Gynäkologe 2015 · [Suppl 1]: 48:S1–S5
DOI 10.1007/s00129-015-3727-7
Published online: 17 June 2015

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Role of vitamin D in postmenopausal bone health

English Version

Epidemiology of fractures in postmenopausal women

After age 75, hip fractures are the most frequent type of fracture. Up to 50 % of postmenopausal women suffering a hip fracture will have permanent functional disability, 15–25 % will require long-term nursing home care, and up to 20 % will die within the first year after the event [1–10]. The exponential increase in hip fractures after age 75 translates into an estimated 1 in 3 women who will have sustained a hip fracture by their ninth decade of life [11].

Similar to hip fractures, the two other most common nonvertebral fractures – distal forearm and proximal humerus fractures – show a steep increase with age [12]. A further 1 in 3 women will have a prevalent vertebral fracture at age 80 [13]. Vertebral fractures also cause disability, back pain, [14], and decreased quality of life [15]. Postmenopausal women with a first vertebral fracture have a more than 19 % risk of developing a second vertebral fracture in the subsequent year [16]. Further, they have a 2.5-fold increased risk for any subsequent fracture [17], and a 2.8-fold increased mortality rate within the following 10 years [18]. Compared with hip fractures, the epidemiology of vertebral fractures is challenging with less than 30 % of vertebral fractures coming to clinical attention [19].

Vitamin D supplementation and fracture reduction in postmenopausal women

Vitamin D is essential for bone growth [20, 21] and preservation [22], and higher 25-hydroxyvitamin D [25(OH)D] levels are associated with higher bone density in younger and older adults [23]. Moreover, in double-blind randomized controlled trials (RCTs) among adults aged 65 and older, vitamin D supplementation increased bone density and reduced bone loss [24, 25].

Regarding the effect of vitamin D supplementation on fracture risk, the data from several study-level meta-analyses and two pooled individual participant-level (IPD) analyses are conflicting. While one trial-level meta-analysis of double-blind (RCTs suggested an 18 % reduction of hip fractures and 20 % reduction of any nonvertebral fractures at a received dose of no less than 482 IU vitamin D per day [26], three study-level meta-analyses [27–29] and one pooled IPD analysis [30] of open-design and blinded trials suggested that vitamin D may have a neutral effect on total fractures [27] or may reduce hip fractures by 7–16 % independent of its dose if combined with calcium supplementation [27–29]. Finally, in the most recent 2012 pooled IPD analysis of 31,022 primarily postmenopausal women enrolled in double-blind RCTs on vitamin D, only an actual intake of 792–2,000 IU per day reduced the risk of fracture, with no benefit seen at a lower dose [31]. At the high intake range (median 800 IU per day), hip fracture risk was reduced by 30 % [31]. The discordant findings may in part be explained by different inclusion criteria of trials with respect to blinding and intake form (oral, injectable), or different accommodations for adherence. A dose–response relationship between vitamin D and fracture reduction as documented in the 2009 meta-analyses of double-blind RCTs [26] and the 2012 IPD pooled analysis [31] is supported by epidemiologic data showing a significant positive trend between serum 25(OH)D concentrations and hip bone density [23] and lower extremity strength [32, 33].

Factors that may obscure the benefit of vitamin D are low adherence to treatment [34], low dose of vitamin D, or the use of less potent vitamin D_2 [35, 36]. Furthermore, open-design trials [37] may bias results toward a null effect because participants who know that they have been randomized to the control group may purchase vitamin D themselves as it is available without prescription.

The inclusion of mixed-quality studies may explain the recent findings and conclusion of the 2014 sequential meta-analysis by Bolland and colleagues [38, 39] that vitamin D may not be effective in fracture reduction. The authors included many studies that had little chance of demonstrating the true potential benefits of vitamin D. In particular, their analysis was based on a great mix of trials with blinded and open designs, follow-up periods that were often too short, administered doses that ranged widely, compliance that ranged widely, and endpoints that ranged from primary to secondary to un-prespecified, and consequently were adjudicated and nonadjudicated. The authors also chose to carry out their sequential meta-analysis with the goal of detecting a 15 % effect threshold for most outcomes and 5 % for mortality. We question this approach, as even

