Vitamin C and Bone Health

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Abstract

Dietary and lifestyle factors have important contributions to skeletal health. Fruit- and vegetable-specific antioxidants, such as vitamin C, might help in preventing osteoporosis because vitamin C may decrease oxidative stress and subsequent bone-resorption. Vitamin C is an essential cofactor for collagen formation (an important component of bone matrix) and potentiates vitamin E activity in cells by regenerating α-tocopherol from its oxidized derivative.

In this chapter, we highlight findings from previous studies on vitamin C intake and bone measures to underscore our current understanding and emphasize the importance of vitamin C on skeletal health. Taken together, previous studies showed a positive association between dietary vitamin C and bone mineral density. Very few examined serum vitamin C status, vitamin C supplementation or bone loss. The reported associations were complex due to multiple interactions with smoking, calcium and vitamin E intakes and current estrogen use in women. One longitudinal study reported that higher vitamin C intake may be protective against bone loss in men with low calcium or vitamin E intake. There is an urgent need to replicate these findings in larger cohorts with data on bone loss over time. Studies have also suggested that vitamin C intake may be protective against hip fracture as well as other fractures, especially among current smokers and estrogen using women. Larger prospective cohort studies are required to further clarify these interactions. Lastly, good-quality randomized controlled trials are needed to confirm these epidemiological findings to ascertain optimal intakes for osteoporosis prevention.

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Introduction

Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 s [1]. Fifty one percent of these fractures occurred in Europe and the Americas, while most of the remainder occurred in the Western Pacific region and Southeast Asia [1]. By 2050, the worldwide incidence of hip fracture is projected to increase by 310 % in men and 240 % in women [2]. Therefore, osteoporosis and related fractures in older adults take a huge personal and economic toll with an annual cost of nearly $22 billion to the US healthcare system [2] and €37 billion to the European Union [3].

Recent findings from the population-based Cohort of Swedish Men (COSM) and Swedish Mammography Cohort (SMC) showed a dose-response association between fruit and vegetable intake and hip fracture such that an intake below the recommended five servings/day conferred higher rates of hip fracture [4]. Previous studies had also shown that higher fruit and vegetable intake has positive effects on bone mineral status [5–10]. Among other nutrients, fruits and vegetables are rich in vitamin C, a powerful water soluble antioxidant that is thought to prevent bone resorption due to its anti-oxidative properties as well as its role in collagen formation. While several studies have confirmed the association between vitamin C intake or status with bone mineral density (BMD) and fractures, the results have not been entirely consistent. This may be due to a complex association that involves interaction of vitamin C with smoking [11–13], postmenopausal estrogen use/hormonal therapy [11, 14, 15], calcium intake [12, 15, 16] and vitamin E intake [13, 17]. In this chapter, we highlight findings from previous studies on this topic to underscore our current understanding and emphasize the potential importance of vitamin C on skeletal health.

Vitamin C Effects on the Skeleton

Vitamin C may affect bone health via several mechanisms. *First*, collagen is the most abundant component of the extracellular bone matrix [18]. In adults, type I collagen represents about 90 % of the total protein matrix [18]. Vitamin C is an essential cofactor required for hydroxylation of proline and lysine into hydroxyproline and hydroxylysine respectively [19]. This post-translational modification of pro-collagen is crucial for the formation of mature collagen molecules and their assembly into fibrils [18]. Defects in this process, as seen in the disease scurvy, lead to the formation of unstable non-hydroxylated pro-collagen chains, which are degraded within the cell at normal body temperature. Without the structural support of collagen, blood vessels, tendons, and skin become fragile. This may also lead to weakening of bones and subsequent fractures. Previous animal studies have demonstrated that experimentally induced deficiency of vitamin C leads to impaired bone mass, cartilage and connective tissue [20, 21]. *Second*, Oxidative stress may increase bone resorption through activation of nuclear factor-kB protein, which is a crucial mediator of tumor necrosis factor-a and osteoclastogenetic activity [22–26]. Vitamin C, a strong antioxidant aids in decreasing this oxidative stress [27] and therefore may play a role in preventing bone resorption. *Third*, vitamin E is another strong antioxidant that has been linked with bone health [28, 29]. Vitamin C potentiates vitamin E activity in cells by regenerating α-tocopherol from its oxidized derivative [30].

