Effects of Vitamin D supplements on musculoskeletal system

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History….

• The syndrome of rickets has been recognized for hundreds of years.

• The role of vitamin D in its genesis and treatment was only documented in the early twentieth century.

• When both sunlight exposure and cod liver oil supplements were found to be curative.

• These discoveries suggested that:

  \textit{vitamin D was good for bone, and it has been regarded by some as a skeletal tonic since that time.}

However, more recent investigations have demonstrated that this is an oversimplification but Vitamin D influences skeletal mineralization principally through the regulation of intestinal calcium absorption.
The role of the vitamin D endocrine system

- the primary role is to maintain
  - normocalcemia
  - and normophosphatemia,
  - thus permitting normal skeletal mineralization

- The principal way in which vitamin D does this is through regulation of intestinal absorption of these minerals.

- Enterocytic VDR expression is necessary and adequate to maintain normal skeletal mineralization.

The role of the vitamin D endocrine system

• A second direct effect of vitamin D on bone is to *increase local pyrophosphate levels* resulting in inhibition of mineralization

• This vitamin D effect is also consistent with *vitamin D being a procalcemic factor* rather than a direct stimulator of bone growth and mineralization

Vitamin D activation and target cell effects

Classical actions
- Mineral homeostasis and skeletal health
  - Intestinal Ca and P absorption
  - Bone metabolism
  - Renal Ca reabsorption
  - Parathyroid function

Non-classical actions
- Renal and cardiovascular protection
  - Induction of FGF-23 and Klotho
  - Reduction of proteinuria
  - Inhibition of the RAS
  - Control of systemic inflammation
Role of Vitamin D on the bone

• VDR is expressed in bone, mainly in osteoblasts and osteocytes

• There its main role is to stimulate bone resorption, in order to maintain the circulating calcium levels.

• VDR in osteoblastic cells does this by regulating RANKL and osteoprotegerin to promote osteoclastogenesis

• Selective knockout of VDR in bone results in increases in bone mass.

Yamamoto Y, Endocrinology 2013;154:1008–20
High levels of Vitamin D and bone metabolism

- Data from human studies showing that *single large doses of vitamin D*:
  - increase bone resorption markers,
  - that vitamin D intoxication is associated with sustained increases in bone resorption
  - and that correction of vitamin D intoxication is associated with increases in BMD

High levels of Vitamin D and bone metabolism

• High levels of vitamin D or its metabolites can increase bone resorption and impair mineralization

• Thus *incautious use of vitamin D or its metabolites could adversely affect bone*

• Studies of high-dose calciferol or vitamin D metabolites that show
  - increased bone loss
  - increase fracture risk
Vitamin D deficiency and bone metabolism

- Profound loss of vitamin D signaling results in hypocalcemia and osteomalacia.

- Partial loss of signaling (e.g., from vitamin D deficiency) stimulates parathyroid hormone (PTH) secretion leading to increased bone resorption and increased renal retention of calcium, but with maintenance of serum calcium levels within the normal range and bone mineralization is maintained, but at the expense of bone mass.
Vitamin D deficiency and bone metabolism

- Preventing such secondary hyperparathyroidism is the principal rationale for using vitamin D in the management of osteoporosis.

- Many individuals with markedly reduced levels of 25-hydroxyvitamin D (eg, <25 nmol/L) do not develop secondary hyperparathyroidism, for reasons that are unclear.

- Accelerated loss of BMD is only observed in vitamin D–deficient older adults who also have secondary hyperparathyroidism,

- BMD is not related to 25-hydroxyvitamin D in a D-deficient cohort, but is related to PTH.

- A bone biopsy study, at serum 25OHD levels less than 12 ng/mL (30 nmol/L), more than half of the population studied failed to demonstrate osteoid accumulation, indicating that factors other than low 25OHD contribute to osteomalacia.

Reid I., Endocrinol Metab Clin N Am 46 (2017) 935–945
Vitamin D deficiency and bone metabolism

• Thus, many individuals do not appear to suffer adverse effects from levels of 25-hydroxyvitamin D that are associated with bone loss or undermineralization in others.