The German version of this article can be found at doi: 10.1007/s00129-015-3723-y.

small effects carry an enormous benefit if an inexpensive intervention such as vitamin D is implemented broadly. In fact, for vitamin D plus calcium, the authors themselves document a significant 8 % reduction in total fractures and a significant 16 % reduction in hip fractures. Further, the authors document a significant 4 % reduction in overall mortality with vitamin D alone or in combination with calcium, which is particularly notable in the context of the limitations of the studies included. A fair question of a clinician may be, „Do I really stop supplementation with vitamin D when it has a significant reduction of hip fracture by 16 % (in conjunction with calcium) and of mortality by 4 % but not 5 %?" Notably, on a public health level, a 4 % reduction of mortality generates an enormous population benefit.

Risk factors for vitamin D deficiency

Most vulnerable to vitamin D deficiency are older adults [40, 41], individuals living in northern latitudes with prolonged winters and thus low UVB exposure [42, 43], obese individuals [44], and individuals of all ages with a dark skin tone [23, 45, 46]. Other risk factors include medical conditions such as malabsorption and the use of anti-epileptic drugs [4].

Optimal 25(OH)D level for fracture prevention in postmenopausal women

A threshold for optimal serum 25(OH)D concentration and fracture prevention has been addressed in a recent benefit–risk analysis [47]. Based on data from RCTs and their achieved 25(OH)D levels in the treatment group, 75 nmol/l (30 ng/ml) is suggested as the best point estimate for an optimal threshold of 25(OH)D for fracture prevention. This threshold is further supported by epidemiologic data for hip bone density in younger and older adults [23], as well as a large bone-biopsy study in which mineralization defects were absent with serum levels of at least 75 nmol/l [48]. Also, the most recent pooled IPD analysis of double-blind RCTs found that among over 4,000 primarily postmenopausal women, fracture risk declined significantly with higher baseline 25(OH)Ds levels [31]. Comparing individuals with starting levels of less than 30 nmol/l with those on starting levels of 61 nmol/l and above, the latter group had a 37 % lower risk of hip fracture and a 31 % lower risk of any nonvertebral fracture [31].

The 25(OH)D threshold of at least 75 nmol/l (30 ng/ml) for optimal fracture prevention is supported by the 2010 IOF position statement on vitamin D [2] and the 2011 US Endocrine Society Task Force on Vitamin D [4]. By contrast, the 2010 Institute of Medicine recommendations suggest that 50 nmol/l may be sufficient for bone health in the population, although (1) no single trial that reached 50 nmol/l in their treatment group achieved fracture reduction, and (2) in their fracture assessment section the IOM report reads that only studies that achieved 25(OH)D levels of at least 75 nmol/l showed significant fracture reduction [49]. Current intake recommendations of 800 IU vitamin D per day will shift over 97 % of postmenopausal women to at least 50 nmol/l and about 50 % to 75 nmol/l [49, 50].

Abstract · Zusammenfassung

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Abstract

Fractures contribute significantly to morbidity and mortality of postmenopausal women. Among postmenopausal women aged 60 years and older, the mortality-adjusted residual lifetime risk of fracture has been estimated to be 44–65 %. Thus, effective strategies are urgently needed to prevent fractures among postmenopausal women. This review summarizes the available evidence that supports vitamin D3 supplementation at a dose of 800 IU per day as a strategy to reduce falls and fractures, including hip fractures, among postmenopausal women by about 20–30 %. This recommendation is supported by the Position Statement on Vitamin D of the International Osteoporosis Foundation, the 2011 World Osteoporosis Day Report, and the US Endocrine Society. Further, this recommendation is supported by the high prevalence of vitamin D deficiency among postmenopausal women. The prevalence of vitamin D deficiency (serum levels below 50 nmol/l or 20 ng/ml) among younger and older postmenopausal women has been found to be about 50 % in many countries around the world, with the highest prevalence (80 %) in older women with hip fractures.

