#### Introduction

A Clinical Update on Vitamin D Deficiency and Secondary Hyperparathyroidism: Vitamin D Testing and Supplementation in CKD Stages 3-4

Part 1

The National Kidney Foundation (NKF) advises that vitamin D deficiency, defined as a serum 25-hydroxyvitamin D [25(OH)D] level <30 ng/mL, is common in patients with chronic kidney disease (CKD) and is associated with morbidity and mortality. In patients with CKD stages 3-4, vitamin D deficiency is present in up to 75% of patients, with further declines in serum levels observed as disease progresses. Treatment of vitamin D deficiency with active vitamin D compounds decreases parathyroid hormone (PTH) levels and improves mineral homeostasis, bone turnover, and physical function. To help clinicians in managing patients with vitamin D deficiency, the NKF has published a new clinical bulletin titled “A Clinical Update on Vitamin D Deficiency and Secondary Hyperparathyroidism: Vitamin D Testing and Supplementation in CKD Stages 3-4.”

This bulletin highlights the latest research on vitamin D deficiency and its impact on patient outcomes. It provides recommendations for vitamin D testing and supplementation in CKD stages 3-4, emphasizing the importance of maintaining serum 25(OH)D levels at or above 30 ng/mL to optimize bone health and reduce the risk of complications associated with vitamin D deficiency, such as falls, fractures, and secondary hyperparathyroidism.

The bulletin includes a summary of recent studies and guidelines on vitamin D testing and supplementation, as well as practical recommendations for healthcare professionals. It is intended to help clinicians become aware of new scientific findings and developments in the field of vitamin D deficiency and hyperparathyroidism. This clinical bulletin is not intended to set out a preferred standard of care and should not be construed as one. Neither should the information be interpreted as prescribing an exclusive course of management.

#### References

**INTRODUCTION**

Subclinical levels of vitamin D are present in patients with CKD, and there is increasing evidence for addressing vitamin D levels. We discuss how vitamin D deficiency is defined, how vitamin D is measured, and the role of vitamin D in chronic kidney disease (CKD). We also discuss the need for vitamin D supplementation in patients with CKD.

**Indications for Vitamin D Replacement**

Vitamin D deficiency is a major concern in patients with CKD. Causes of deficiency include inadequate serum 25(OH)D levels due to limited exposure to sunlight, poor vitamin D intake, and impaired renal function. Renal failure decreases the production of 1,25(OH)D from 25(OH)D. Therefore, vitamin D deficiency is common in patients with CKD, especially in those with CKD stages 3-5.

**Vitamin D Metabolism**

Vitamin D is absorbed in the small intestine, where most vitamin D is absorbed. The vitamin D analogs, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), are both absorbed by intestinal cells, but vitamin D3 is absorbed more efficiently than vitamin D2. The vitamin D analogs are then transported to the liver, where they are converted to 25-hydroxyvitamin D (25(OH)D). The liver is the primary site of vitamin D activation, and the 25(OH)D level is the most sensitive and best indicator of vitamin D status.

**Figure 1. Associations between 25(OH)D levels and CVD mortality.**

Most studies have observed a U-shaped relationship between 25(OH)D levels and CVD mortality. Patients with vitamin D deficiency or insufficiency have a higher risk of CVD mortality than patients with optimal or high vitamin D levels. However, the optimal 25(OH)D level and the threshold for deficiency have not been established. Additional studies are needed to determine the optimal 25(OH)D level and to identify the threshold for vitamin D deficiency.

**Strategies for Vitamin D Supplementation**

There is a current need to develop strategies for vitamin D supplementation in patients with CKD. New vitamin D analogs, such as calcifediol and calcipotriol, have been developed to improve vitamin D metabolism and clinical outcomes. These vitamin D analogs are more effective than traditional vitamin D analogs in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.

**Table 1. Nutritional Vitamin D Supplements**

- **Calcifediol**: Oral calcifediol is the primary form of vitamin D supplementation. It is a prodrug that is activated in the liver to form 25(OH)D. Calcifediol is effective in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.
- **Calcitriol**: Oral calcitriol is the primary form of vitamin D supplementation. It is a prodrug that is activated in the liver to form 25(OH)D. Calcitriol is effective in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.
- **Calcipotriol**: Oral calcipotriol is a vitamin D analog that is effective in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.
- **Calcitriol**: Oral calcitriol is the primary form of vitamin D supplementation. It is a prodrug that is activated in the liver to form 25(OH)D. Calcitriol is effective in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.
- **Calcipotriol**: Oral calcipotriol is a vitamin D analog that is effective in treating vitamin D deficiency and improving clinical outcomes in patients with CKD.

**Vitamin D Supplementation**

Vitamin D supplementation is important for patients with CKD. There is a need for further research to determine the optimal 25(OH)D level and the threshold for vitamin D deficiency in patients with CKD. Additional studies are needed to determine the optimal 25(OH)D level and to identify the threshold for vitamin D deficiency.

