

Viewpoint

Pinpointing a Role for Vitamin D in Frailty: A Time for Animal Models?

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ABSTRACT

Frailty is a condition marked by greater susceptibility to adverse outcomes, including disability and mortality, which affects up to 50% of those 80 years of age and older. Concurrently, serum vitamin D insufficiency and deficiency, for which as many as 70% of older adults may be at risk, potentially play an important role in frailty onset and progression. Large population driven studies have uncovered associations between low serum vitamin D levels and higher incidence of frailty. However, attempts to apply vitamin D therapeutically to treat and/or prevent frailty have not yielded consistent support for benefits. Given the complexity and inconsistency arising from human studies involving vitamin D, our research group has recently published on animal models of vitamin D insufficiency. Combining our model with the emerging development of animal frailty assessment, we identified that higher than standard levels of vitamin D supplementation may delay frailty in mice. In this viewpoint article, we will discuss current knowledge regarding the importance of vitamin D in frailty progression, the emerging significance of animal models in addressing these relationships, and the future for pre-clinical and clinical research.

KEYWORDS: mouse models; cholecalciferol; vitamin D3; supplementation; functional capacity

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FRAILTY AND VITAMIN D INSUFFICIENCY/DEFICIENCY ARE PREVALENT IN OLDER INDIVIDUALS, YET THE BENEFITS OF SUPPLEMENTATION REMAIN ELUSIVE

Frailty is a prevalent condition for which susceptibility increases with age and carries an increased risk for adverse outcomes including disability, loss of independence, and mortality [1]. Low serum 25-OH vitamin D levels are often associated with the presence of frailty in older individuals in studies originating from around the world [2–9], although exceptions have been reported [10,11], and the possibility of sex specific differences raised [12]. Vitamin D status may also predict future frailty onset or progression.

Lower 25-OH vitamin D levels in non-frail individuals predicted higher occurrence of frailty two years [13] and 4.5 years [14] later. Additionally, pre-frail individuals that exhibited poorer vitamin D status were more likely to become frail and die at a 6-year follow-up [15]. Interestingly, vitamin D levels at 75 years of age associated with frailty incidence at 80 years of age, but not when subjects reached 85 years of age [16]. Moreover, one study found vitamin D levels predicted mortality up to 12 years later, yet did not predict of frailty progression [17]. Although studies are mixed, benefits of vitamin D supplementation for enhancing physical performance in frail individuals have been reported [18–20], however to our knowledge only one study examined if vitamin D might attenuate frailty progression. In the study by Bolzetta et al. [21], in ~4400 participants averaging 400IU/daily of vitamin D supplementation versus those who were not, there was no difference in frailty progression over an 8-year period. This was a modest dose, and 25-OH vitamin D levels were not assessed. Two recent prospective trials investigated whether vitamin D supplementation reduces falls or improves physical performance and found no benefit [22,23]. In contrast, a systematic review concluded that vitamin D improved muscle mass and physical performance in older women [24]. These trials were in community dwellers in general good health and were not studying frailty per se. In the STURDY trial just over 70% of the participants were either pre-frail or frail, and vitamin D did not reduce falls [25]. However, there was no information as to whether baseline vitamin D status correlated with frailty nor whether supplementation resulted in changes in frailty. The paucity of clinical trials investigating the impacts of vitamin D status on frailty suggests that future interventional studies need to reach substantial levels of supplementation and sufficient length of time to truly determine potential benefits. Additionally, genetic and lifestyle factors may confound interpretations of human studies. Activity levels [26,27] and smoking [28] may affect 25-OH vitamin D levels and exert independent impacts on physical performance, thus leading to greater difficulty in isolating the individual contributions of each. Such impacts could arise from diminished or enhanced bioactive potential of serum 25-OH vitamin D and the more active metabolite 1,25(OH)₂ vitamin D, or from differences in vitamin D binding protein [29]. Polymorphisms in vitamin D synthesis and metabolism [30,31] can also lead to potentially erroneous conclusions.

