

Vitamin D and Physical Function in Community-Dwelling Older Adults

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The active form of vitamin D, serum 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), is synthesized in a series of steps starting with the conversion of 7-dehydrocholesterol to previtamin D_3 by ultraviolet light in the skin, which is then isomerized to vitamin D_3 .¹ Dietary sources of vitamin D contain either the D_3 (cholecalciferol) or D_2 (ergocalciferol) form of the vitamin. In the liver, vitamin D_3 or D_2 is hydroxylated into 25-hydroxyvitamin D ($25(\text{OH})\text{D}$), the preferred analyte for monitoring vitamin D status. In the kidney, $25(\text{OH})\text{D}$ is further hydroxylated into $1,25(\text{OH})_2\text{D}$, a process tightly regulated by parathyroid hormone (PTH) and serum calcium and phosphorus concentrations. Classical actions of vitamin D include calcium homeostasis, increased intestinal calcium and phosphorus absorption, and promotion of bone health.¹ However, a growing list of extra-renal organs has been shown to have 25-hydroxyvitamin D-1- α -hydroxylase activity and can synthesize the active form of the vitamin, $1,25(\text{OH})_2\text{D}$, from $25(\text{OH})\text{D}$.² Vitamin D receptors (VDRs) also have been identified in at least 36 different cell types including brain, prostate, breast, colon, lymphocytes, and skeletal muscle.² Over the last 2 decades, the role of vitamin D has been shown to extend beyond bone health to encompass cardiovascular health, immunomodulation, and regulation of cell growth, and the potential health consequences of vitamin D deficiency shown to include autoimmune diseases, cardiovascular disease, diabetes, infections, and several types of cancers including breast, colon, and prostate cancer.³

Little consensus exists on the cut-point to discriminate between vitamin D-deficient and sufficient states. While 25(OH)D concentrations <10 ng/mL (<25 nmol/L; to convert ng/mL to nmol/L, multiply by 2.496) are generally agreed upon to define severe clinical vitamin D deficiency, cut-points to define vitamin D insufficiency or normal vitamin D concentrations of between 20 and 40 ng/mL of 25(OH)D have been suggested.⁴⁻⁶ Although data from the National Health and Nutrition Examination Survey (NHANES) 2000-2004 indicate that severe clinical vitamin D deficiency is rare in the US ($\leq 5\%$), approximately 30% of adults had 25(OH)D concentrations <20 ng/mL and almost three-fourths had 25(OH)D concentrations <32 ng/mL.⁷

Many factors may cause vitamin D deficiency. Production of vitamin D in the skin is affected by use of sunscreen, melanin content of the skin, latitude, and season of year. Liver and renal failure, obesity, malabsorptive conditions, as well as certain medications and supplements can result in vitamin D deficiency. Older adults are at greater risk of vitamin D insufficiency because of reduced exposure to ultraviolet B radiation, reduced efficiency of previtamin D₃ synthesis in the skin, inadequate dietary intake of vitamin D, and decreased renal function.^{1,8,9} Current Institute of Medicine Dietary Reference Intakes for vitamin D are 400 IU/d in adults aged 51-70 years and 600 IU/d in adults aged >70 years¹⁰; however, these amounts may not be adequate to achieve optimal 25(OH)D concentrations.¹¹

Several potential mechanisms exist by which vitamin D status may play a role in muscle strength and physical performance. Osteomalacic myopathy, found in adults with severe clinical vitamin D deficiency, results in proximal muscular weakness and gait impairment. Muscle biopsies from vitamin D-deficient individuals show atrophy of type II muscle fibers, which are the first to be

recruited to recover from a fall.¹² The active form of vitamin D, 1,25(OH)₂D, affects muscle metabolism through genomic pathways by binding to nuclear VDRs and inducing de novo protein synthesis that regulates cell proliferation and induction of terminal differentiation into mature muscle fibers, as well as through non-genomic pathways by binding to membrane-bound VDRs and inducing the activation of protein kinase C and the release of calcium into the cytosol for muscle contractility.¹² Recent findings have implicated vitamin D insufficiency in many comorbid conditions, including inflammatory and autoimmune conditions, osteoporosis, knee and hip osteoarthritis, diabetes, hypertension, and cardiovascular disease¹³—conditions that also are related directly to the development of limitations in physical function. Vitamin D insufficiency may play a role in the inflammatory response by promoting the production of inflammatory cytokines such as interleukins 1 (IL-1) and 6 (IL-6) and tumor necrosis factor alpha (TNF- α), which have been linked to lower muscle strength and poor physical performance.^{14,15}