Keywords

Menopause · Osteoporosis · Fractures · Fall events · Calcium

Vitamin D und postmenopausale Knochengesundheit. Englische Version

Zusammenfassung

Knochenfrakturen tragen in signifikantem Ausmaß zu Morbidität und Mortalität in der Postmenopause bei. Schätzungen des mortalitätsadjustierten Frakturrisikos in der verbleibenden Lebenszeit für Frauen im Alter ≥60 liegen zwischen 44 und 65%. Unbedingt notwendig sind also effektive Präventionsstrategien. Im Review-Beitrag wird die verfügbare Evidenz zur Vitamin-D3-Supplementierung (800 I.E. täglich) für eine 20- bis 30%ige Reduzierung von Sturzereignissen und (Hüft-)Frakturen bei postmenopausalen Frauen zusammengefasst. Diese Empfehlung wird gestützt von Positionspapieren der International Osteoporosis Foundation, des 2011 World Osteoporosis Day Report und der US-amerikanischen Endocrine Society, ferner von der hohen Prävalenz eines Vitamin-D-Mangels bei postmenopausalen Frauen. Die Vitamin-D-Mangel-Prävalenz (Serum-Konzentrationen <50 nmol/l bzw. 20 ng/ml) bei jüngeren wie älteren postmenopausalen Frauen wurde in vielen Ländern weltweit mit etwa 50 % angegeben, am höchsten (80 %) war sie bei älteren Frauen mit Hüftfrakturen.

Schlüsselwörter

Menopause · Osteoporose · Frakturen · Sturzereignisse · Kalzium

Infobox 1 Key messages

1. Vitamin D supplementation reduces the risk of fracture; however, this benefit is dose dependent. All recent recommendations support 800 IU vitamin D per day for fracture reduction.
2. Vitamin D reduces fracture risk through both its benefit on bone and its effect on fall reduction.
3. To achieve optimal fracture reduction, a 25(OH)D threshold of at least 61 nmol/l and ideally 75 nmol/l may be warranted.

Vitamin D benefits in fracture prevention and the effect of vitamin D on muscle

The beneficial effect of vitamin D on calcium absorption and bone mineral density may not be the only explanation for its protective effect against fractures [26]. In fact, vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur [51].

Four lines of evidence support the role of vitamin D in muscle health. *First*, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [52]. Clinical findings in vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as a waddling way of walking [53]. *Second*, the vitamin D receptor (VDR) is expressed in human muscle tissue [54–56], and VDR activation may promote de novo protein synthesis in muscle [56–58]. Mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [59, 60]. *Third*, several observational studies suggest a positive association between 25(OH)D and muscle strength or lower extremity function in older persons [32, 33]. *Fourth*, vitamin D supplementation increases muscle strength and balance [61, 62], and reduces the risk of falling in community-dwelling individuals [62–64], as well as in institutionalized individuals [61, 65], in several double-blind RCTs summarized in a 2009 meta-analysis [66].

Thus, relevant to fracture prevention in older postmenopausal women, vitamin D supplementation for fall prevention should not be delayed. This suggestion is in line with the Agency for Healthcare Research and Quality (AHRQ) of the US Preventive Services Task Force [67], the 2010 American Geriatric Society/British Geriatric Society Clinical Practice Guideline [68], the 2010 assessment by the IOF [2], and the 2011 Endocrine Society Recommendations, all four of which identified vitamin D as an effective intervention to prevent falling in older adults.

Amount of vitamin D needed to overcome vitamin D deficiency

Most healthy adults overcome vitamin D deficiency by reaching 25(OH)D serum concentrations of about 50 nmol/l with 600–800 IU vitamin D per day [50, 69]. Among healthy postmenopausal white women, a recent multidose comparison suggested that a dose of 1,600 IU per day may be sufficient for 97.5 % of the study population to reach 75 nmol/l [69]. Notably, however, this dose has not been tested for fracture prevention.

Conclusion

Postmenopausal women have a high risk of vitamin D deficiency and vitamin D is relevant to bone and muscle health, as supported by several lines of evidence summarized in this review article. Meta-analyses of double-blind RCTs provide strong support for vitamin D supplementation at a dose of 800 IU per day in postmenopausal women for fall and fracture prevention.

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Compliance with ethical guidelines

Conflict of interest. Heike Bischoff-Ferrari declares that she has no conflict of interest.

This article does not contain any studies with human participants or animals performed by any of the authors.

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