Literature review

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Vitamin K and hip fractures: what do we know?

Abstract

Hip fractures remain highly prevalent oftentimes life-threatening events among older populations, despite years of multiple related preventive endeavors. In an effort to explore options for mitigating hip fracture disability and premature death, this mini-review strove to examine whether: 1) Vitamin K, an important dietary compound is a potentially important hip fracture determinant, and 2) whether more research and consideration of this vitamin is warranted. After exploring relevant data concerning this topic as extracted from three well-established preselected electronic data bases housing English language research or commentary reports published over the last 20 years (2000-2022) it is concluded that more intense and thoughtfully designed research to examine the multiple ways vitamin K may mediate bone health, may help towards reducing the persistent global age-associated hip fracture burden and its immense associated human and social costs.

Keywords: bone health, fractures, bone mineral density, hip fractures, intervention, prevention, supplementation, vitamin k1, vitamin k2

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Abbreviations: PK/K1, Phyloquinone; MKn/K2, Menaqionones; K3, Menadione

Introduction

According to Emmerson et al.,[1] fractures of the hip, common among the elderly, are not only painful and costly, [2]but also highly disabling, and commonly severely impede the ability of the older adult to live independently, while raising the risk of premature mortality, especially among men,[3] and adults with a number of comorbid health conditions, including renal disease.[4] However, to date, preventive programs that mostly focus on obviating falls risk, including balance and strength training, plus various pharmacologic and environmental management strategies are often not employed,[5] and/or less than optimally effective as a whole, especially at preventing subsequent or second hip fractures.[4,5] Yet it is possible that a more targeted program of intervention designed to not only avert falls, but to foster underlying bone strength and bone protection through inherent non pharmacologic mechanisms, rather than any pharmacologic approach that may be less than effective in preventing many hip fractures,[5] while inducing possible undesirable side effects would be clinically desirable. In this respect some evidence acquired over the past 20 years points to a possible favorable supportive impact of the presence of sufficient levels of vitamin K, or its three variants, known as Phyloquinone [PK/K1], Menaqionones [MKn/K2] and Menadione [K3][3,6,7] given that the elderly may have more challenges to maintain endogenously produced vitamin K subtypes that are unique, and/or may possibly be malnourished or unable to access foods containing vitamin K readily and consistently.[8] They may be especially likely to have a vitamin K deficiency if they have renal disease or diseases that impede vitamin K synthesis and absorption.[4]

Review aims

Since bone fractures, such as those that occur readily at the hip joint in older populations are potentially affected to a considerable degree by vitamin K1 and K2 due to its potential influence on bone mineral density, bone turnover, and bone fragility,[6] this report examined the weight of the evidence that has emerged since 2000 when it was observed that low vitamin K intakes may increase hip fracture risk in women.[9] In this regard, this current mini review aimed to examine the degree of support for the idea that vitamin K is a possible adjunctive factor that could help to foster hip fracture prevention and rehabilitation efforts.[10] It also aimed thereby to establish whether a need exists for more research in this realm, and if so in what regard. Whether vitamin K, a collective term for a family of fat soluble vitamins and its supplementation will reduce the rate of bone loss in postmenopausal women remains a matter of debate.[11]

Materials and methods

To obtain the desired data to fulfill the study aims, an extensive scan of available documents housed in the PUBMED, Scopus, and WEB of SCIENCE CONSOLIDATED, including most full length articles published in English and derived from research conducted as of January 2000 up until March 2022 using the key terms Vitamin K and Hip Fractures and others outlined in Table 1 were sought. After scanning the available article listings those that addressed some aspect of the current topic of interest were specifically selected, downloaded and scrutinized in more depth by the author without regard to research design. After reviewing the available data, it was clear that no systematic overview of such a limited diverse data base was possible and would not be of sufficient value for definitively advancing current practice or research. Hence, while it is acknowledged that the present body of data may not be exhaustive-and that others have attempted meta-analyses or aggregate reviews on a similar theme, it was felt a more qualitative descriptive approach was the only approach that could possibly help to highlight any trends and tentative conclusions regarding this relatively uncharted topic. To this end, a narrative tabular descriptive approach to highlight the material deemed to meet the basic review aims is presented, rather than any aggregated approach.

Results

General observations

As of March 2022, the data examined and that covered all years between 2000-2022 with no restrictions revealed only a small number of directly relevant studies of approximately 133 associated articles listed under the key words vitamin K and hip fractures, with very limited numbers being published in the past 5 years, and especially if compared to the wider array of allied themes such as vitamin D and

hip fractures that included at least 1593 articles dating back to 2000. Among those articles of current interest that were published between 2000 and 2022 on vitamin K and hip fractures or allied themes, articles that appeared pertinent to fulfilling the present review aims were duly accessed and carefully reviewed. [see Table 1 for recent publication numbers in the context of the current topic of interest].