Vitamin C and Bone Density

Evidence from Cross-Section and Case–Control Studies

Several cross-sectional and case-control studies have examined the association of vitamin C intake with dual-energy X-ray absorptiometry (DXA)-derived BMD at multiple bone sites. Most of these studies were focused on either total or dietary vitamin C intake. Most of the studies except one [14] showed positive associations between vitamin C and one or more BMD sites. Very few examined serum vitamin C status or vitamin C supplementation. However, the results of these studies are complicated by multiple interactions observed between vitamin C intake/status and other nutritional [13, 15, 16] and non-nutritional [11, 13–15] factors (Table 8.1).

Interaction with Smoking

In the Framingham Osteoporosis study, the association of vitamin C (total, supplemental, and dietary) intake with BMD at the hip [femoral neck, trochanter], spine, and radial shaft was examined in 334 men and 540 women (mean age = 75 years) [13]. Mean BMD was estimated, for men and women, by tertile/category of energy adjusted vitamin C intake. Negative associations were reported between total and supplemental vitamin C intake and trochanter-BMD among current male smokers (P-trend = 0.01). Among male nonsmokers, total vitamin C intake was positively associated with femoral neck BMD (P-trend = 0.04). No significant associations were reported among women. Smoking is an established risk factor of osteoporosis as outlined in our recent review [31].

Interaction with Smoking and Estrogen Use

Simon and Hudes analyzed data collected from 13,080 adults (aged 20–90 years) enrolled in the Third National Health and Nutrition Examination Survey (NHANES III) during 1988–1994. Because they identified three-way interactions among smoking, history of estrogen use, and dietary and serum ascorbic acid in post-menopausal women, they analyzed these relations stratified by smoking and estrogen use. Dietary ascorbic acid intake was independently associated with BMD among pre-menopausal women ($P = 0.002$). Among men, serum ascorbic acid was associated in a nonlinear fashion with BMD ($P < 0.05$). Among post-menopausal women without a history of smoking or estrogen use, serum ascorbic acid was unexpectedly associated with lower BMD ($P = 0.01$). However, among post-menopausal women with a history of smoking and estrogen use, a standard deviation increase in serum ascorbic acid was associated with a 49 % decrease in fracture prevalence ($P = 0.001$) [11]. Estrogen-use increases the turnover of ascorbic acid [32] and is associated with lowered ascorbic acid levels in animals and humans [33–35]. Studies have also demonstrated that smoking decreases the absorption and increases the turnover of ascorbic acid, thereby lowering blood ascorbic acid levels [36]. Therefore, interaction of vitamin C with smoking and estrogen use is expected. However, results of these interactions have been inconsistent.

Interaction with Calcium Intake

Using the data from Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, Hall and Greendale examined the association of food frequency questionnaire (FFQ) based dietary vitamin C with BMD at the femoral neck, total hip and lumbar spine in women aged 45–64 years. They reported that with each 100 mg increment in dietary vitamin C intake, there was a 0.017 g/cm^2 increment in BMD at the femoral neck ($P = 0.002$) and total hip ($P = 0.005$). Association with lumbar spine BMD was not statistically significant ($P = 0.08$). This study further reported an effect modification by calcium intake. Upon stratification by calcium intake (>500 mg/day and ≤500 mg/

Table 8.1 Studies of BMD according to vitamin C intake or status in men and women