• The reason is unclear and might be related
to their diet (eg, intake of calcium or of calcium binders such as phytates)
or to other factors (such as the efficiency of renal calcium conservation)

Reid I., Endocrinol Metab Clin N Am 46 (2017) 935–945
Vitamin D deficiency and bone metabolism

• However, the 25-hydroxyvitamin D threshold for an increase in bone turnover markers was about 30 nmol/L.

• Adverse biochemical consequences of vitamin D deficiency arise when 25-hydroxyvitamin D is in the region of 15 to 30 nmol/L.

Reid I., Endocrinol Metab Clin N Am 46 (2017) 935–945

• This variability between individuals may contribute to the variability seen in the outcomes of trials of vitamin D as an intervention.
Vitamin D supplementation is widely recommended and used in the prevention and treatment of osteoporosis
What is the effect of Vitamin D supplementation on bone mineral density?
Effects on osteomalacia

- Vitamin D treatment of patients with severe vitamin D deficiency resulting in osteomalacia:
  - produces increases in absolute BMD of as much as 50% in 12 months

Trials on the effects of Vitamin D supplements on bone mineral density

• Trials assessing the effects of vitamin D on bone administer *vitamin D alone*

• And trials use a combined intervention of *calcium plus vitamin D*.

• Calcium is biologically active, these 2 groups of trials must be considered separately
Trials with Vitamin D Monotherapy

- Systematic review of trials assessing the effects of vitamin D supplementation alone on BMD in adults
  - Data from 23 trials,
  - Mean duration of 23.5 months
  - 4082 participants,
  - 92% women,
  - With an average age of 59 years.
  - BMD was measured at between 1 and 5 skeletal sites,

- Results
  - Six of these found significant benefit;
  - 2 found significant detriment,
  - And the rest were nonsignificant.
  - Only one study showed significant benefit at more than one measurement site, both of which were in the femur.

Reid IR Lancet 2014;383:146–55
Different effects on different bone sites

- When the trial results were meta-analyzed:
  - there was no significant effect in the lumbar spine,
  - there were nonsignificant negative effects in the total body and forearm,
  - but in the femoral neck there was a positive treatment effect of 0.8% (95% confidence interval 0.2% to 1.4%, \( P < .005 \)).

- The femoral neck data showed evidence of heterogeneity among the trials and also of publication bias.
Meta-analyses of the effects of vitamin D supplementation on BMD at the lumbar spine and femoral neck.
Results depending on baseline vitamin D levels

• When the trials were grouped by mean baseline 25-hydroxyvitamin D
  -with starting levels less than 50 nmol/L showed a significant increase in femoral neck BMD,

  -with levels above 50 nmol/L did not.
Results depending on Vitamin D dose

- Treatment effects also differed by vitamin D dose:
  - a supplement of less than 800 units per day was associated with significant increases in both lumbar spine and femoral neck

  - but higher doses were not
Duration of treatment

- Trial duration did not impact the between-groups differences,
- Thus if there is a benefit it does not cumulate over time.
Coadministration of calcium

- The coadministration of calcium to both groups tended to reduce the treatment effect
  consistent with other evidence that a higher calcium intake can partially compensate for low vitamin D levels.
Meta-analysis of vitamin D effects on femoral neck BMD in subgroups of trials classified by trial characteristics.
4 other trials published after the metanalysis

<table>
<thead>
<tr>
<th>Study</th>
<th>t (m)</th>
<th>N</th>
<th>Mean Age (Range)</th>
<th>Baseline 25OHD (nmol/L)</th>
<th>Spine</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
<th>Forearm</th>
<th>Total Body</th>
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<tr>
<td>Iuliano-Burns et al,\textsuperscript{33} 2012</td>
<td>12</td>
<td>110</td>
<td>41 (24–65)</td>
<td>60</td>
<td>NS</td>
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<td>Wamberg et al,\textsuperscript{31} 2013</td>
<td>6</td>
<td>52</td>
<td>40 (18–50)</td>
<td>35</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>+/NS\textsuperscript{a}</td>
<td>NS</td>
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<tr>
<td>Macdonald et al,\textsuperscript{30} 2013</td>
<td>12</td>
<td>305</td>
<td>(60–70)</td>
<td>34</td>
<td>NS</td>
<td>+/NS\textsuperscript{b}</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hansen et al,\textsuperscript{32} 2015</td>
<td>12</td>
<td>230</td>
<td>61 (PM and &lt;75)</td>
<td>52</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>
• Thus significant benefit at any skeletal site was only seen in trials where the mean baseline 25(OH)D was in the range 25 to 40 nmol/L.