Although limited in number and quite diverse, the data accessed and deemed salient do show however, that measures of vitamin K 1 present in the serum are linked to the vitamin K status of bone and that some evidence points to low vitamin K concentrations being associated with an increased fracture risk in the older population. In addition, the presence of vitamin K at adequate serum concentrations appears to an accepted cofactor that is required for the formation of bone building proteins such as gamma-carboxyglutamate [Gla] residues secreted by osteoblasts and that include: osteocalcin, matrix Gla-protein, and protein S, These proteins are reportedly important because the primary component of each is said to be uniquely bound structurally to the bone matrix thus strengthening the bone structure.[6] However, a deficient vitamin K status, may disrupt this bonding process and is not unsurprisingly associated with an increased risk of osteoporotic bone fractures.[11] As well, the bone protein osteocalcin tends to be less completely carboxylated in adults with low vitamin K serum concentrations, such as many hemodialysis patients with a history of bone fractures, including hip fractures.[10]

Additional studies over time have demonstrated that vitamin K can both increase bone mineral density in osteoporotic situations, as well as being able to actually reduce fracture rates.[12] Further, there is evidence in human intervention studies that vitamins K and D, a classic in bone metabolism, work synergistically on bone density,[12] and results of several studies have indicated a statistically significant inverse association to exist between dietary vitamin K intake and fracture risk.[13] In addition, a dose–response analysis indicated that the pooled relative risk of fracture was 0.97 in response to an increase of 50 μg of dietary vitamin K intake per day, and was reportedly 0.76 in studies with more than 10 years of follow-up, thus revealing fairly strong support for the ability of a higher dietary vitamin K intake to moderately impact the risk of fracturing a bone, [13] even though this has been disputed as lacking sufficiently strong evidence.[14]

Thus, although disputed by some,[14] it seems hard to refute a more general prevailing consensus that vitamin K is an important fat soluble vitamin and co-factor for fostering bone mass, and may be an especially important nutrient to target in efforts directed towards preventing excess bone loss leading to hip fragility fractures in the elderly. Other benefits that appear relevant to a possible role for vitamin K in the context of reducing hip fracture risk are: its role in mediating blood homeostasis, while being implicated in chronic low-grade inflammatory processes and diseases such as cardiovascular disease, osteoarthritis, dementia, cognitive impairment, mobility disability, and frailty among the elderly,[15,16] Vitamin K2 may also be harnessed to foster bone healing,[17,18] thus offering clinicians a promising and low-cost strategy for reparative osteogenesis.

Other data show hip fracture risk and post injury recovery, while largely related to falls injuries and possible neurological and comorbid disease factors, also strongly implicates nutrition and a necessity for improving bone health secondarily post hip fracture.[19]

Research observations

As outlined briefly above, several diverse studies conducted over time have shown vitamin K may impact bone metabolism, as well playing a more established role in blood coagulation processes.[8] Moreover, current research reveals vitamin K is in fact required for osteocalcin carboxylation that in turn regulates bone mineral accretion, while its presence is able to promote the transition of bone osteoblasts to osteocytes, as well as limiting the process of osteoclastogenesis.[8] Vitamin K may also inhibit bone resorption, plus osteoclast like cell formation.[20] These actions that can inhibit bone loss, along with vitamin K administration found to increase osteoblast like actions, as well as bone mineral density in cases of osteoporosis,[20] can potentially have a marked effect on preserving bone mass in cases vulnerable to vitamin K deficiencies.[6] An additional related role for vitamin K points to a favorable influence not only on osteoporosis risk, but on hip fracture risk and injuries, as well surgical outcomes post hip fracture,[21] other pathological fractures and vascular calcifications [22] due to its effect on bone turnover physiology and profiles.[23]

Another report has revealed that a low intake of vitamin K is associated with an increase in bone deterioration,[8] as well as the risk of hip fracture in the general population. However, while treatment with vitamin K may reduce the relative risk for non vertebral and hip fractures, more study is needed to overcome multiple design limitations and others that prevail.[8]

As per Capozzi et al.,[24] however, given that vitamin K may be important for harnessing the bone building effects of calcium and vitamin D, and thereby possibly crucial to the maintenance of skeletal health, its supplementation where deficient might yet improve bone quality and reduce fracture risk in the osteoporotic older patient, even if not conclusive. Villa et al.,[25] tend to agree that the commonly used dosage of vitamin K 2 in human studies of 45 mg/day and its application may indeed benefit bone as well as vascular health, especially among osteoporotic post-menopausal women, despite being poorly studied. Shah et al.[26] however, conclude that the current evidence from randomized controlled trials is not strongly supportive of vitamin K supplementation in older adults for the intent of improving bone health, although food limitations that might include foods lacking vitamin K are found to be involved in mediating bone health.[27]