Study	Sample, age (years)	Vitamin C	Measurement/Site	Principal finding
New SA et al. (1997) [41]	994 healthy pre-menopausal women aged 45–49 years	FFQ based total vitamin C	BMD lumbar spine, femoral neck (FN), femoral trochanter, and femoral Wards	Non-linear association observed. Participants in 3rd quartile of total vitamin C intake had higher lumbar spine BMD ($P<0.002$) and femoral neck BMD ($P<0.01$) compared to those in the lowest quartile
Hall and Greendale, (1998) [16]	775 women aged 45–64 years from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial	FFQ based dietary vitamin C	BMD femoral neck, total hip and lumbar spine	Each 100 mg increment in dietary vitamin C intake, was associated with a 0.017 g/cm^2 increment in BMD ($P=0.002$ femoral neck; $P=0.005$ total hip). Association with lumbar spine BMD was not statistically significant ($P=0.08$). Effect modification by calcium intake, significant associations were seen with higher calcium intake (>500 mg/day) but not with lower calcium intake
Simon and Hudes (2001) [11]	3204 pre-menopausal women, 2906 post-menopausal women and 5739 men from the Third National Health and Nutrition Examination Survey (NHANES III)	Dietary vitamin C from 24-h recall and serum ascorbic acid	BMD hip	Three-way interactions among smoking, history of estrogen use, and dietary and serum ascorbic acid were identified. Dietary ascorbic acid intake was associated with BMD among premenopausal women ($P=0.002$). Among men, serum ascorbic acid was associated in a nonlinear fashion with BMD ($P<0.05$). Among post-menopausal women without a history of smoking or estrogen use, serum ascorbic acid was unexpectedly associated with lower BMD ($P=0.01$)

Morton et al. (2001) [15]	994 post-menopausal women	Vitamin C supplement use	BMD ultradistal and midshaft radius, hip, and lumbar spine	Vitamin C users had higher BMD at the femoral neck ($P<0.02$) and total hip ($P<0.06$). Women taking both estrogen and vitamin C had higher BMD levels at all sites. Among current estrogen users, those also taking vitamin C had higher BMD levels with marginal significance achieved at the ultradistal radius ($P<0.07$), femoral neck ($P<0.07$), and total hip ($P<0.09$). Women who took vitamin C plus calcium and estrogen had the highest BMD at the femoral neck ($P<0.001$), total hip ($P=0.05$), ultradistal radius ($P=0.02$)
Wolf et al. (2005) [14]	11,068 women aged 50–79 years from Women's Health Initiative	Dietary and total vitamin C intake from FFQ	BMD whole body, L2–L4 spine, total hip, femoral neck, trochanter, total hip BMD t score	No significant associations with diet or total vitamin C intake (P range = 0.08–0.33). Effect modification by use of hormone therapy. Current hormone therapy associated with higher BMD at multiple bone sites in women with high total vitamin C intake (P range = 0.03–0.05)
Sahni et al. (2008) [13]	334 men and 540 women (mean age 75 years) from the Framingham Osteoporosis Study	Total, dietary and supplemental vitamin C intake from FFQ	BMD femoral neck, trochanter, spine, and radial shaft	Interaction by sex and smoking. Total and supplemental vitamin C intakes were negatively associated with trochanter-BMD among current male smokers (P-trend = 0.01). Among male nonsmokers, total vitamin C intake was positively associated with femoral neck BMD (P-trend = 0.04)

day), women with higher calcium intake had an increment of 0.0190 g/cm^2 in femoral neck BMD ($P=0.002$), 0.0172 g/cm^2 in total hip BMD (P = 0.01) and 0.0199 g/cm^2 in lumbar spine BMD (P = 0.02) per 100 mg vitamin C. No relation between BMD and vitamin C was evident in the lower calcium stratum for any of the bone sites examined. Vitamin C aids in the absorption of calcium, therefore, interactive effects of these two nutrients upon BMD have been reported with cross-sectional studies reporting a beneficial role of higher vitamin C intake with higher calcium intakes.

Interaction with Calcium Intake and Estrogen Use

In the Rancho Bernardo study, Morton et al. evaluated the independent relation of daily vitamin C supplement use with BMD in a population-based sample of 994 post-menopausal women. Daily vitamin C supplement intake ranged from 100 to 5000 mg; the mean daily dose was 745 mg and average duration of use was 12.4 years. Vitamin C users had BMD levels ~3 % higher at the mid-shaft radius, femoral neck, and total hip ($P<0.05$) after adjustment for confounders and covariates. In the fully adjusted model, significant differences remained at the femoral neck ($P<0.02$) and marginal significance was observed at the total hip ($P<0.06$). Women taking both estrogen and vitamin C had significantly higher BMD levels at all sites. Among current estrogen users, those also taking vitamin C had higher BMD levels at all sites, with marginal significance achieved at the ultradistal radius ($P<0.07$), femoral neck ($P<0.07$), and total hip ($P<0.09$). Women who took vitamin C plus calcium and estrogen had the highest BMD at the femoral neck ($P=0.001$), total hip ($P=0.05$), ultradistal radius ($P=0.02$), and lumbar spine. Vitamin C supplement use appears to have a beneficial effect on levels of BMD, especially among postmenopausal women using concurrent estrogen therapy and calcium supplements [15].

