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Medical Policy Manual

Topic: Vitamin D Testing

Date of Origin: February 2011

Section: Laboratory

Last Reviewed Date: December 2013

Policy No: 52

Effective Date: May 1, 2014

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.[1] 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$(OH)_2$D], calcitriol

  Although the most metabolically active form, circulating 1,25$(OH)_2$D 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).[2-5] For these conditions, *1,25(OH)$_2$D* 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.

MEDICAL POLICY CRITERIA

I. 25-hydroxyvitamin D [25(OH)D], calcidiol, serum testing

A. 25(OH)D 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.

B. 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.

II. 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] calcitriol, serum testing

A. 1,25(OH)$_2$D 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.

B. 1,25(OH)$_2$D 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.

SCIENTIFIC EVIDENCE

Background

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.[6] 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:

- *Technical feasibility*, including reproducibility and precision. For comparison among studies, a common standardized protocol for the new diagnostic technology is established.

- *Diagnostic performance* (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.[1,7,8] [9] The appropriate testing method[1,7] and cut-off values for optimal serum levels of vitamin D have not been defined.[1,9,10]

  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."[8] 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).[8]

- *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.

Literature Appraisal

Alzheimer's Disease

Systematic Reviews and Meta-Analyses

Several systematic reviews[11-14] 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;[15] however, these reviews are based upon non-randomized prospective studies, which are not considered reliable for establishing the clinical utility of testing.

Randomized Clinical Trials

Stein and colleagues evaluated vitamin D and nasal insulin treatment on memory and disability in 32 patients with mild-moderate Alzheimer's disease (AD).[16] 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).

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address Alzheimer's disease and vitamin D treatment.

Conclusions

There is a substantial lack of high quality evidence from randomized controlled trials regarding the effects of vitamin D supplementation in patients with Alzheimer's disease. Therefore, the efficacy of vitamin D testing and treatment in patients with Alzheimer's disease is uncertain and the clinical utility of the test has not been established.

Depression

Systematic Reviews and Meta-Analyses

- Authors of the IOM report conducted an extensive systematic review to clarify the benefits of vitamin D supplementation for a variety of indications.[8] For depression, five randomized controlled trials (RCTs) on general depression and seasonal affective disorder were identified. The shorter, smaller studies[17-19] reported some improvement in mood with increased vitamin D supplementation, while the longer, larger studies[20] 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."
- 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 reviews of published studies regarding vitamin D treatment to prevent or treat depression have been published;[21] however, these reviews are based upon non-randomized trials and are therefore are not considered reliable for establishing the clinical utility of vitamin D testing or treatment for depression.

Randomized Clinical Trials

- In 2012, Kjaergaard and colleagues assessed the effect of vitamin D treatment on depression scores in participants with both low and high 25-hydroxyvitamin D (25-D) levels.[22] 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.[23] 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 3 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 et al., 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.[24] 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 and colleagues evaluated the effects of vitamin D supplementation as a prevention of seasonal affective disorder (SAD), a sub-type of depression.[25] 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 6 month SF-12 questionnaires. At the 6 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, cross-sectional study by Jorde et al., the effect of vitamin D supplementation was evaluated on symptoms of depression in 441 overweight subjects.[26] 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 1 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.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address or recommend vitamin D treatment for depression or seasonal affective disorder (SAD).

Conclusion

Although some association between symptoms of depression and vitamin D deficiency may exist, causality has not been established. Evidence from large randomized trials has not demonstrated that vitamin D supplementation improves symptoms of depression. Further, studies which control for potential confounding factors in various study populations are needed before a conclusion can be reached regarding the efficacy of vitamin D supplementation in patients with or at-risk for depression.

Diabetes

Systematic Reviews And Meta-Analyses

- In the 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.[8] 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 2012, George and colleagues 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.[27] 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;[28-32] 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 Clinical 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 and colleagues 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.[33] 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 et al. 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.[34] 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 μg 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.[35-38]
- Yiu and colleagues studied the effect of vitamin D supplementation on endothelial dysfunction and cardiovascular disease in 100 type 2 diabetes patients[39] 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 et al. examined the effects of vitamin D treatment on insulin sensitivity and glycemia in 89 overweight African Americans for 12 weeks.[40] 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 and colleagues evaluated the effects of a vitamin D-fortified yoghurt drink (doogh) on systematic inflammation biomarkers in 100 patients with type 2 diabetes[41] 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 and colleagues examined the effects of vitamin D supplementation on glucose homeostasis in 92 adults at high risk for diabetes.[42] 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;[43-48] 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.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address or recommend vitamin D as a treatment of diabetes.