Shiraki et al.,[20] who studied 241 osteoporotic patients in a 24-month randomized open label study wherin the vitamin K2–treated group received a vitamin K analog known as MK-4 (menatetrenone) in doses of 45 mg per day delivered orally showed the treatment enhanced vitamin K dependent bone Gla protein γ-carboxylation processes, a marker of bone formation,[28] while markers of bone turnover were unchanged.. Other data verify serum vitamin K1 is associated with fracture risk and hip bone structural features in post-menopausal osteoporosis.[29] That is, serum vitamin K1 was significantly lower in the group with fractures and was independently associated with fracture risk deemed possibly related to its effects on bone strength. Other evidence implies that vitamin K mediates osteocalcin development through well defined biochemical pathways-and if deficient may yet foster an increased risk of femoral neck fractures or reduce healing potential.[30,31] As such, it may be that higher concentrations of serum vitamin K1 may be required to generate vitamin K's skeletal effects. Booth et al.,[32] suggest vitamin K, is indeed associated with bone mineral density estimates as well as the risk of hip fracture.

Mott et al.,[33] on the other hand found that for post-menopausal or osteoporotic patients, there is no evidence that vitamin K affects bone mineral density or vertebral fractures, but it may reduce clinical fractures, even though available studies examining on a role for vitamin K in mediating osteoporosis may well differ.[34,35] In addition to possibly benefitting general wellbeing, bone and vascular health,[36] especially with regard to osteoporotic post-menopausal women, where bone tissue is weak and readily subject to fractures in the face

of minimal trauma[25,36] vitamin K may also improve bone health among haemodialysis patients with end stage kidney disease.[22]

The application of vitamin K supplements may however, have to account for the differential impact of vitamins K1 and K2, as well as vitamin K4 and their possible role in reducing the risk of fracturing a bone such as the hip. Apalset et al.,[37] found that it was a low vitamin K1 intake, but not vitamin K2 that was associated with an increased risk of sustaining a hip fracture. This finding is also supported by Vergnaud et al.,[38] while a systematic review of vitamin K usage to prevent fractures in older women showed the base-case results did tend to favor vitamin K1, but this relied on many assumptions.[39] Vitamin K4 even in very low doses also improved bone status among post menopausal osteoporotic women who regained bone marker levels associated with healthy pre menopausal women with no side effects.[40] Applications of vitamin K 7 supplementation also significantly decreased the age-related decline in bone mineral density and bone strength. in postmenopausal women.[31] Others however, have found either no association between dietary vitamin K intake and fracture risk in Chinese cases[41] or other cases.[36] While these data provide moderate albeit non conclusive evidence at best, a brief summary of some of these key findings shows this topic may yet imply there is value in further exploration of this topic [see Table 2].

Table 1 Summary of Numbers of articles posted at key data bases as reported between January 1, 2018-March 2022 [past 5 years] showing variations across and within databases as regards current topic and related themes

Keywords	Data base		
	PubMed	Scopus	Web of science
Hip Fractures	38,815	54974	68817
Vitamin K	109142	303379	712689
Hip Fracture Prevention Strategies	904	760	1368
Vitamin K + Osteoporosis	690	1584	1886
Vitamin K + Hip Fractures	59	218	285
Vitamin K + Falls Injuries	21	72	227
Vitamin K Deficiency + Hip Fractures	13	50	50
Vitamin K Supplementation + Hip Fractures	3	38	49

Table 2 Table showing possible benefits of ensuring/attaining optimal serum vitamin k levels in efforts to ameliorate hip fracture correlates in most related studies, albeit not all *

