vitamin D at baseline, GCS treatment was less than two weeks, if GCS was received for renal or hepatic disease or after transplant, or if patients had Cushing's syndrome. Data was pooled and vitamin D status in patients treated with GCS was compared to steroid-naïve controls and in patients before and after receiving GCS. Authors reported that serum 25-OHD was significantly lower in GCS users than in healthy controls ($p=0.03$); however, there was no observed difference between GCS users and disease controls. Although an association between diminished vitamin D serum levels and GCS use was noted, this study did not demonstrate how supplementation based on screening could lead to improved overall health outcomes or prevention of

osteoporosis. In addition, it is unclear how many of the studies included in this review were RCTs which directly compared vitamin D levels in patients receiving GCS versus GCS-naïve patients. Randomized trials are needed to exclude confounding factors and assess the impact of long-term GCS use on vitamin D levels and related health outcomes.

In a review by Sandhu, the role of vitamin D on asthma pathogenesis and steroid resistance was evaluated.^[142] An association between vitamin D deficiency and increased airway hyperresponsiveness, lower pulmonary functions, worse asthma control, and possibly steroid resistance was noted, however the effects of vitamin D supplementation upon steroid effectiveness and health outcomes, was not evaluated.

RANDOMIZED CONTROLLED TRIALS

Majak evaluated the effectiveness of oral steroids in 54 children with or without vitamin D(3) or placebo for a specific immunotherapy (SIT).^[143] At one-year follow-up, the clinical or immunological effects of the SIT were not affected by the steroid plus vitamin D group.

Bak assessed the effects of vitamin D plus calcium on bone and mineral metabolism in 40 children receiving prednisone treatment.^[144] All patients received four weeks of prednisolone treatment followed by alternating days of treatment for another four weeks. In addition, patients were randomized to receive 400IU of vitamin D and 1g of calcium or placebo. After two months, bone mineral density was found to be significantly decreased in the treatment group compared to the non-treatment group ($p < 0.001$). In this study, vitamin D supplementation did not appear to directly improve bone mineral density or prevent bone loss in children with nephrotic syndrome taking steroids.

In a small trial by Worth, 14 asthmatics were assigned to vitamin D treatment (1,000 IU/d), calcium (1 g/d), and ethane-1-hydroxy-1,1-diphosphonate (EHDP; 7.5 mg/kg body weight) and compared to an untreated control group of 19 asthmatics.^[145] All patients were undergoing long-term treatment with systemically applied corticosteroids. Primary outcomes of the study were vertebral bone mass measured by dual-photon absorptiometry before and after the trial at six months. The treatment group experienced a 5% increase in bone density compared to a 4.3% decrease in the control group ($p < 0.01$). No radiologically visible fractures were observed in the treatment group, while four were reported in the control group. Although the results of this study are suggestive of a possible treatment benefit, it is limited by a very small sample size and, in addition, it is unclear which of the three treatments may be responsible for the positive findings.

VITAMIN D SCREENING IN HEALTHY POPULATIONS

Vitamin D screening is often performed in healthy patients as a preventive measure, usually as part of a routine wellness exam.

SYSTEMATIC REVIEWS

Evidence which focused on the effects of vitamin D supplementation in relation to general risks for deficiency, such as age or geographic location, was identified; however, there were numerous gaps in the data concerning the impact of routine screening in these populations. The current gaps are discussed in several major evidence reports:

It is not clear how vitamin D test results guide treatment decisions differently compared to decisions that would be made in the absence of test results.

The IOM report concluded that the benefits of vitamin D for conditions not related to bone health, conditions which were often spotlighted in the media,^[146] “...were from studies that provided often mixed and inconclusive results and could not be considered reliable.”^[7] However, the IOM and other evidence reports highlighted the importance of maintaining an average range requirement of vitamin D and calcium across the general population, as a means of avoiding deficiency and ensuring optimal bone health. Given the conclusions reported in the WTA TEC assessment, that a substantial proportion of patients across all populations were vitamin D deficient, routine supplementation without screening was suggested for certain populations.^[9] In recognition that all people require a sufficient level of vitamin D, the IOM committee issued age-based dietary reference intakes (DRI) that included, “Estimated Average Range Requirements (EAR)s and the Recommended Dietary Allowances (RDA), that are intended to serve as a guide for good nutrition and to provide the basis for the development of nutrient guidelines in both the United States and Canada.”^[7] The IOM recommendations are intended to suit the needs of nearly all people and are proposed as a guide for daily supplementation. For the purposes of daily vitamin D maintenance in the general population, testing is not required, as patients may choose to follow the general IOM vitamin D intake guidelines based on age and/or condition. In addition, serum measurements are often rendered uninformative due to invalidated cut-off points and unreliable test results, leaving providers and patients to choose whether or not to follow recommended supplementation guidelines.

