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Renal Nutrition Forum

A Peer Reviewed Publication of the Renal Dietitians Dietetic Practice Group

Volume 29 • Number 2

In This Issue

Benefits of Vitamin D Supplementation on Physical Function in Chronic Kidney Disease (CKD) Patients

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Introduction

The CKD population is at an especially high risk for vitamin D deficiency. In one study, 78% of hemodialysis (HD) patients were found to be vitamin D deficient and 18% were severely deficient (1). Serum 25(OH) vitamin D levels of 16-30 ng/mL, 5-15 ng/mL, and <5 ng/mL are considered insufficient, mildly deficient, and severely deficient, respectively (2). As people age, CKD and vitamin D deficiency becomes more common. In older adults, low serum vitamin D levels have been associated with muscle weakness, poor physical performance, balance problems, and falls (3,4).

Vitamin D deficiency causes renal osteodystrophy, which encompasses many metabolic and morphologic abnormalities of the bone (5). These abnormalities include fractures, tendon ruptures, soft-tissue calcifications, calciphylaxis and bone pain (6-8). Further abnormalities include bone deformities, bone cysts, osteopenia, resistance to erythropoietin caused by marrow fibrosis, intractable pruritis, prearthritis, and myopathy (9). In addition, vitamin D deficiency triggers an increase in parathyroid hormone (PTH) secretion. PTH is the major regulator of bone remodeling and skeletal turnover. It promotes the development of osteoblasts and osteoclasts. As PTH levels increase, the rate of bone formation and resorption also increases. These effects result in weak bone and high-turnover skeletal lesions due to immature and structurally inferior bone (10). This condition is called secondary hyperparathyroidism and is a major component of renal osteodystrophy. Secondary hyperparathyroidism not only impairs bone function, but also has deleterious effects on lymphocytes, erythrocytes, the brain, heart, smooth muscles, and adrenal glands (11). Secondary hyperparathyroidism in HD patients is treated with intravenous active vitamin D (1,25-OH_2D_3) compounds, which reduce serum PTH levels.

Loss of skeletal muscle mass, strength, and a decrease in type II muscle fiber circumferences are associated with the frail elderly population. These are important independent predictors of disability in population-based studies linked to functional impairment, increased need for assistance in activities of daily living, risk of falls, fractures, and mortality (12). Ninety-seven percent of patients with vitamin D deficiency have muscular weakness (3). This relationship is due to the fact that a vitamin D receptor that specifically binds to 1,25(OH) vitamin D_3 exists in muscle cells (3,12). The absence of vitamin D receptors is associated with decreased muscular development in mice, suggesting that vitamin D is required for the growth and development of muscle (13).

This paper reviews current research on the benefits of vitamin D supplementation on physical function in the elderly population and discusses the potential for benefits in the CKD population.

Research Review Methods

Medline and PubMed searches were limited to articles published between 1998 through 2008. Search terms used were vitamin D, cholecalciferol, alphacalcidol, ergocalciferol, calcitriol, muscle mass, muscle strength, physical performance and elderly. The search was confined to English reports on human subjects. Length and dose of vitamin D therapy varied, as well as baseline vitamin D status, and age of patients. Review articles were also included in this report.

Studies Supporting Improved Physical Function in Elderly Subjects Supplemented with Vitamin D

Most of the current research on vitamin D supplementation related to physical function in the elderly indicates beneficial effects. Refer to Table 1 for a summary of the studies presented in this section.

In a study with ergocalciferol (vitamin D_2) supplementation, 96 elderly women with poststroke hemiplegia were randomly assigned to receive either 1000 IU ergocalciferol daily or a placebo and were followed for two years. The frequency of falls, the incidence of hip fractures, and the number, size, and strength of muscle fibers were compared. The group treated with ergocalciferol had improved serum vitamin D levels, a 59% reduction in falls ($p=0.003$), an increase in number and size of type II muscle fibers, and improved muscle strength (14). A similar study with ergocalciferol supplementation was conducted in men with advanced hormone refractory prostate cancer. Sixteen men, with a mean age of 67.5 years, were supplemented with 2,000 IU ergocalciferol/day and 500 mg calcium for 12 weeks. Seven of 16 men had decreased levels of serum vitamin D. Strength improvement was assessed by timed chair rises (testing muscle strength) and a timed ten meter walk (testing gait speed). Overall, six subjects showed consistent improvements in strength parameters (15).