**Table 2. Factors influencing vitamin D levels**

- **Gender**: Women have lower vitamin D levels than men due to differences in skin exposure to sunlight and in the amount of vitamin D intake.
- **Age**: Older adults have lower vitamin D levels due to decreased skin exposure to sunlight and decreased vitamin D intake.
- **Race/ethnicity**: Non-Hispanic black individuals have lower vitamin D levels than non-Hispanic white individuals due to differences in skin exposure to sunlight and in the amount of vitamin D intake.
- **Body Mass Index (BMI)**: Higher BMI is associated with lower vitamin D levels due to decreased skin exposure to sunlight and decreased vitamin D intake.
- **Medication use**: Certain medications, such as antiepileptic drugs, antiretroviral drugs, and statins, can affect vitamin D metabolism and levels.
- **Smoking**: Smoking is associated with lower vitamin D levels due to decreased skin exposure to sunlight and decreased vitamin D intake.
- **Dietary intake**: Dietary intake of vitamin D is important for maintaining adequate vitamin D levels. Supplements, fortified foods, and vitamin D-rich foods are important sources of vitamin D.

**Vitamin D and Chronic Kidney Disease**

Vitamin D deficiency is common in patients with CKD, and there is increasing evidence for addressing vitamin D levels. Vitamin D deficiency is associated with increased risk of cardiovascular disease (CVD) and other health outcomes. Vitamin D supplementation has been shown to improve clinical outcomes in patients with CKD.

**Vitamin D and Chronic Kidney Disease**

Vitamin D deficiency is common in patients with CKD, and there is increasing evidence for addressing vitamin D levels. Vitamin D deficiency is associated with increased risk of cardiovascular disease (CVD) and other health outcomes. Vitamin D supplementation has been shown to improve clinical outcomes in patients with CKD.
Subclinical vitamin D deficiency is a common concern in patients with chronic kidney disease (CKD). The best approach to assess vitamin D status is through the measurement of serum 25(OH)D, the major circulating form of vitamin D. Clinical practice guidelines suggest that serum total 25(OH)D levels should be measured in patients with CKD stages 3-5D, and that practice guidelines suggest that serum total 25(OH)D levels should be measured in patients with CKD stages 3-5 (non-renal osteodystrophy stages). The guidelines also suggest individualized treatment by promoting the standard measurement of vitamin D status in patients with CKD, as treatment with active vitamin D (cholecalciferol or ergocalciferol) is less potent in patients with CKD than in healthy patients. In a clinical trial comparing ergocalciferol and paricalcitol for treatment of secondary hyperparathyroidism (SHPT) in stages 3-4 CKD patients, the paricalcitol group showed significantly higher efficacy at decreasing PTH levels compared to the ergocalciferol group. In a smaller, randomized clinical trial, there was no significant difference between cholecalciferol and paricalcitol for treatment of SHPT in patients with CKD stages 3-4, with 17% decreases in 17% respectively. The best approach to assess vitamin D status in patients with CKD is by standardizing the measurement of vitamin D status in clinical practice guidelines (CKD stage 3).
Subclinical vitamin D deficiency is a major concern in patients with CKD. Causes of 25(OH)D deficiency include inadequate vitamin D intake due to a low calcium diet, limited exposure to sunlight secondary to season or geographical location, or the use of certain medications. CKD patients with higher risk for vitamin D deficiency include those with diabetes, obesity, chronic kidney disease, and individuals with prednisone use due to their inhibitor of vitamin D metabolism. The weight loss drug orlistat also interferes with vitamin D absorption.

**Vitamin D therapy in CKD**

The goal of vitamin D therapy in CKD is to correct vitamin D deficiency and maintain levels of 25(OH)D above 30 ng/ml. This is achieved by addressing vitamin D deficiency, as defined by low serum 25(OH)D levels, and addressing vitamin D resistance, as defined by high PTH levels despite correction of vitamin D deficiency. Vitamin D therapy should be individualized based on patient characteristics, including age, sex, race, body mass index, comorbidities, and use of medications that affect vitamin D metabolism. The target level of 25(OH)D is above 30 ng/ml, as this level is associated with the lowest risk for fractures in healthy adults.

**Vitamin D analogs**

Vitamin D analogs are synthetic compounds that differ from the naturally occurring hormone vitamin D3. They are used in clinical practice to address vitamin D deficiency and resistance in CKD patients. Vitamin D analogs can be divided into two categories: those that are 1,25(OH)2D analogs and those that are 1α,25(OH)2D analogs.

**1,25(OH)2D analogs**

These analogs are designed to be more potent in increasing serum 25(OH)D levels and maintaining serum 25(OH)D levels above 30 ng/ml. Examples include doxercalciferol, paricalcitol, and alfacalcidol. These analogs are used in patients with CKD stages 3-5 due to their potential to reduce PTH levels and improve bone health.