Researchers	Key findings
Apalset et al.[37]	A low intake of vitamin K1, but not vitamin K2*, was associated with an increased risk of hip fractures.
Bulio et al.[42]	A low dietary vitamin K intake was associated with a low bone mineral density in women of all ages.
Bultynck et al.[21]	The prevalence of a subclinical vitamin K deficiency on admission was 36% (20/55) based on reference range of > 0.15µg/L
	The proportion with a subclinical K deficiency after surgery rose to 64% (35/55), $p < 0.05$.
	The prevalence of vitamin K deficiency in hip fracture patients is high and increases further following a short period of fasting.
Cockayne et al.[43]	Supplementation with vitamin K reduces bone loss. Moreover, the vitamin K4 derivative has a strong effect on incident fractures among Japanese patients.
	Adults at risk for fractures should be encouraged to consume diets rich in vitamin K even if routine supplementation is not yet justified*.
Finnes et al.[44]	The combination of low concentrations of both vitamin D and vitamin K1 is a significant hip fracture risk factor.
Fusaro et al.[45]	Vitamin K, mainly known as an agent involved in blood coagulation, has recently been shown to be implicated in bone health.
	Conversely, epidemiological studies have suggested a lack of vitamin K may be associated with several diseases, including osteoporosis.
Gigante et al.[46]	Supplementation with vitamin K7, along with vitamin D3 and a combination of both was able to modulate the expression of genes involved in both mineralization and angiogenesis.
	Vitamin K7 enhanced the observed vitamin D3 effects on osteoblast precursors in a stem cell model.
Iwamota et al.[47]	Vitamin K supplementation at high doses has a positive effect on the postmenopausal skeleton including a reduced incidence of fractures.
Knapen et al.[31]	Next to an improved vitamin K status, vitamin K7 supplementation significantly decreases the age-related decline in bone mineral density and bone strength.
	Low-dose vitamin K7 supplements may help prevent bone loss in postmenopausal women.
Kohlmeyer et al.[10]	Serum vitamin K levels are linked to bone status.
Mott et al.[33]	For post-menopausal or osteoporotic older adults, there is no evidence that vitamin K affects bone mineral density or vertebral fractures*.
	Vitamin K may however, reduce clinical fractures.

Table Continued...

Researchers	Key findings
Nakano et al.[48]	A study of a total of 147 Japanese hip fracture male and female cases [n=99] and controls [n=48] showed hip fracture cases to have vitamin D and K deficiencies independent of general malnutrition.
	Plasma concentrations of vitamin K1 and menaquinone-7 (vitamin K7) were significantly lower in the fracture group than in the control group in both genders.
	Circulating vitamin K serum concentrations were significant predictors of fracture risk, with higher concentrations associated with a decreased fracture risk.
Moore et al.[29]	Vitamin K appears to impact hip fracture risk by enhancing bone strength and hip bone structure, especially as regards the narrow neck of the femur, a consistent hip fracture site.
	Higher concentrations of serum vitamin K1 may be required for vitamin K's skeletal effects compared to its coagulation needs.
Shiraki et al.[20]	A 24-month controlled trial of 241 osteoporotic patients and 121 controls showed 45 mg/day of vitamin K2 treatment effectively prevented new fracture occurrences.
	Furthermore, vitamin K2 treatment enhances the vital γ-carboxylation of the osteocalcin bone protein molecule.
Torbegsen et al.[49]	Vitamin K1 and vitamin D are lower in hip fracture patients compared with controls and independently associated with incurring the risk of a hip fracture.
Tsugawa et al.[50]	Among the organs that produce vitamin K-dependent proteins, bone has attracted the most recent attention.
	Most consistently associated with bone fractures, vitamin K treatments that address vitamin K deficiency and that are believed to promote bone health yield conflicting conclusions*.
	Low vitamin K was observed to be a fracture predictor among the 379 health Asian women who were studied.
Yaegashi et al.[51]	Low vitamin K concentrations correlated with increased fracture risk.
	Increased vegetable intakes may decrease the extent of any hip fracture risk in susceptible Japanese elders in the future.
Weber et al.[12]	In addition to vitamin K2, low dose vitamin K1 supplements may benefit bone health when co-administered with vitamin D.
	Increasing evidence also shows vitamin K can positively affects calcium balance, a key mineral in bone metabolism.

Discussion

Hip fractures, an ongoing major health concern among aging populations may not only severely restrict mobility and independence, but may increase the risk of premature mortality. [19] Often associated with an elevated risk of multi morbidity, possible subsequent hip fractures, pain, enormous medical and social costs, and slow recovery rates in survivors, it is possible a host of lifestyle factors, including associated nutrition intakes play a causative and/or mediating role in this negative cycle of health events found in hip fracture patients as outlined by Fusaro et al.,[6] and Mortensen et al.,[52] In addition, even if not considered by Fiatarone Singh[53] to be relevant in efforts to address hip fracture recovery, a persistently deficient food intake, and related cardiovascular complications may well impact hip fracture mortality risk[54] as well as bone blood supply.[54] As well, osteoporosis found to often accompany hip fracture injuries may ensue[52,54,55] in the absence of adequate vitamin K1[56] especially in those cases who are already vitamin K compromised.