• Recent study from Aberdeen supports this
  Macdonald HM, Journal of Bone and Mineral Research, 2018

• Exceptions are the 2 Dawson-Hughes studies,
  - But they were carried out in a cohort of women who had dietary calcium intakes of less than 400 mg/d.
  - and 25-hydroxyvitamin D assays used were poorly calibrated,

Conclusion

- Thus, there is a consistent body of evidence that vitamin D supplements do not influence BMD when baseline levels are greater than 40 nmol/L.

- A daily dose of 400 to 800 IU vitamin D3 is usually adequate to correct such deficiency.

Reid I., Endocrinol Metab Clin N Am 46 (2017) 935–945
Reid IR J Int Med, 2017
Macdonald HM, Journal of Bone and Mineral Research, 2018
Trials with Vitamin D Plus Calcium

• Calcium given as a supplement or as part of a modified diet does \textit{consistently increase BMD, by about 1\%}.  

• This change is detectable at 1 year and does not increase with longer-term supplement use.
Trials with Vitamin D Plus Calcium

• A recent comprehensive meta-analysis of calcium trials, either as a monotherapy or together with vitamin D, showed:
  - **no further benefit to BMD from the addition of vitamin D to a calcium supplement.**

• At 1 year,:
  - calcium alone produced a benefit to spine BMD of 1.3 (0.8–1.7)% compared with placebo (21 trials)
  - and calcium plus vitamin D (7 trials) produced a benefit of 1.1 (0.2–2.1)% (between groups comparison, \( P < 0.81 \)).
  - Results were similar at the femoral neck (\( P \leq 0.86 \)).

Tai V, BMJ 2015;351:h4183.
Effects Vitamin D supplementation on fracture prevention

- Trials assessing the effects of *vitamin D alone*
- Trials of coadministration *calcium and vitamin D*. 
Vitamin D monotherapy and fracture prevention

- systematically reviewed and meta-analyzed by Bolland and colleagues

- In trials involving greater than 28,000 participants,
  - there were *no demonstrable benefits* in terms of either total fracture or hip fracture

  - the available trials provide a sufficiently large cohort to rule out a clinically significant benefit from vitamin D in the prevention of these fracture types.

  - further studies of this intervention in comparable populations are most unlikely to produce a significant change in the meta-analytic outcome

Meta-analyses of the effects of supplementation with vitamin D alone on risk of any fracture or of hip fracture.

Vitamin D monotherapy and fracture prevention

• The DIPART individual patient meta-analysis.
  - In 3 trials involving a total of 14,024 participants, there was no effect of vitamin D alone on either total fracture numbers (hazard ratio 1.01 [0.92–1.12]) or on hip fractures (hazard ratio 1.09 [0.92–1.29]).
  - When they pooled these findings with trial level data from 4 other studies, the combined hazard ratio for hip fracture was 1.11 (0.96–1.29).

• A Cochrane Review agrees with these findings, concluding that
  - “there is high quality evidence that vitamin D alone is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; risk ratio 1.12 [0.98–1.29]) or any new fracture (15 trials, 28,271 participants; risk ratio 1.03 [0.96–1.11]).”

Vitamin D monotherapy and fracture prevention

2 trials showed statistically **significant increases in fractures**, either in the hip or for total fractures.

Each study used annual administration of a high-dose supplement, so many investigators have since concluded that infrequent bolus dosing is unsafe.

These findings emphasize that
- hypercalcemia is not the only potential toxicity from vitamin D supplements,
- and that it is not dose frequency that creates the risk but the absolute levels of 25-hydroxyvitamin D that are achieved.

Smith H Rheumatology 2007;46:1852–7
Sanders KM AMA 2010;303: 1815–22.
Vitamin D plus Calcium on fracture prevention

- In the Bolland meta-analysis, randomization to vitamin D plus calcium reduced total fracture and hip fracture.