Studies were conducted using supplementation of alphacalcidol, a synthetic analog of calcitriol (1,25-OH_2D_3). Supplementation improved muscle strength, functional mobility, and muscle mass (3,16). In one study, ten vitamin D-deficient elderly women and thirteen elderly women with normal vitamin D serum levels were treated with 0.5 mcg alphacalcidol for six months. Assessments of muscle strength and functional mobility were taken at baseline and compared with results after the 6-month intervention period. Knee extensor strength was measured as force was applied at the ankle with the subject seated in a chair, the lower leg unsupported, and the knee flexed at a 90-degree angle. The force was measured with a strain gauge, recorded with a strain meter, and the best of three attempts was documented. The walking test measured the time taken by an individual to stand up from a standard arm chair, walk a distance of three meters, turn, and walk back to the chair and sit down again. Treatment led to improvement in isometric knee extensor strength in the vitamin D-deficient group (left leg: $p= 0.03$; right leg: $p= 0.02$), as well as an increase in the walking distance over two minutes ($p= 0.03$) (3).

In another study, researchers observed the treatment effects of anabolic steroids, calcium and vitamin D supplementation after a hip fracture (16). Sixty-three women who had surgery due to a hip fracture were randomly assigned to receive treatment for one year with anabolic steroids. They were supplemented with vitamin D and calcium, or calcium only. Vitamin D (alphacalcidol 0.25 mcg) and calcium (500 mg) were administered daily. Parameters were measured by bone mineral density (BMD) and thigh muscle volume, which was measured after surgery and after 6 and 12 months; quantitative CT; and quantitative ultrasound. The group supplemented with vitamin D and calcium (anabolic group) did not lose muscle volume within the first 12 months after surgery, whereas the control group did ($p< 0.01$). The anabolic group also had a significant increase in muscle volume in the non-surgical side, and had improved BMD scores in all sites. Hip fractures commonly lead to a catabolic state and are associated with a high mortality rate. The results from this study showed that an increase in muscle volume and BMD will reduce the risk of falls, further fractures, functional dependency, generalized weakness, and mortality (16).

A study using cholecalciferol as the vitamin D supplement showed effects of increased musculoskeletal function and reduced frequency of falls (17). In a double-blind randomized control trial, 122 vitamin D-deficient women, ages 63-99 years, residing in long-stay geriatric care centers were supplemented with vitamin D and calcium. Participants received 1200 mg calcium per day in

Table 1
Studies that Support Improved Physical Function in Elderly Subjects Supplemented with Vitamin D

Author	Subjects	Vitamin D Status	Groups	Supplement	Duration	Outcome Measures	Findings	Study Limitations
Sato and colleagues (14)	96 Women	Deficient		1000 IU ergocalciferol /day	2 years	fall rate, hip fracture incidence, muscle fiber number and size, strength	59% decrease in falls (p=0.003)	
vanVeldhuizen and colleagues (15)	16 Men	Deficient=7 Not Deficient=9		2000 IU ergocalciferol/day 500 mg Ca^{2+}/day	12 weeks	muscle strength, gait speed	improved strength in 6 subjects	small sample size, short duration
Verhaar and colleagues (3)	23 Women	Deficient=10 Not Deficient=13		0.5 mcg alphacalcidol /day	6 months	muscle strength, functional mobility	improved knee extensor strength (left leg p= 0.03, right leg p=0.02), walking speed (p=0.03)	not placebo controlled, small sample size
Hedstrom and colleagues (16)	63 Women		vitamin D and Ca^{2+} vitamin D and anabolic steroids Ca^{2+} only	0.25 mcg alphacalcidol /day 500 mg Ca^{2+}/day	1 year	muscle mass, clinical function	vitamin D group did not lose muscle volume (p<0.01), increase in muscle volume on non-surgical side	
Bischoff and colleagues (17)	122 Women	Deficient	vitamin D and Ca^{2+} Ca^{2+} only	800 IU cholecalciferol/day 1200 mg Ca^{2+}/day	3 months	fall rate, gait speed, muscle strength	49% decrease in falls (p=0.01), improved muscle function (p=0.0094)	not generalizable
Gallagher and colleagues (18)	489 Women	Not Deficient	supplement placebo	0.25 mcg calcitriol BID $Ca^{2+} \leq 1000$ mg/day	3 years	fall rate	38% decrease in falls (p=0.0015)	

addition to 800 IU cholecalciferol, or 1200 mg calcium alone for three months during the winter to determine the effects of these supplements on musculoskeletal function and falls. Outcomes were measured by the number of falls during the treatment period, a timed up and go test, knee flexor strength, knee extensor strength, and grip strength. Assessments were performed at baseline and after a three-month follow-up. The vitamin D group accounted for a 49% reduction in falls (p= 0.01) and a significant improvement of musculoskeletal function in 62 women (p= 0.0094) (17).