The evidence from cross-sectional studies indicating that 25(OH)D concentrations are associated with muscle strength and physical performance in older adults is relatively consistent.¹⁶⁻²⁵ For example, in NHANES III a positive association is shown between 25(OH)D concentrations and 8-ft walk speed and timed sit-to-stand tests.²¹ In the InCHIANTI study (Invecchiare in Chianti, aging in the Chianti area), 25(OH)D deficiency was associated with significantly worse physical performance measured by a battery of tests, including gait speed over a short distance, timed sit-to-stand, and balance, and 25(OH)D insufficiency was associated with significantly weaker grip strength.²⁴

Data from the few longitudinal studies are inconsistent, showing either an increased decline in muscle strength and physical performance among those with low 25(OH)D concentrations²⁵⁻²⁷ or no association between 25(OH)D concentrations and muscle strength or physical performance.²⁸⁻³⁰ In the Longitudinal Aging Study Amsterdam, older men and women with low 25(OH)D concentrations were significantly more likely to lose grip strength and were twice as likely to have declines in physical performance over 3 years.^{26,27} Although baseline vitamin D status was not associated with change in physical performance over 1 year follow-up in the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study, physical performance scores improved significantly among those individuals whose 25(OH)D concentrations were insufficient at baseline but sufficient at follow-up.³¹ The discrepancies among these studies may stem from differences in study population characteristics (eg, already moderately to severely disabled versus well-functioning older adults or prevalence of vitamin D insufficiency), different 25(OH)D assay methodologies and cut-points used to define vitamin D insufficiency, and different methods to assess physical performance.

It has been suggested that 25(OH)D concentrations ≥ 30 ng/mL are optimal for various health outcomes, but few studies have examined the optimal 25(OH)D concentration for physical performance.³² In the NHANES III study, most of the improvement in physical performance occurred in individuals with 25(OH)D concentrations < 24 ng/mL.²¹ In the Longitudinal Aging Study Amsterdam, older adults with 25(OH)D concentrations < 20 ng/mL were significantly more likely to decline in physical performance over 3 years.²⁷ Data from the Health, Aging, and Body Composition Study show that physical performance improved significantly up to 25(OH)D

concentrations of approximately 30 ng/mL; however, further significant improvement in physical performance was not observed at 25(OH)D concentrations beyond 30 ng/mL.³³

Randomized controlled trials of vitamin D supplementation have shown mixed effects on muscle strength and physical performance among older adults.³⁴⁻⁴⁰ Possible reasons for the inconsistencies include inclusion of participants with sufficient 25(OH)D concentrations, inadequate vitamin D supplement dose, lack of sufficient 25(OH)D concentrations at follow-up, length of follow-up, and sample selection (eg, institutionalized, home-bound and falls clinic participants vs. healthy community-dwelling older adults). For example, in the Women's Health Initiative randomized controlled trial of calcium (1,000 mg/d) and vitamin D (400 IU/d), vitamin D supplementation was not beneficial in protecting against decline in physical performance in older women over 7 years of follow-up.³⁹ However, vitamin D dose provided was likely too low. Vitamin D supplementation of 700-1000 IU/d has been suggested to prevent falls and fractures in older adults.^{41,42}

While observational studies provide important preliminary data on the association between vitamin D status and muscle strength and physical performance in older adults, well-designed interventions to improve vitamin D status are needed to definitively determine whether treatment of vitamin D deficiency and/or insufficiency improves low muscle strength and poor physical performance. In designing these trials, researchers will need to decide which individuals to include based on factors such as 25(OH)D concentrations (eg, vitamin D deficient or insufficient older adults, or all older adults) and which risk factors to target (eg, sarcopenia, frailty, disability, fractures, or other health outcomes). In addition, trial designers will need to consider the

appropriate dose of vitamin D supplementation to ensure that 25(OH)D concentrations improve to sufficient levels.

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