- DIPART and Cochrane have also found that vitamin D with calcium reduces both total fractures and hip fractures by similar amounts.

- The marked difference between these findings and those with vitamin D alone suggests that it is the calcium supplement that is critical to these benefits, or the characteristics of those trials using the combination.

Conclusions

• Vitamin D was discovered a century ago as the factor that could cure osteomalacia, and that remains its principal therapeutic role.

• Its effect on bone mineral density and prevention of fractures seems to depend on baseline Vitamin D status.

• In the recent large studies in which vitamin D has been administered, positive effects on BMD or fracture rates have not been observed.
Conclusions

• It is time to move past the simplistic concept that vitamin D is good for bone and that the more we provide the better.

• There are specific regulatory systems to prevent soft tissue calcification,

• but overenthusiastic use of supplements runs the risk of overwhelming these defenses and producing adverse outcomes.
Vitamin D and the skeletal muscle
History…..

• Clinical observation more than 3 decades ago:
  - patients with rickets and osteomalacia displayed proximal myopathy

• The suggestion of a direct link between hypovitaminosis D and muscle function was made

Vitamin D and skeletal muscle

• Recent evidence has confirmed that vitamin D may modulate muscle growth.

• Vitamin D receptors (VDR) are in skeletal muscle cells, indicating the potential for widespread effects.

• Two mechanisms by which vitamin D may act in skeletal muscle have been proposed.
  - genomic
  - non-genomic

Effects of 1,25 vitamin D on muscle cells: molecular and nuclear pathways

Effects of 1,25 vitamin D on muscle cells: molecular and nuclear pathways

• in elderly women, a supplementation of vitamin D (4000 IU/day) during 4 months was associated with:
  - a 30% increase in intramyonuclear VDR concentration
  - and a 10% increase in muscle fiber crosssectional area, especially type 2 fibers

• The VDR has several polymorphisms
  - Some of which may have clinical significance
  - and may determine muscle strength

Hypovitaminosis D and Physical Performance

• Data from the majority of observational studies found:
  - significant association between low levels of vitamin D and poor physical performance and muscle dysfunction in all ages except in very old individuals

• On the contrary, vitamin D levels greater than 50 nmol/L are associated with the lowest probability of muscle dysfunction.

• Some studies suggest that gender may influence the association between vitamin D and skeletal muscle function.