By contrast, efforts to limit or prevent osteoporosis while raising vitamin K levels to desired levels, and which have been observed to be safe and to mostly affect bone quality, rather than bone mineral density, may yet have a positive impact on bone mineral density.[6,22] Vitamin D status affecting bone health may also be impacted by the degree of available vitamin K as may femoral neck bone status and fracture risk.[57,58,64] Moreover, treating osteoporotic patients with vitamin K may have the additional advantage of protecting arteries from vascular calcification, which might prove particularly important in those patients with chronic kidney disease, where other treatments for osteoporosis, such as biphosphonates or hormone therapy, may be riskly to apply, but where subjects are at high risk for fracturing a hip especially if they have advanced osteoporosis.[61]

Vitamin K administration may also be helpful in speeding up hip fracture recovery in cases taking wafarin medication,[62] as well as for protecting against fractures in postmenopausal women with osteopenia.[59] That is, even if not all studies have been examined in this report, and their quality cannot be ensured, far fewer report vitamin K presence to be of no relevance to multiple aspects of bone health including bone metabolism, and bone quality than not. It has also been suggested if more efforts are directed towards examining why circulating osteocalcin is undercarboxylated in elderly women,[63]and the clinical relevance of vitamin K in this regard, this will prove highly insightful in the context of osteoporosis and hip fracture prevention.[35,65,66] More research to unravel vitamin K effects on bone tissue molecular actions such as its ability to link calcium and vitamin D actions on osteocalcin gene translation.[67] and extra-cellular matrix mineralization, among other metabolic processes [60] will also prove valuable in all likelihood.

In the interim, while mechanistic studies are largely all indicative of multiple and important bone associated vitamin K linkages, clinical studies are inconsistent on most points in this respect, regardless of year of study, and samples examined. As well this body of clinical research that has emerged from the body of knowledge although promising is highly diverse, ranging from deficiency effects of vitamin K in the context of bone health and fractures, to its possible health associated anti coagulant and cardiovascular effects, to its supplementary effects, and they thus precluded any in depth systematic analysis. There is also a lack of intense or focused study on the molecular actions of vitamin

K on bone cells from both healthy as well as damaged or fractured bone to advance our understandings and specific implications of the current knowledge base. Another current limitation is arriving at any comprehensive conclusive set of understandings on the current topic is the common failure to distinguish various vitamin K subtypes and their independent or interactive mechanisms that may impact bone structure and metabolism, as well as the highly heterogeneous samples and research methodologies.

Nonetheless, it appears plausible to hypothesize that the pathways below if subject to careful well designed study designs will enable researchers to rule out competing conclusions and arrive a more conclusive set of highly needed understandings**.**

In the interim, and based on what we do know, it appears reasonable to encourage hip fracture preventive program organizers to not overlook the utility of ensuring their vulnerable elderly clients are able to obtain foods that incorporate adequate vitamin K levels on a daily basis, and/or make these or supplements available, if necessary. Educators and care givers of the elderly can be especially helpful in this often neglected realm in this regard in our view by carefully expounding upon the importance of maintaining adequate vitamin K serum levels since these may be implicated in numerous essential physiological processes, including bone maintenance, and directing these older adults accordingly. The possible utility of combining vitamin K and vitamin D in the context of hip fracture prevention should also be highlighted to avert the hypothesized downward cycle of irreversible health negating events shown in Figure 1 below.

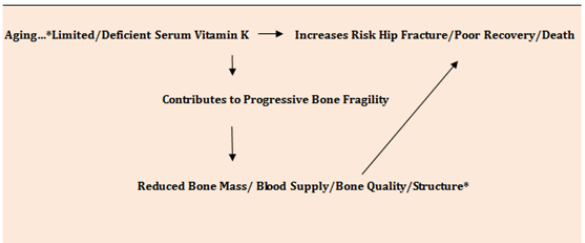

Figure 1 Points* at which vitamin K or a lack thereof may influence the hip fracture risk cycle. [20,29,38,54,55,60,64,65,68]

Conclusion

Based on an in depth examination of the research published over the last 20 years, it is clear:

Hip fractures, which produce high levels of mortality and morbidity remain a major challenge to treat, and prevent despite multiple laudable programs to address this issue, most commonly by targeting multiple risk factors considered to heighten hip fracture risk.

Despite much attention to the role of bone quality in this regard, efforts to safely promote bone mineral density remain limited.

While calcium and vitamin D are well studied in this regard, less attention has seemingly been put forth to encourage providers to consider vitamin K and vitamin K subtypes as additional bone building micro nutrients that may adversely impact hip fracture risk, if deficient.