**1α,25(OH)2D analogs**

These analogs are designed to be more potent in raising serum 25(OH)D levels and maintaining serum 25(OH)D levels above 30 ng/ml. Examples include calcitriol and its derivatives. These analogs are used in patients with CKD stages 3-5 due to their potential to improve bone health and reduce PTH levels.

**Dose response**

The dose response of vitamin D analogs varies depending on the specific analog and the patient's CKD stage. Generally, a higher dose of vitamin D analogs is required in patients with CKD stages 3-5 compared to patients with CKD stages 1-2 due to their lower capacity to activate vitamin D.

**Calcifediol**

Calcifediol is a metabolite of vitamin D3 that is used as a maintenance dose of vitamin D. It is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D. Calcifediol is associated with fewer side effects than other vitamin D analogs, including hypercalcemia, hyperphosphatemia, and hyperparathyroidism.

**Calcitriol**

Calcitriol is a 1α,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D. Calcitriol is associated with fewer side effects than other vitamin D analogs, including hypercalcemia, hyperphosphatemia, and hyperparathyroidism.

**Paricalcitol**

Paricalcitol is a 1α,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D. Paricalcitol is associated with fewer side effects than other vitamin D analogs, including hypercalcemia, hyperphosphatemia, and hyperparathyroidism.

**Doxercalciferol**

Doxercalciferol is a 1,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D. Doxercalciferol is associated with fewer side effects than other vitamin D analogs, including hypercalcemia, hyperphosphatemia, and hyperparathyroidism.

**Outcomes of vitamin D therapy**

Vitamin D therapy has been shown to improve bone health, reduce PTH levels, and improve cardiovascular outcomes in patients with CKD. However, the optimal dose and duration of vitamin D therapy have not been established. Clinical trials have shown that high doses of vitamin D analogs are required in patients with CKD stages 3-5 to achieve and maintain serum 25(OH)D levels above 30 ng/ml.

**Summary**

Vitamin D therapy is effective in improving bone health and reducing PTH levels in patients with CKD. However, the optimal dose and duration of vitamin D therapy have not been established. Clinical trials have shown that high doses of vitamin D analogs are required in patients with CKD stages 3-5 to achieve and maintain serum 25(OH)D levels above 30 ng/ml.

**Table 1. Nutritional Vitamin D Supplements**

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Description</th>
<th>Dose</th>
<th>Results</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcifediol</td>
<td>Calcifediol is a metabolite of vitamin D3 that is used as a maintenance dose of vitamin D.</td>
<td>0.5-1.0 µg/day</td>
<td>May be required to treat vitamin D deficiency</td>
<td>May be required to treat vitamin D deficiency</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Calcitriol is a 1α,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D.</td>
<td>0.5-1.0 µg/day</td>
<td>May be required to treat vitamin D deficiency</td>
<td>May be required to treat vitamin D deficiency</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>Paricalcitol is a 1α,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D.</td>
<td>0.5-1.0 µg/day</td>
<td>May be required to treat vitamin D deficiency</td>
<td>May be required to treat vitamin D deficiency</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>Doxercalciferol is a 1,25(OH)2D analog that is used in patients with CKD stages 3-5 who are unable to take vitamin D oral supplements due to their inability to absorb vitamin D.</td>
<td>0.5-1.0 µg/day</td>
<td>May be required to treat vitamin D deficiency</td>
<td>May be required to treat vitamin D deficiency</td>
</tr>
</tbody>
</table>

**Medication Interactions**

Vitamin D may interact with other medications. For example, corticosteroids reduce the bioavailability of vitamin D. Therefore, it is important to monitor serum 25(OH)D levels in patients taking vitamin D supplements with other medications.

**Conclusion**

Vitamin D therapy is effective in improving bone health and reducing PTH levels in patients with CKD. However, the optimal dose and duration of vitamin D therapy have not been established. Clinical trials have shown that high doses of vitamin D analogs are required in patients with CKD stages 3-5 to achieve and maintain serum 25(OH)D levels above 30 ng/ml.
Introduction
Indications for Vitamin D Replacement
Vitamin D25(OH) Measurement
Strategies for Vitamin D Supplementation
Summary

A Clinical Update on Vitamin D Deficiency and Secondary Hyperparathyroidism: Vitamin D Testing and Supplementation in CKD Stages 3-4 Part 2

References
Introduction

Indicators for Vitamin D Replacement

Vitamin D(25)OH Measurement

Strategies for Vitamin D Supplementation

Summary

A Clinical Update on Vitamin D Deficiency and Secondary Hyperparathyroidism: Vitamin D Testing and Supplementation in CKD Stages 3-4: Part 2

References