A 2014 update of the previously published AHRQ report included 154 newly identified primary studies and two systematic reviews which included an additional 93 primary studies.^[22] The group concluded that the, “majority of the findings concerning vitamin D, alone or in combination with calcium, on the health outcomes of interest were inconsistent. Associations observed in prospective cohort and nested case-control studies were inconsistent, or when consistent, were rarely supported by the results of randomized controlled trials.” No RCTs were identified which assessed how vitamin D screening and testing improved health outcomes in the general population.^[9] New studies indicate that despite the increase in vitamin D testing, improvements in vitamin D deficiency have not been observed.^[7,8,147-149]

The IOM report indicated that the current evidence regarding vitamin D intake has not translated into improved patient well-being for conditions not related to bone health.^[7] In addition, the IOM committee concluded that, “higher levels have not been shown to confer greater benefits, and in fact, they have been linked to other health problems, challenging the concept that ‘more is better.’”^[7]

The WTA TEC evidence report was specifically commissioned to evaluate the evidence related to the impact of vitamin D testing and screening on health outcomes.^[9] Overall, the report determined, “No definitive conclusions can be drawn about the effectiveness of vitamin D screening or testing since no trials have been conducted to directly assess the impact of screening or testing on health outcomes, patient behavior, or clinical decision making.” With the exclusion of populations with known or highly suspected osteoporosis, the WTA report concluded, “...the available evidence suggested no benefit from vitamin D screening (low quality evidence) or was insufficient to permit conclusions.”^[9]

In addition, the WTA TEC report indicated a lack of evidence demonstrating the effectiveness of supplementation in younger populations, pregnant or lactating women, and subgroups defined by ethnicity and race.^[9,148,150]

Lack of evidence demonstrating the effectiveness of supplementation according to baseline serum 25-OHD levels.^[9,10]

The AHRQ report indicated that there is uncertainty regarding how much vitamin D is needed to maintain bone health and normal calcium metabolism in healthy people. The report notes that the optimal level of circulating 25(OH)D required for bone health may also vary depending on the functional outcome.^[6] The AHRQ report identified the need for further research to better understand these modifiers of vitamin D effect.

The IOM report does not specify any conditions, including in healthy populations, for which testing of 25(OH)D serum levels may be indicated.

The reviewed studies of these conditions provided mixed and inconclusive results. Consequently, it cannot be reliably determined whether or how vitamin D affects the risks associated with these conditions, or whether changing the exposure to vitamin D provides a protective effect.

In addition, a 2013 systematic review and meta-analysis by Reid investigated whether vitamin D supplementation affects bone mineral density in the general population.^[151] Authors were specifically interested in assessing whether wide-spread vitamin D supplementation is justified in light of recent meta-analyses which have not shown fracture prevention. A literature review was conducted from database inception to July, 2012 and included only RCTs of adults without other metabolic bone disease. A total of 23 studies met inclusion criteria with a mean duration of 23.5 months, comprised 4082 patients, of which 92% were women. The primary outcome of the study was bone mineral density change from baseline. Only eight studies had a mean baseline serum 25-OHD of less than 50 nmol/L (n=1791). Authors also noted that 10 studies administered less than 800 IU of vitamin D per day (n=2294). Bone mineral density was measured in at least one of the following sites: lumbar spine, femoral neck, total hip, trochanter, total body, or forearm. A small benefit at the femoral neck (0.8%) was reported; however, a bias toward positive results was also noted at the femoral neck and total hip. No beneficial effect of vitamin D supplementation was noted at any other site. Authors concluded, “Continuing widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seems to be inappropriate.”

RANDOMIZED CONTROLLED TRIALS

There were no RCTs identified which evaluated vitamin D impacts on mortality.

PRACTICE GUIDELINE SUMMARY

ENDOCRINE SOCIETY

The 2011 Endocrine Society Clinical Practice Guideline for evaluation, treatment, and prevention of vitamin D deficiency published the following recommendations:^[152]

- 25(OH)D serum level testing is recommended to evaluate vitamin D status only in patients who are at risk of deficiency. The guideline does not recommend screening of individuals who are not at risk of vitamin D deficiency.
- 1,25(OH)₂D testing is not recommended to evaluate vitamin D status. However, the guideline does recommend monitoring calcitriol levels in certain conditions.
- In addition, the Task Force recommends supplementation of the general population, “at

suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances.”