Evidence from Longitudinal Studies of Vitamin C and Bone Loss

To our knowledge only two studies have examined the effect of vitamin C intake on bone loss (Table 8.2). Kaptoge et al. examined the association of dietary vitamin C intake (from 7-day food dietary) with total hip BMD loss over 3 years in 470 men and 474 women (aged 67–79 years) [37]. No associations were reported in men but in women, low intake of vitamin C was associated with faster rate of total hip BMD loss. Women in the lowest tertile (7–57 mg/day) of vitamin C intake lost BMD at an average rate of −0.65 % p.a., which was significantly faster compared to loss rates in the middle (58–98 mg/day) and upper (99–363 mg/day) tertiles of intake, which were −0.31 % p.a. and −0.30 % p.a., respectively (P = 0.016).

In the Framingham Osteoporosis study, Sahni et al. examined the association of vitamin C (total, supplemental and dietary) intake with BMD loss over 4 years in 213 men and 393 women (mean age was 75 years). In contrast to the study by Kaptoge et al. [37], results from the Framingham Osteoporosis Study showed vitamin C to be protective against bone loss but only in men not women. In this study, higher total vitamin C intake was associated with less femoral neck and trochanter-BMD loss in men with low calcium (all P-trend ≤ 0.03) or vitamin E intakes (all P-trend = 0.03, Fig. 8.1). Higher dietary vitamin C intake tended to be associated with lower femoral neck-BMD loss (P-trend = 0.09). These associations were attenuated but retained borderline significance (P-trend <0.1) after adjusting for potassium intake (a marker of fruit and vegetable intake), suggesting that vitamin C effects may not be separated from other protective factors in fruit and vegetables. No significant associations were observed among women. In light of the studies highlighted in this review that examined vitamin C with BMD and BMD loss, there is a strong evidence that higher vitamin C intake is associated with higher BMD. However, the associations are complex due to several reported

Table 8.2 Studies of change in BMD according to vitamin C intake in men and women

Study	Sample, age (years)	Vitamin C	Measurement/Site	Principal finding
Kapotge et al. (2001) [37]	470 men and 474 women aged 67–79 years from the EPIC-Norfolk study	Dietary vitamin C from 7-day food diaries	3-year BMD change in total hip	In men, no effect of dietary vitamin C on total hip bone loss. In women, low intake of vitamin C was associated with greater bone loss. Women in the lowest tertile (7–57 mg/day) of vitamin C intake lost BMD at an average rate of −0.65 % per annum (p.a.), which was significantly greater compared to loss rates in the middle (58–98 mg/day) and upper (99–363 mg/day) tertiles of intake, which were −0.31 % p.a. and −0.30 % p.a., respectively (P = 0.016)
Sahni et al. (2008) [13]	213 men and 393 women (mean age 75 years) from the Framingham Osteoporosis Study	Total, dietary and supplemental vitamin C intake from FFQ	4-year BMD change in femoral neck, trochanter, spine, and radial shaft	Interaction by sex, calcium and vitamin E intake. Higher total vitamin C intake was associated with less femoral neck and trochanter-BMD loss in men with low calcium (median vitamin C intake across tertiles = 74,139, and 200 mg/day, all P-trend ≤ 0.03) or vitamin E intakes (all P-trend = 0.03). Higher dietary vitamin C intake tended to be associated with lower femoral neck-BMD loss (P-trend = 0.09). These associations were attenuated but retained borderline significance (P-trend < 0.1) after adjusting for potassium intake (a marker of fruit and vegetable intake)