Conclusion

Current RCTs regarding type 1 diabetes are limited in number. Reviews and RCTs concerning vitamin

D supplementation in patients with type 2 diabetes reported no observable benefit with respect to the preventive or therapeutic nature of treatment. Large, long-term, well-designed randomized controlled trials, which also take into consideration the variety of confounding factors associated with the diabetic condition, are needed in order to establish whether vitamin D supplementation is valuable for patients with type 1 or 2 diabetes.

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 and Meta-Analyses

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

Randomized Clinical Trials

- Schreuder et al. 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.[49] Patients randomized to the treatment group received 150,000 IU vitamin D at baseline; at 6 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 6 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 6 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 and colleagues conducted a RCT of 216 elderly, long-term care patients to evaluate the treatment of vitamin D on reported symptoms of pain.[50] 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."
- Warner et al. conducted a comparison of vitamin D levels in patients with diffuse musculoskeletal pain and osteoarthritis with controls to evaluate the effects of vitamin D treatment on diffuse pain.[51] One-hundred eighty-four patients with vitamin D deficiency (vitamin D levels $\leq$ 20 ng/ml) were randomized to receive placebo or 50,000 IU of ergocalciferol once a week for 3 weeks. Primary outcomes were assessed with a visual analog scale (VAS) and functional pain score (FPS). Authors observed no differences in pain scores compared to baseline in either group. In addition, no between group differences were observed. Vitamin D

treatment was not shown to affect diffuse musculoskeletal pain levels in this study.

- McAlindon and colleagues evaluated the effects of vitamin D supplementation on knee pain and cartilage volume in 146 patients with symptomatic osteoarthritis.[52] Patients were randomized to receive placebo or oral cholecalciferol (2000 IU/daily) with dose escalation to achieve serum levels of at least 36 ng/mL, for two years. Pain was measured with the Western Ontario and McMaster University (WOMAC) pain scale. Cartilage volume loss was measured by magnetic resonance imaging. Loss-to-follow-up rates were high with only 85% of patients completing the study. Despite a significant increase in 25-OHD levels in the treatment group over the control group (16.1 ng/mL vs. 2.1 ng/mL), no significant differences in knee pain or cartilage volume were observed between groups.
- 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: cancer, multiple sclerosis, menopause and fibromyalgia. In many of these studies, no significant difference between groups was observed.[53-56] In addition, these and other studies suffered from methodological limitation such as: small sample size[53,55,57-60] (n<100), short-term follow-up (< 1 year)[55,57-60], or inclusion of participants who did not have vitamin D deficiency at the start of the study.[54,55,58,60] 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.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address the effect of vitamin D treatment in patients with non-specific pain or fatigue.

Conclusion

Current evidence regarding vitamin D treatment for relief of specific (e.g., knee pain and musculoskeletal pain) and non-specific pain is limited to several RCTs which demonstrated conflicting outcomes, highlighting the need for additional large, long-term RCTs evaluating pain across differing populations. No RCTs were identified which examined the effect of vitamin D on non-specific fatigue. Studies which evaluated pain or fatigue in relation to certain conditions either found no symptom improvement with treatment or were hindered by various study limitations. Current evidence does not permit conclusions regarding the efficacy of vitamin D supplementation as a treatment for pain or fatigue.

Fibromyalgia

Systematic Reviews and Meta-Analyses

In a review by Daniel and Pirotta, evidence regarding and association between vitamin D deficiency and fibromyalgia was assessed to determine whether vitamin D testing and subsequent treatment is warranted.[57] 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 Clinical Trials

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

Clinical Practice Guidelines

No evidence-based clinical practice guidelines, including guidelines from the American College of Rheumatology, were identified which specifically recommend vitamin D treatment in patients with fibromyalgia.

Conclusion

There is a substantial lack of high quality evidence regarding the effect of vitamin D supplementation in patients with fibromyalgia. Therefore, the causal relationship between vitamin D and relief of symptoms related to fibromyalgia is not established and as a result, the clinical utility of vitamin D testing and treatment cannot be determined.

Hyperlipidemia

Systematic Reviews and Meta-Analyses

- In 2012, Wang et al. conducted a meta-analysis of RCTs evaluating the effects of vitamin D treatment on blood lipids.[61] 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 and colleagues 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.[62] 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 Clinical Trials

- Ponda and colleagues 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.[63] 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 and colleagues evaluated vitamin D treatment on conventional cardiovascular disease (CVD) markers in 305 healthy post-menopausal women.[64] 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 et al. 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).[65] 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 and colleagues evaluated the effects of vitamin D supplementation and hormone replacement therapy on serum lipids in 464 postmenopausal women.[66] 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 et al. 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-loos intervention program.[67] 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 with varying dose levels of administered vitamin D were identified which showed no difference between treatment and placebo groups for multiple cardiovascular disease risk markers.[68-72]

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically addressed vitamin D treatment in patients with hyperlipidemia or high cholesterol.