Based on this current mini-review, and in agreement with the fact that vitamin K does impact diverse actions that can promote health, including bone health, it is likely that its adequate presence in the serum can serve a favorable protective role against excess bone attrition in the elderly while, its deficiency is likely to raise the risk of bone fragility especially among those older adults with cardiovascular health conditions.

Moreover, even if not considered by some to be relevant in efforts to address hip fracture recovery vitamin K play yet play a vital role in fostering optimal bone healing after any fracture or fracture surgery, especially in those elderly unable to utilize bone building pharmacologic medications and who are malnourished.

While one must be mindful that some studies have reported vitamin K to be of no importance in any of the above bone related contexts, and publication bias may favor studies with positive impacts, several studies in animal models as well as the clinic support more investigation of this issue.

As such, and since no single 'magic bullet' or 'cure' has been developed to counter hip fracture disability to any meaningful degree in more than 20 years, it is possible that some advancement can be made among those elderly who are either at risk for frailty and osteoporosis, and are living with cardiovascular disease if their vitamin K status is wanting.

Future research that attempts to reproduce some of the key basic and clinical studies that have emerged over the past 25 years, and those that examine the possible role vitamin K might have in mediating osteoblast functions may yet prove extremely valuable in efforts to offset unwanted age-associated bone attrition processes, while mediating or moderating favorable bone health impacts via its possible synergistic impact on vitamin D and calcium metabolism, as well as directly on bone cell molecular mechanismss and their genetic influences.

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Conflicts of interest

The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

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References

1. Emmerson B R, Varacallo M, Inman D. Hip Fracture Overview. In: Stat Pearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
2. Ferris H, Brent L, Sorensen J. Cost of hospitalisation for hip fracture–findings from the Irish hip fracture database. *Osteoporos Int.* 2022;01–09.
3. Porter JL, Varacallo M. Osteoporosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
4. Fu TS, Huang TS, Sun CC, et al. Impact of bisphosphonates and comorbidities on initial hip fracture prognosis. *Bone*. 2022;154:116239.
5. Mc Carthy C J, Kelly MA, Kenny PJ. Assessment of previous fracture and anti–osteoporotic medication prescription in hip fracture patients. *Ir J Med Sci*. 2022;191(1):247–252.
6. Fusaro M, Cianciolo G, Brandi ML, et al. Vitamin K and osteoporosis. *Nutrients*. 2020;12(12):3625.
7. Hamidi MS, Gajic–Veljanoski O, Cheung AM. Vitamin K and bone health. *J Clin Densitom*. 2013;16(4):409–413.
8. Palermo A, Tuccinardi D, D'Onofrio L, et al. Vitamin K and osteoporosis: myth or reality? *Metabolism*. 2017;70:57–71.
9. Feskanich D, Weber P, Willett WC, et al. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr.* 1999;69(1):74–79.

10. Kohlmeier M, Salomon A, Saupe J, et al. Transport of vitamin K to bone in humans. *J Nutr.* 1996;126(4):1192–1196.

11. Vermeer C, Jie KS, Knapen MH. Role of vitamin K in bone metabolism. *Ann Rev Nutr*. 1995;15(1):01–21.

12. Weber P. Vitamin K and bone health. *Nutrition*. 2001;17(10):880–887.

13. Hao G, Zhang B, Gu M, et al. Vitamin K intake and the risk of fractures: a meta–analysis. *Medicine (Baltimore).* 2017;96(17):6725.

14. Nino S, Soin SP, Avilucea FR. Vitamin D and metabolic supplementation in orthopedic trauma. *Orthop Clin North Am.* 2019;50(2):171–179.

15. Simes DC, Viegas CSB, Araújo N, et al. Vitamin K as a diet supplement with impact in human health: current evidence in age–related diseases. *Nutrients*. 2020;12(1):138.

16. Ediz L, Hiz O, Meral I, Alpayci M. Complex regional pain syndrome: a vitamin K dependent entity? *Med Hypotheses.* 2010;75(3):319–323.

17. Iwamoto J, Seki A, Sato Y, et al. Vitamin K2 promotes bone healing in a rat femoral osteotomy model with or without glucocorticoid treatment. *Calcif Tissue Int.* 2010;86(3):234–241.

18. Gigante A, Torcianti M, Boldrini E, et al. Vitamin K and D association stimulates in vitro osteoblast differentiation of fracture site derived human mesenchymal stem cells. *J Biol Regul Homeost Agents*. 2008;22(1):35–44.

19. LeBlanc KE, Muncie HL Jr, LeBlanc LL. Hip fracture: diagnosis, treatment, and secondary prevention. *Am Fam Physician*. 2014;89(12):945–951.