Can Vitamin D Supplementation Improve Muscle Function?
Summary of RCT and meta-analysis regarding effects of vitamin D on muscle function and falls.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Author</th>
<th>Number of subjects</th>
<th>Type of subjects</th>
<th>Mean age (years)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Kenny et al. (2003) [48]</td>
<td>65</td>
<td>Healthy men</td>
<td>76</td>
<td>1,000 IU/d vitamin D versus placebo</td>
<td>6 months</td>
<td>No increase in muscle strength or improvement in physical performance.</td>
</tr>
<tr>
<td>RCT</td>
<td>Songpatanasilp et al. (2009) [33]</td>
<td>72</td>
<td>Postmenopausal females</td>
<td>70</td>
<td>Ca 1500 mg/d + alfalcacidol 0.5 µg/d versus Ca 1500 mg/d</td>
<td>12 weeks</td>
<td>Improvement in muscular strength.</td>
</tr>
<tr>
<td>RCT</td>
<td>Lips et al. (2010) [49]</td>
<td>226</td>
<td>Elderly males and females with vitamin D &lt;50 nmol/L</td>
<td>77</td>
<td>8400 IU/week vitamin D versus placebo</td>
<td>16 weeks</td>
<td>Improvement of balance in a subgroup with severe balance impairment at baseline.</td>
</tr>
<tr>
<td>RCT</td>
<td>Ward et al. (2010) [46]</td>
<td>69</td>
<td>Postmenarchal females (12 to 14 years old) with vitamin D &lt;25 nmol/L</td>
<td>13</td>
<td>4 doses of 150,000 IU vitamin D every 3 months versus placebo</td>
<td>12 months</td>
<td>Increase in jump velocity in girls with low vitamin D levels. No improvement in strength in others.</td>
</tr>
<tr>
<td>RCT</td>
<td>Gupta et al. (2010) [44]</td>
<td>40</td>
<td>Healthy males and females</td>
<td>31</td>
<td>60,000 IU/week for 8 weeks followed by 60,000 IU/month for 4 months vitamin D + 1000 mg Ca/d versus placebo</td>
<td>6 months</td>
<td>Enhanced skeletal muscle strength and physical performance.</td>
</tr>
<tr>
<td>RCT</td>
<td>Zhu et al. (2010) [45]</td>
<td>300</td>
<td>Elderly females with vitamin D &lt;60 nmol/L</td>
<td>77</td>
<td>1,000 IU/d vitamin D + Ca 1000 mg/d versus placebo</td>
<td>12 months</td>
<td>Enhanced skeletal muscle strength and physical performance in patient with the lowest vitamin D level.</td>
</tr>
<tr>
<td>RCT</td>
<td>Taskapan et al. (2011) [39]</td>
<td>25 (CKD stages 3-4) 47 (PD)</td>
<td>CKD and PD with vitamin D &lt;50 nmol/L</td>
<td>NA</td>
<td>50000 IU/week vitamin D</td>
<td>4 to 8 weeks</td>
<td>Improvement in physical performance tests.</td>
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<tr>
<td>UCT</td>
<td>Schacht and Ringe (2012) [56]</td>
<td>2100</td>
<td>Males and postmenopausal females</td>
<td>75</td>
<td>1 mcg/d calciferol</td>
<td>6 months</td>
<td>Improved physical performance.</td>
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<tr>
<td>RCT</td>
<td>Glendenning et al. (2012) [52]</td>
<td>690</td>
<td>Elderly females (age &gt;70)</td>
<td>77</td>
<td>150,000 IU/week vitamin D versus placebo</td>
<td>9 months</td>
<td>No differences in falls and physical performance between the groups.</td>
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<tr>
<td>RCT</td>
<td>Goswami et al. (2012) [53]</td>
<td>173</td>
<td>Healthy females</td>
<td>22</td>
<td>60,000 IU/week every 8 weeks then 60,000 IU/fortnight + Ca 500 mg/d versus 60,000 IU/week every 8 weeks then 60,000 IU/fortnight + placebo versus Ca 500 mg/d + placebo versus placebo</td>
<td>6 months</td>
<td>No differences in muscle strength between the groups.</td>
</tr>
<tr>
<td>RCT</td>
<td>Coglia and Harris (2013) [21, 27]</td>
<td>21</td>
<td>Females with limited mobility</td>
<td>78</td>
<td>4000 IU/d vitamin D</td>
<td>4 months</td>
<td>Increase of intramyonuclear VDR concentration. Increase in muscle fibers.</td>
</tr>
<tr>
<td>RCT</td>
<td>Wyon et al. (2014) [47]</td>
<td>24</td>
<td>Elite ballet dancers</td>
<td>28</td>
<td>2000 IU/d vitamin D versus placebo</td>
<td>4 months</td>
<td>Increased muscle performance and less injury.</td>
</tr>
</tbody>
</table>
Summary of RCT and meta-analysis regarding effects of vitamin D on muscle function and falls continue