Conclusion

Overall, the evidence suggests vitamin D treatment provides no improvement on high cholesterol and hyperlipidemia measurements across various study populations. Additional RCTs which control for elements of dosing, length of treatment, study homogeneity, other medications, vitamin D deficiency at baseline and other health conditions, are needed. Uniformity in study design is essential before conclusions regarding the utility and causal relationship of vitamin D supplementation and hyperlipidemia can be established.

Hypertension

Systematic Reviews and Meta-Analyses

- The WA TEC report concluded that evidence from a single meta-analysis of 7 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 and colleagues 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.[73] Of the 244 studies reviewed, only 4 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 et al. conducted a systematic review and meta-analysis to determine the effects of vitamin D supplementation on blood pressure in patients with hypertension.[74] A total of 11 small RCTs with variable methodological quality were included in the review. A meta-analysis was performed on 8 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 from767 patients.[62] No significant difference between treatment and control groups was reported.

Additional reviews of published studies regarding vitamin D supplementation to prevent or treat hypertension have been published;[75-79] however, these reviews are 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 Clinical Trials

- Larsen and colleagues 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.[80] 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.[81] Over 17,122 hypertensive women were randomized and to either vitamin D treatment or placebo and followed for 7 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 et al., data were evaluated to determine the effect of vitamin D supplementation on cardiovascular risk markers in 330 overweight and obese patients.[72] 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.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically addressed vitamin D supplementation in patients with hypertension.

Conclusion

The accumulated body of evidence is conflicting regarding the effect of vitamin D supplementation on symptoms or measures of hypertension. Additional, long-term RCTs with similar vitamin D dosing, baseline measures of hypertension and vitamin D deficiency are needed in order to determine the efficacy or clinical utility of supplementation in patients with high blood pressure or hypertension.

Hypothyroidism

There were no systematic reviews, meta-analysis or RCTs identified which evaluated vitamin D treatment in patients with hypothyroidism.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address hypothyroidism and vitamin D treatment.

Conclusion

There is a substantial lack of high quality evidence regarding the effect of vitamin D supplementation in patients with hypothyroidism. Therefore, the causal relationship between vitamin D and relief of symptoms related to hypothyroidism is uncertain and as a result, the clinical utility of vitamin D testing and treatment has not been established.

Multiple Sclerosis (MS)

Systematic Reviews and Meta-Analyses

- The 2007 Agency for Healthcare Research and Quality (AHRQ) report[7], evaluated the evidence related to MS and vitamin D and found only case-controlled, non-randomized trials. 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."[8]
- The WTA TEC report reviewed evidence from 3 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]
- In a 2013 systematic review, Torkildsen and colleagues evaluated the evidence regarding vitamin D and MS and found only observational and experimental studies which suggested MS was associated with lower levels of vitamin D.[82] Again, no high quality RCTs were identified which assessed the effects or clinical utility of vitamin D treatment in this population.

Randomized Clinical Trials

- Mosayebi et al. studied the effects of vitamin D supplementation on symptoms of MS in 62 patients.[83] Treatment groups were given intramuscular injections of 300,000 IU/month for 6 months. No differences were observed in the expanded disability score or in the number of gadolinium-enhancing lesions.
- Soilu-Hänninen and colleagues evaluated vitamin D treatment as an add-on therapy to interferon β-1b (IFNB) in 66 patients with MS.[84] Patients were randomized to receive vitamin D or placebo for 1 year. A significantly lower number of T1 lesions were observed in the treatment group (P=0.004) compared to the control group. No other statistically significant differences were observed between groups. Limitations of small sample size and the relatively high cut-off of vitamin D deficiency (defined as 25 OHD level>85 nmol/l) preclude conclusion regarding the benefits of vitamin D treatment within this study.
- Kampman et al. studied the effects of vitamin D treatment on symptoms of MS in 68 fully ambulatory MS patients.[53] Patients were randomized to receive 20,000 IU vitamin D/week or placebo for 96 weeks. No differences were observed in the annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), MS functional composite (MSFC), grip strength test, or in fatigue symptoms in the treatment group compared to the placebo group. Authors note that although the study was underpowered to effectively address these clinical outcomes, the available data did not suggest a beneficial trend in vitamin D supplementation.
- Stein and colleagues conducted an evaluation of vitamin D treatment on tumor progression and symptoms in 23 active relapse-remitting MS patients.[85] Treatment groups were given dose-adjusted vitamin D to achieve daily serum levels of 130-175 25OHD. All patients were given 1,000 IU/daily to prevent deficiency. No differences were observed in the cumulative number of new gadolinium-enhancing lesions or change in total number of T2 lesions. EDSS scores and relapse rates were also similar in both groups. This study is limited by an extremely small sample size and lack of control for current treatment. Some patients were undergoing interferon or glatiramer acetate treatment during the study, which may have an impact on vitamin D levels or the effectiveness of supplementation.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address MS and

vitamin D treatment.