20. Shiraki M, Shiraki Y, Aoki C, et sl. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res*. 2000;15(3):515–521.

21. Bultynck C, Munim N, Harrington DJ, et al, Prevalence of vitamin K deficiency in older people with hip fracture. *Acta Clin Belg*. 2020;75(2):136–140.

22. Fusaro M, Noale M, Viola V, et al. Vitamin K, vertebral fractures, vascular calcifications, and mortality: VItamin K Italian (VIKI) dialysis study. *J Bone Miner Res.* 2012;27:2271–2278.

23. Bügel S. Vitamin K and bone health in adult humans. *Vitamins & Hormones*. 2008;78:393–416.

24. Capozzi A, Scambia G, Lello S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas*. 2020;140:55–63.

25. Villa JKD, Diaz MAN, Pizziolo VR, et al. Effect of vitamin K in bone metabolism and vascular calcification: A review of mechanisms of action and evidences. *Crit Rev Food Sci Nutr*. 2017;57(18):3959–3970.

26. Shah K, Gleason L, Villareal DT. Vitamin K and bone health in older adults. *J Nutr Gerontol Geriatr.* 2014;33(1):10–22.

27. Tucker KL. Osteoporosis prevention and nutrition. *Curr Osteoporos Rep.* 2009;7(4):111–117.

28. Brown JP, Malaval L, Chapuy MC, et al. Serum bone Gla–protein: a specific marker for bone formation in postmenopausal osteoporosis. *The Lancet*.1984;323(8386):1091–1093.

29. Moore AE, Kim E, Dulnoan D, et al. Serum vitamin K₁ (phylloquinone) is associated withfracture risk and hip strength in post–menopausal osteoporosis: a cross–sectional study. *Bone*. 2020;141:115630.

30. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos Int*. 2007l;18(7):963–972.

31. Knapen MH, Drummen NE, Smit E, et al. Three–year low–dose menaquinone–7 supplementation helps decrease bone loss in healthy postmenopausal women. *Osteoporos Int*. 2013;24:2499–2507.

32. Booth SL, Tucker KL, Chen H, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr.* 2000;71(5):1201–1208.

33. Mott A, Bradley T, Wright K, et al. Effect of vitamin K on bone mineral density and fractures inadults: an updated systematic review and meta–analysis of randomised controlled trials. *Osteoporos Int.* 2019;30(8):1543–1559.

34. Kanai T, Takagi T, Masuhiro K, et al. Serum vitamin K level and bone mineral density in post–*menopausal women. Int J Gynecol Obstetr. 1997;56(1):25–30.*

35. Binkley N, Harke J, Krueger D, et al. Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal North American women. *J Bone Mineral Res*. 2009;24(6):983–991.

36. Elshaikh AO, Shah L, Joy MC, et al. Influence of vitamin K on bone mineral density and osteoporosis. *Cureus*. 2020;12(10).

37. Apalset EM, Gjesdal CG, Eide GE, et al. Intake of vitamin K1 and K2 and risk of hip fractures: the Hordaland Health Study. *Bone*. 2011;49(5):990–995.

38. Vergnaud P, Garnero P, Meunier PJ, et al. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. *J Clin Endocrinol Metab.* 1997;82(3):719–724.

39. Stevenson M, Lloyd–Jones M, Papaioannou D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. *Hlth Technol Assess*. 2009;13(45):03–11.

40. Giri TK, Newton D, Chaudhary O, et al. Maximal dose–response of vitamin–K2 (menaquinone–4) on undercarboxylated osteocalcin in women with osteoporosis. *Int J Vitam Nutr Res*. 2020,90: 42–48.

41. Chan R, Leung J, Woo J. No association between dietary vitamin K intake and fracture risk in Chinese community–dwelling older men and women: a prospective study. *Calcified Tissue Int*. 2012;90(5):396–403.

42. Bulló M, Estruch R, Salas–Salvadó JO. Dietary vitamin K intake is associated with bone quantitative ultrasound measurements but not with bone peripheral biochemical markers in elderly men and women. *Bone*. 2011;48(6):1313–1318.

43. Cockayne S, Adamson J, Lanham–New S, et al. Vitamin K and the prevention of fractures. Systematic review and meta–analysis of randomized controlled trials. *Arch Intern Med*. 2006;166(12):1256–1261.

44. Finnes TE, Lofthus C.M, Meyer HE et al. A combination of low serum concentrations of vitamins PK and D is associated with increased risk of hip fractures in elderly Norwegians: a NOREPOS study. *Osteoporos Int.* 2016;27:1645–1652.