Vitamin D supplementation appears to improve physical function even in elderly who present with adequate serum levels of vitamin D. A group of 489 vitamin D-sufficient elderly women were randomly assigned to receive 0.25 mcg calcitriol twice a day or a placebo for three years. Data on frequency of falls was collected at 6-month intervals. A 38% decrease (p= 0.0015) in fall rate was seen in the calcitriol-supplemented group at the end of the intervention period (18).

Studies Not Supporting Improved Physical Function in Elderly Subjects Supplemented with Vitamin D

Several studies showed no benefits on physical performance from vitamin D supplementation. However, it is likely that these studies did not demonstrate positive results due to limitations on study designs and methods. Refer to Table 2 for a summary of the studies presented in this section.

A randomized, double-blind, placebo-controlled study was conducted to determine if vitamin D supplementation improves neuromuscular function in older adults with fall histories. A group of 139 people, ages 65 years and older, with a history of falls and 25(OH) vitamin D deficiency were randomized to receive either a single intramuscular injection of 600,000 IU ergocalciferol or a placebo. Measurements were taken at baseline and six months after the intervention. Improvements were seen in functional performance ($p< 0.01$), choice reaction time ($p= 0.01$), and postural stability ($p= 0.02$), although both the intervention and placebo groups showed a loss of strength over the trial period. Although the number of falls may be reduced due to improved neuromuscular function, vitamin D supplementation did not improve muscle strength in this population (19).

To determine the effects of vitamin D supplementation on a healthy population, 65 men, ages 65 years or older, were randomized to receive 1000 IU cholecalciferol per day or a placebo for six months. Both groups were administered 500 mg per day of calcium. In the treatment group, serum levels of 25(OH) vitamin D increased and PTH decreased. No significant difference in strength or physical function was found between the treatment and control

Table 2
Studies that Do Not Support Improved Physical Function in Elderly Subjects Supplemented with Vitamin D

Author	Subjects	Vitamin D Status	Groups	Supplement	Duration	Outcome Measure	Findings	Limitations
Dhesi and colleagues (17)	139 Men and Women	deficient	supplement placebo	600,000 IU ergocalciferol	single dose	strength, functional performance, reaction time, stability, fall rate	decreased strength and fall rate, improved functional performance ($p<0.01$), improved reaction time ($p=0.01$), improved stability ($p=0.02$)	single, large supplement dose
Kenny and colleagues (20)	65 Men	not deficient	supplement placebo	1000 IU cholecalciferol/day 500 mg Ca^{2+}/day	6 months		increased 25(OH) vitamin D levels	did not account for seasonal change in vitamin D, not generalizable, subjects not vitamin D deficient
Faulkner and colleagues (21)	389 Women			Not stated	4 years	muscle function, fall rate	no improvement on fall rate	dose and falls self-reported, multivitamins were included as acceptable vitamin D supplements
Latham and colleagues (22)	183 Men and Women		supplement placebo	300,000 IU calciferol	single dose	fall rate	no improvement	single, large supplement dose

groups (20). A four-year randomized prospective cohort examining the relationship between vitamin D supplementation and calcitropic hormones with neuromuscular function and falls found no association with vitamin D supplementation and fall risk. This study included 389 older community-dwelling Caucasian women from multiple cities within the United States. Supplementation was self-reported and included the use of vitamin D supplements or multivitamins. Neuromuscular function was measured by grip strength, chair-stand time, gait speed, and balance-walk (21).

A randomized, controlled trial using calciferol was conducted to determine the effectiveness of vitamin D and quadriceps resistance exercise on the reduction of falls and improvement of physical health. The subjects of this study consisted of 243 frail people ages 65 and older. Participants received either a single dose of 300,000 IU calciferol or a placebo, along with 10 weeks of high-intensity quadriceps resistance exercises. There were no significant effects on physical health or number of falls in the intervention group or control group (22).

Discussion

There is potential for vitamin D supplementation to improve physical function in CKD patients, but more research is needed within this population. The high prevalence of vitamin D deficiency in the CKD population and the negative effects of deficiency are similar in the elderly, allowing the assumption of comparable benefits in both populations. Several studies have been performed to determine the effects of vitamin D supplementation on muscle function in elderly people although current research is inconsistent (23,24).