Conclusion

Currently, there is limited evidence concerning the association of vitamin D deficiency with MS symptoms and progression. Evidence from RCTs is limited to small studies with methodological flaws, showing no benefit to vitamin D supplementation. Therefore, the efficacy and clinical utility of vitamin D treatment and testing in patients with MS remains unknown.

Steroid Use

The use of systematic 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,[86] however evidence is limited regarding the benefit of vitamin D supplementation in patients with extended steroid use.

Systematic Reviews and Meta-Analyses

- Davidson and colleagues conducted a review of the relationship between glucocorticosteroid (GCS) use and serum 25-hydroxyvitamin D 25-OHD.[87] 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 2-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 in order 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 and Casale, the role of vitamin D on asthma pathogenesis and steroid resistance was evaluated.[88] 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 Clinical Trials

- Majak and colleagues evaluated the effectiveness of oral steroids in 54 children with or without vitamin D(3) or placebo for a specific immunotherapy (SIT).[89] At 1-year follow-up, the clinical or immunological effects of the SIT were not affected by the steroid plus vitamin D group.
- Bak and colleagues assessed the effects of vitamin D plus calcium on bone and mineral metabolism in 40 children receiving prednisone treatment.[90] All patients received 4 weeks of prednisolone treatment followed by alternating days of treatment for another 4 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 and colleagues, 14 asthmatic 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.[91] 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 6-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 4 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.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which specifically address steroid use and vitamin D treatment.

Conclusion

Despite an observed association between vitamin D deficiency and long-term steroid use, evidence regarding the benefits of vitamin D supplementation upon bone mineral density and bone loss is lacking. Large RCTs are needed which compare health outcomes in patients taking long-term steroids with and without vitamin D supplementation. Without these additional trials the efficacy of vitamin D testing and treatment cannot be adequately assessed.

<u>Vitamin D Screening in Healthy Populations</u>

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

Systematic Reviews and Meta-Analyses

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,[92] "…were from studies that provided often mixed and inconclusive results and could not be considered reliable."[8] 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." [8] 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.

- 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.[1,8,93,94]

      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.[8] 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.'"[8]

    - 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.[9,94]

- 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.[7] The AHRQ report identifies 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 more recent 2013 systematic review and meta-analysis by Reid et al., investigated whether vitamin D supplementation affects bone mineral density in the general population.[95] 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 8 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."

In a subsequent review of the Reid study, the author notes that these results are, "…consistent with the understanding that vitamin D acts primarily to increase gut absorption of calcium (not directly on bone metabolism), and these results support the Institute of Medicine's conclusion that adults with baseline 25-hydroxyvitamin D levels >20 ng/mL do not require supplementation."[96]

Clinical Practice Guidelines

Currently, no evidence-based clinical practice guideline recommends vitamin D screening in individuals without a clinically documented underlying disease/condition which is specifically associated with the risk of decreased bone density/osteoporosis.

- The 2011 Endocrine Society Clinical Practice Guideline for evaluation, treatment, and prevention of vitamin D deficiency published the following recommendations:[97]
  - 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.

- The U.S Preventive 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.[98] 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.

- The American College of Obstetricians and Gynecologists (ACOG) issued the following statement regarding vitamin D supplementation in pregnant women:[99]

  "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."

Conclusion

To date, there is limited evidence to support vitamin D screening in average-risk, healthy populations. There are substantial gaps in the evidence, causing uncertainty about the health benefits associated with testing or treatment decisions based on test results. Furthermore, no evidence-based clinical practice guideline, including the USPSTF guidelines, or systematic reviews recommend generalized screening of healthy populations. Due to wide-spread vitamin D deficiency across most populations, several large evidence reports have indicated that screening has not been found to be beneficial and suggested patients follow the dietary reference intake guidelines outlined by the IOM.

Summary

Although there is evidence that vitamin D plays an essential role in promoting bone growth and maintenance, there is considerable uncertainty with respect to the reliability and 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 systematic reviews and technology reports are consistent in reporting a lack of evidence demonstrating how vitamin D testing alters treatment decisions or improves health outcomes, including rates of vitamin D deficiency. In addition, these reports note a lack of well-established cut-off values with which to define deficiency. There are no evidence-based clinical practice guidelines which 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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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	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
Disorder of calcium metabolism
Disorders of phosphorus metabolism
End stage renal disease
Hypercalcemia
Hypercalciuria
Hypervitaminosis D
Hypocalcemia
Hypocalcemia and hypomagnesemia of newborn
Intestinal malabsorption
Obstructive jaundice
Osteomalacia
Osteoporosis
Osteosclerosis/petrosis
Pancreatic Steatorrhea
Parathyroid disorders
Protein-calorie malnutrition
Rickets
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)