<table>
<thead>
<tr>
<th>Type of study</th>
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<tr>
<td>Meta</td>
<td>Muir and Montero-Odasso (2011) [54]</td>
<td>2268 (13 RCTs)</td>
<td>Elderly males and females (age &gt;65)</td>
<td>78</td>
<td>Vitamin D supplementation</td>
<td></td>
<td>Beneficial effects on strength and balance.</td>
</tr>
<tr>
<td>Meta</td>
<td>Stockton et al. (2011) [55]</td>
<td>5072 (17 RCTs)</td>
<td>Males and females of all ages</td>
<td>NA</td>
<td>Vitamin D supplementation</td>
<td></td>
<td>Increase in muscle strength in adults with baseline vitamin D &lt;25 nmol/L.</td>
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<tr>
<td>RCT</td>
<td>Bischoff et al. (2003) [63]</td>
<td>122</td>
<td>Elderly females</td>
<td>85</td>
<td>Ca 1200 mg and 800 IU/d vitamin D versus Ca 1200 mg/d</td>
<td>12 weeks</td>
<td>Reduced risk of fall.</td>
</tr>
<tr>
<td>RCT</td>
<td>Pfeifer et al. (2009) [62]</td>
<td>242</td>
<td>Community-dwelling elderly males and females</td>
<td>77</td>
<td>800 IU/d vitamin D + Ca 1000 mg/d versus Ca 1000 mg/d</td>
<td>12 months</td>
<td>Reduced number of falls and improvement in muscle function.</td>
</tr>
<tr>
<td>Meta</td>
<td>Gillespie (2003)</td>
<td>461 (3 RCTs)</td>
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<td>Meta</td>
<td>Bischoff-Ferrari et al. (2004) [66]</td>
<td>10001 (10 RCTs with sensitivity analysis) 1237 (5 RCTs without sensitivity analysis)</td>
<td>Elderly males and females, age &gt;65</td>
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<td>Vitamin D supplementation</td>
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<td>Meta</td>
<td>Michael et al. [64] (2010)</td>
<td>5809 (9 RCTs)</td>
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<td>Meta</td>
<td>Murad et al. (2011) [65]</td>
<td>45782 (26 RCTs)</td>
<td>Males and females (all ages)</td>
<td>NA</td>
<td>Vitamin D + Ca supplementation</td>
<td></td>
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</tbody>
</table>

Overall, data from RCT and metanalysis support:
- a positive effect of daily vitamin D supplementation on muscle function,
- especially in older individuals with vitamin D insufficiency/deficiency at baseline.

-A daily dose of 1000 UI appears to be sufficient to obtain significant improvements.

In contrast, large intermittent doses of vitamin D do not appear to be efficient at improving muscle strength.

Relationship between Vitamin D Status, Muscle, and Falls
Clinical effects of vitamin D on muscles, gait and falls.
Summary of RCT and meta-analysis regarding effects of vitamin D on muscle function and falls continue

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</table>

• The Endocrine Society Clinical Practice Guidelines recommends vitamin D supplementation depending on age and clinical circumstances, in particular in order to prevent falls in populations at risk.

• However, the effects of vitamin D on the prevention of falls are still a matter of debate due to conflicting interpretation of data.

• *Rationale and design of the Study to Understand Fall Reduction and vitamin D in You (STURDY): A randomized clinical trial of vitamin D supplement doses for the prevention of falls in older adults.*

  Contemp Clin Trials. 2018 Aug 20. pii: S1551-7144(18)30316-1
Vitamin D and Frailty?
The term “frailty” popular in geriatric medicine but its definition is vague.

In Oxford dictionary “the condition of being weak and delicate.”

A more precise definition is given by Fried who defined frailty as

“a biologic syndrome of decrease reserve and resistance to stressors that results from cumulative declines across multiple physiologic systems and causes vulnerability to adverse outcomes.”

Association of Vitamin D and Frailty

• Overall, a clear association between vitamin D level and frailty has been demonstrated.

• Interplays between vitamin D status, frailty, and mortality appear plausible.

• Whether vitamin D supplementation in frail subjects may reduce mortality is challenging and needs to be investigated in the future.

Conclusion

• Vitamin D supplementation has beneficial effects on muscle strength, balance, and gait in diverse settings including adolescents, the elderly, and CKD patients.

• However, the effects of vitamin D on the prevention of falls are still a matter of debate due to conflicting interpretation of data.

• Differences in the dose of supplementation, type of vitamin D, and discrepancies in the threshold to define vitamin D deficiency/insufficiency may partly explain these disagreements.
Conclusion

• Vitamin D supplementation is safe and inexpensive,

• it is worthy to recommend vitamin D supplementation in patients at risk for falls, such as elderly patients, nursing home residents, frail patients with gait and balance and visual impairments, and patients with chronic diseases.

• These patients are most likely to have low levels of vitamin D and muscle loss/dysfunction, thus justifying supplementation independent of a putative effect on the prevention of falls.
Future considerations

• The key research agenda moving forward is to
  - define more precisely the level of 25-hydroxyvitamin D at which adverse skeletal effects on the skeleton become apparent,
  - and to determine whether levels optimal for bone are also optimal for extraskeletal tissues.

• These data will determine who is vitamin D deficient and likely to benefit from supplementation, and the form such supplementation should take.