Studies that support vitamin D supplementation confirmed various benefits on muscle function in subjects with and without vitamin D deficiency. These benefits include increased muscle strength and muscle mass, improved gait speed, and decreased frequency of falls. Vitamin D supplementation increased muscle strength, as measured by various physical performance assessments (3,14,15,17). Muscle mass also increased, which was seen by reduced atrophy of type II muscle fibers (14,16). Timed up and go tests verified improvement in gait speed (17). The number of falls also decreased (14,17). Beneficial supplement effects were shown in these studies; however, limitations in study designs suggest that results be regarded with caution. One study was limited by a small sample size (3). Another study was limited by the short intervention period, small sample size, and variability in health status due to the cancer diagnosis of the subjects (15). A third study was limited by the lack of generalizability. These subjects were white institutionalized elderly women from Switzerland with low serum vitamin D levels (17).

Studies that did not support a benefit from vitamin D supplementation also had flaws in their study designs. These flaws included the use of subjects who were not vitamin D deficient or a study design in which a single treatment dose of vitamin D was used. Review articles show that muscle function does improve with vitamin D supplementation in subjects who have a vitamin D deficiency (23,24). One study had multiple limitations (20). It did not take into account seasonal change of vitamin D; the men in the study were not typical of the general population, as they were exceptionally strong to begin with; and they were not deficient in 25(OH) vitamin D levels, which would have been required to notice an improvement (20). In another study, fall rates were calculated based on the participants' self-reports, which tends to be subject to error (21). These results must take into consideration that the vitamin D was not supplemented with calcium, which may have limited its absorption (22). The studies that used a single, large dose of a vitamin D supplement should be taken into consideration as a factor that may have greatly affected the study results (19,22). Multiple doses may be necessary to see treatment results and one large, single dose may not be biologically optimal for the human body to absorb.

One mechanism that could support a relation between vitamin D and muscle strength is that an increase in the relative number and cross-sectional area of fast-twitch fibers exists with adequate vitamin D levels. Vitamin D also has an indirect effect on skeletal muscle through the secretion of insulin (25). Higher serum 25(OH) vitamin D concentrations are associated with improved physical performance, muscle strength, and musculoskeletal function (26-28). A study in Japanese elderly women who had low 25(OH) vitamin D levels showed a significantly higher percentage of falls because of inferior physical performance (29).

Recommendations

CKD patients may benefit from early vitamin D supplementation to improve physical function. Current studies show improvement in physical function in vitamin D deficient non-CKD patients. With the high prevalence of vitamin D deficiency in CKD, it is hypothesized that this population is at even greater risk than non-CKD elderly for decreased physical function. If a significant benefit exists, physicians may be more likely to consistently initiate a vitamin D supplement for their patients in the early stages of CKD (Stages 2, 3, and 4). Patients with optimal vitamin D status could maintain their normal muscle strength, muscle mass and physical performance. This has great implications for a population that suffers from frequent falls, hip fractures, hospitalizations, and poor quality of life. Maintaining muscle strength and muscle mass by ensuring adequate vitamin

D levels will likely prevent falls and fractures, decrease hospitalizations, and improve quality of life. In turn, there is potential to improve mortality rates and decrease health care expenses.

Current National Kidney Foundation Kidney Disease Outcome Quality Initiative recommendations encourage initiating vitamin D supplementation in patients with CKD Stages 3 and 4. The recommendation for treatment of vitamin D insufficiency is 50,000 IU/month orally for six months (2). In the mildly deficient population, 50,000 IU/week for four weeks, then 50,000 IU/month orally for six months is recommended. For the severely deficient population, 50,000 IU/week orally for 12 weeks, then monthly for a total duration of six months is recommended (2). Physicians should test serum vitamin D levels earlier and more regularly to monitor vitamin D status and initiate supplementation before patients become deficient.

There is a need for vitamin D research in the CKD population related to physical function. Future studies should be conducted in CKD patients with insufficient or deficient vitamin D status to determine the effects of supplementation on physical function. ◆

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Our Thanks to all of our clinical peer reviewer members who made this issue possible:

Marianne Hutton, RD, CSR, CDE • Mary Sundell, RD, LDN, CCRP
Christina Nelms, MS, RD, CSP, CNSC • Megan Sliwa, RD, LDN
Natalie Lussier, MS, RD, LD • Alison Steiber, PhD, RD, LD
Lynn Munson, RD, LD

Thank You also to:
Amy Hess-Fishl, MS, RD, LDN, BC-ADM, CDE
for providing our CPEU test questions.

Additional Thanks are extended to:
RNF Managing Editor **Rachael R. Majorowicz, RD, LD**; web site editor **Cathy M. Goeddeke-Merickel, MS, RD, LD**; RPG chair **Patricia Williams, RD, CSR, LDN**; Manager, DPG/MIG/Affiliate Relations **Susan DuPraw, MPH, RD** and ADA DPG Relations Director **Diane Juskelis, MA, RD, LDN** for proof copy review.