45. Fusaro M, Mereu MC, Aghi A, et al. Vitamin K and bone. *Clin Cases Miner Bone Metab.* 2017;14(2):200–206.

46. Gigante A, Brugè F, Cecconi S, et al Vitamin MK–7 enhances vitamin D3–induced osteogenesis in hMSCs: modulation of key effectors in mineralization and vascularization. *Tissue Eng Regen Med.* 2015;9(6):691–701.

47. Iwamoto J, Sato Y, Takeda T, et al. High–dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a review of the literature. *Nutr Res*. 2009;29(4):221–228.

48. Nakano T, Tsugawa N, Kuwabara A, et al. High prevalence of hypovitaminosis D and K in patients with hip fracture. *Asia Pacific J Clin Nutr.* 2011;20(1):56–61.

49. Torbergsen AC, Watne L.O, Wyller TB, et al. Vitamin PK and 25(OH) D are independently and synergistically associated with a risk for hip fracture in an elderly population: a case control study. *Clin. Nutr.* 2015;34:101–106.

50. Tsugawa N, Shiraki M. Vitamin K nutrition and bone health. *Nutrients*. 2020;12(7):1909.

51. Yaegashi Y, Onoda T, Tanno K, et al. Association of hip fracture incidence and intake of calcium, magnesium, vitamin D, and vitamin K. *Eur J Epidemiol.* 2008;23:219–225.

52. Mortensen SJ, Beeram I, Florance J, et al. Modifiable lifestyle factors associated with fragility hip fracture: a systematic review and meta–analysis. *J Bone Miner Metab*. 2021;39(5):893–902.

53. Fiatarone Singh MA. Exercise, nutrition and managing hip fracture in older persons. *Curr Opin Clin Nutr Metab Care.* 2014;17(1):12–24.

54. Ramponi DR, Kaufmann J, Drahnak G. Hip Fractures. *Adv Emerg Nurs J.* 2018;40(1):08–15.

55. Barceló M, Torres OH, Mascaró J, et al. Hip fracture and mortality: study of specific causes of death and risk factors. *Arch Osteoporos*. 2021;16(1):15.

56. Hart JP, Shearer MJ, Klenerman L, et al Electrochemical detection of depressed circulating levels of vitamin K1 in *osteoporosis. J Clin Endocrinol Metab*. 1985;60(6):1268–1269.

57. Hodges SJ, Pilkington MJ, Stamp TC, et al. Depressed levels of circulating menaquinones in patients with osteoporotic fractures of the spine and femoral neck. *Bone.* 1991;12:387–389.

58. Szulc P, Chapuy MC, Meunier PJ, et al. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. *J Clin Invest*. 1993;91(4):1769–1774.

59. Cheung AM, Tile L, Lee Y, et al. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med.* 2008;5:196.

60. Rodríguez–Olleros Rodríguez C, Díaz Curiel M. Vitamin K and bone health: a review on the effects of vitamin K deficiency and supplementation and the effect of non–vitamin K antagonist oral anticoagulants on different bone parameters. *J Osteoporosis.* 2019;31:

61. Inoue T, Fujita T, Kishimoto,H, et al. Randomized controlled study on the prevention of osteoporotic fractures (OF study): a phase IV clinical study of 15–mg menatetrenone capsules. *J Bone Miner Metab*. 2009;27:66–75.

62. Tal A, Rubin G, Rozen N. Treatment with vitamin K in hip fracture patients receiving warfarin. *Isr Med Assoc J.* 2013;15(7):348–351.

63. Plantalech L, Guillaumont M, Vergnaud P, Leclercq M, Delmas PD. Impairment of gamma carboxylation of circulating osteocalcin (bone gla protein) in elderly women. *J Bone Miner Res*. 1991;6(11):1211–1216.

64. Kaneki M, Hedges SJ, Hosoi T, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip–fracture risk. *Nutrition.* 2001;17(4):315–321.

65. Douglas AS, Robins SP, Hutchison JD, et al. Carboxylation of osteocalcin in post–menopausal osteoporotic women following vitamin K and D supplementation. *Bone.* 1995;17(1):15–20.

66. Takahashi M, Naitou K, Ohishi T, et al. Effect of vitamin K and/or D on undercarboxylated and intact osteocalcin in osteoporotic patients with vertebral or hip fractures. *Clin Endocrinol*. 2001;54(2):219–224.

67. Akbari S, Rasouli–Ghahroudi AA. Vitamin K and bone metabolism: a review of the latest evidence in preclinical studies. *BioMed Res Int*. 2018;

68. Hodges SJ, Akesson K, Vergnaud P, et al. Circulating levels of vitamins K1 and K2 decreased in elderly women with hip fracture. *J Bone Min Res*. 1993;8(10):1241–1245.