ANIMAL MODELS OF FRAILTY DEMONSTRATE A ROLE OF VITAMIN D

Animal studies therefore offer better control of these confounding elements, via the use of genetically identical mice and similar husbandry, allowing for elucidation of vitamin D action. Towards this strategy, we generated a mouse model of vitamin D insufficiency and hyper-sufficiency via altering the amount of cholecalciferol provided in the animal chow [32,33]. This methodology thus allows rapid (within 2 weeks) alteration of

25-OH vitamin D levels to that which mimic human relevant levels of insufficiency and hyper-sufficiency, and permit maintaining such levels for months or years in the life of a mouse that is the equivalent to decades of relative aging in a human. We found that low levels of 25-OH vitamin D from the ages of 6 to 18 months (roughly equivalent for a human from 30 to 56 years old) resulted in poorer physical performance in mice including worse grip endurance, uphill sprint speed, and stride length [32]. Our research group also applied this model to aged mice (aged 24-months—roughly equivalent to a 70 year old human) to investigate impacts on frailty progression [34]. To determine frailty in mice, our research group used an assessment strategy based upon the Fried et al. physical frailty phenotype [1,35]. Specifically, frailty was defined as falling below a cutoff in ≥ 3 parameters, while pre-frail was below cutoff in 1 or 2 parameters. The first parameter was the loss of $>5\%$ body weight in a one-week period preceding the frailty assessment. The next four parameters included cutoffs at 1.5 standard deviations below the mean for grip strength, treadmill endurance, activity monitoring, and gait speed. In our experiment [34], the aged mice were given either 125, 1000, or 8000 IU cholecalciferol/kg chow for a 4-month period resulting in 25-OH vitamin D levels of approximately 12, 35, and 60 ng/mL respectively. At the end of the study, our data revealed less frailty progression in the 8000 IU/kg chow group than in the 125 and 1000 IU/kg chow groups. To our knowledge, this study represents the first demonstration that frailty status can be affected by adjusting vitamin D levels in an organism, although surprisingly, the effect was only observed for higher serum levels of 25-OH vitamin D [34].

GOALS FOR FUTURE RESEARCH

However, one limitation to our study in these older mice was that vitamin D insufficiency was initiated for a short time (16 weeks) at an advanced age (24-months) [34], which does not mimic the common scenario whereby individuals have low vitamin D levels for decades leading up to old age. The use of animal models in this sense could provide very valuable insights into how frailty develops during aging, particularly the importance—if any—of maintaining sufficient serum levels at young and middle age. In addition, an animal model permits establishment of long-term vitamin D deficiency followed by supplementation and repletion, which is a clinically relevant scenario when individuals present to clinicians who find low 25-OH vitamin D levels in older adults. Also, the range of strategies to assess frailty in mice and rats continues to expand, which is important in light of the complexity of this multifactorial syndrome [35]. In addition to us and others who model the Fried et al. frailty physical phenotype [35,36], others have generated strategies to emulate the deficit accumulation model of frailty in mice [37]. Building from this latter strategy, Schultz et al. have devised a method to estimate biologic age and life expectancy in mice [38], all potential areas for future studies involving vitamin D. Animal studies such as these also have the

potential to inform clinical trials. Future clinical work may seek to investigate the benefits of higher levels of supplementation to prevent the onset of frailty as an example. Furthermore, for greater success in identifying vitamin D benefits in clinical trials, investigators may need to consider longer trials, a focus on truly deficient participants, and/or routine measurement of serum 25-OH vitamin D levels to understand the impacts of supplementing at specific levels. This will enhance the reproducibility and validity of vitamin D impacts on frailty, sarcopenia, and falls in older adults. Importantly, each of these factors can be first investigated in pre-clinical models to provide guidance on clinical trial design. In summary, the emerging development of animal models provides an exciting opportunity to develop novel and clinically relevant research strategies to investigate the physiology and impacts of vitamin D on preventing and ameliorating frailty during aging.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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