The guideline is based on a mixed quality of evidence. Recommendations for testing for some indications were not specifically supported with scientific evidence.

U.S. PREVENTIVE SERVICE TASK FORCE

The United States (U.S.) Preventative Service Task Force (USPSTF) gave a B level recommendation for vitamin D supplementation (the median dose of vitamin D in available studies was 800 IU) to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls because of a history of recent falls or vitamin D deficiency.^[153] A B level recommendation indicates that, “there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.”

The USPSTF guidelines for preventive care are an authoritative standard and are recognized as such by the Affordable Care Act. The USPSTF guidelines do not recommend Vitamin D testing for screening purposes. In a 2015 update of their recommendations regarding screening for vitamin D deficiency in adults, the USPSTF concluded, “that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.”^[154]

AMERICAN ACADEMY OF FAMILY PHYSICIANS

The American Academy of Family Physicians (AAFP) Summary of Recommendations for Clinical Preventive Services (July 2017) include statements regarding vitamin D supplementation for numerous populations.^[155] Vitamin D screening is not addressed. The AAFP recommendations are based upon the USPSTF guidelines noted above.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2011 ACOG issued the following statement regarding vitamin D supplementation in pregnant women, which was reaffirmed in 2017:^[156]

“At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, maternal serum 25-OH-D levels can be considered and should be interpreted in the context of the individual clinical circumstance. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 international units per day of vitamin D is safe.”

SUMMARY

There is research showing that vitamin D plays an essential role in promoting bone growth and maintenance, however, there is considerable uncertainty with respect to the clinical utility of testing, both in healthy, asymptomatic populations and for conditions not directly associated with bone health or deficiencies in vitamin D metabolism. Several studies consistently report a lack of evidence demonstrating how vitamin D testing alters treatment decisions or improves health outcomes. In addition, these reports note a lack of information on the levels of vitamin D that define a deficiency. There are no evidence-based clinical practice guidelines that recommend routine vitamin D testing or screening. Additionally, the

United States Preventive Services Task Force guidelines, a nationally recognized standard, do not recommend routine screening as a preventive health measure. Therefore, vitamin D testing is considered not medically necessary in the absence of conditions specifically associated with underlying diseases or conditions associated with vitamin D deficiency, decreased bone density, or defects in vitamin D metabolism.

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CODES

Codes	Number	Description
CPT	0038U	Vitamin D, 25 hydroxy D2 and D3, by LCMS/MS, serum microsample, quantitative
	82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
	82652	Vitamin D; 1,25 dihydroxy, includes fraction(s), if performed
HCPCS	None	

Appendix I
Conditions Specifically Associated with Vitamin D Deficiency
Blind loop syndrome
Calculus of kidney
Calculus of ureter
Celiac disease
Chronic kidney disease
Chronic liver disease

Appendix I
Conditions Specifically Associated with Vitamin D Deficiency
Disorder of calcium metabolism
Disorders of phosphorus metabolism
End stage renal disease
Granulomatous disease
HIV/AIDS
Hypercalcemia
Hypercalciuria
Hypervitaminosis D
Hypocalcemia
Hypocalcemia and hypomagnesemia of newborn
Intestinal malabsorption
Obstructive jaundice
Osteomalacia
Osteogenesis imperfecta
Osteopenia (ICD-10 codes M85.831-M85.839, M85.851-M85.859, M85.80, M85.88, M85.89, M85.9, and M89.9 only)
Osteoporosis
Osteosclerosis/petrosis
Pancreatic Steatorrhea
Parathyroid disorders
Protein-calorie malnutrition
Rickets
Transplant
Vitamin D deficiency when on replacement therapy related to a condition listed above; to monitor the efficacy of treatment

Appendix II
Conditions that may be associated with defects in vitamin D metabolism
Calculus of kidney and ureter
Disorders of calcium metabolism
Familial hypophosphatemia
Fanconi syndrome
Hyperparathyroidism
Hypoparathyroidism
Neonatal hypocalcemia
Nephrolithiasis or hypercalciuria
Osteomalacia
Rickets
Sarcoidosis
Unexplained hypercalcemia (suspected granulomatous disease or lymphoma)
Unexplained hypercalciuria (suspected granulomatous disease or lymphoma)

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