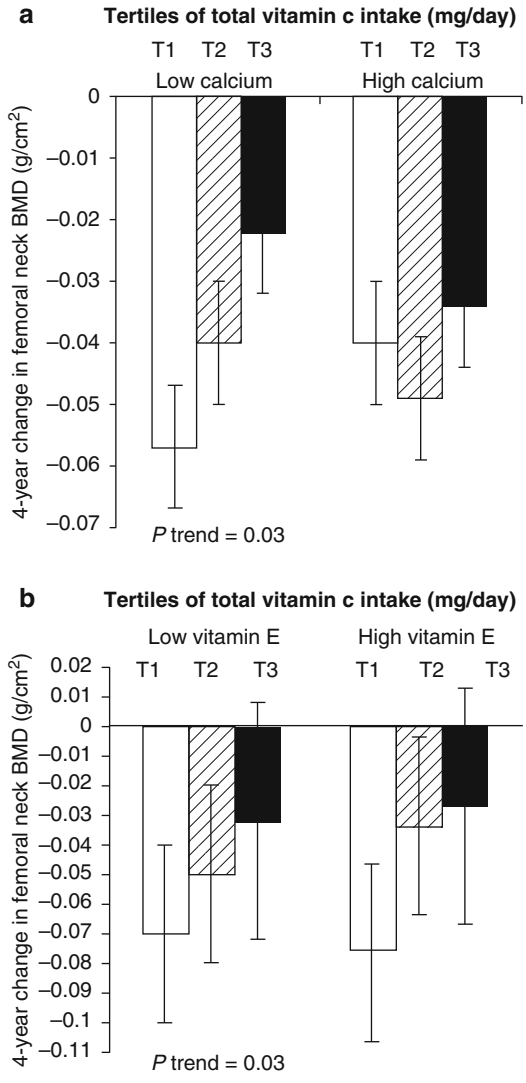

Fig. 8.1 Adjusted mean 4-year changes in femoral neck by tertiles of total vitamin C intake among men stratified by (**a**) total calcium intake and (**b**) total vitamin E intake. Low calcium group: total calcium intake ≤ median intake (661 mg/day); high calcium group: total calcium intake > median intake. Low vitamin E group: total vitamin E intake ≤ median intake (7.7 mg TE/day); high vitamin E group: total vitamin E intake > median intake. Models were adjusted for age at the baseline (years), BMI (kg/m^2), height at the time of enrollment (m), total energy intake (MJ/day), baseline physical activity index, alcohol intake (none/moderate: <26.4 g/day of alcohol; high: ≥26.4 g/day of alcohol), smoking (never/former/current smokers), and intake of total vitamin D (mcg/day), caffeine (mg/day), and multivitamin use (yes/no). Models for panel **b** were further adjusted for total calcium intake (mg/day). Values are means ± SE, n = 201. Analysis was based on a general linear model with Dunnett's adjustment for multiple comparisons. *Different from T1, $P < 0.05$

interactions with smoking, calcium and vitamin E intakes and current estrogen use in women. Some of these interactions were also replicated in longitudinal studies of bone loss. While two prospective cohort studies provided strong evidence for vitamin C intake reducing hip bone loss, there is still a need to replicate these data in other larger cohorts. These data may be sufficient to support a randomized controlled trial of vitamin C supplementation. In the study by Kaptoge et al. [37] and by Sahni et al. [13], the bone protective effects of vitamin C intakes were seen at intake levels that were greater than the dietary recommended intakes of 75 mg/day for women and 90 mg/day for men. This information can be useful in designing future randomized controlled trials to ascertain optimal intakes of vitamin C for osteoporosis prevention.

Evidence from Intervention Studies

To date there has been one double-blind randomized control trial of vitamin C (along with vitamin E) and bone density in 30 men and women [38]. The treatment groups received 400 IU of vitamin E daily and either 500 or 1000 mg/day of vitamin C for 12 months. The group with the highest vitamin C intake had significantly less hip bone loss compared with the placebo group but no significant association was seen for lumbar spine BMD. Another study by Chuin et al. was a 6-month randomized controlled of 34 women that examined the effect of vitamin C in combination with other treatments and bone density [39]. Vitamin group received ascorbic acid (1000 mg/day) and a-tocopherol (600 mg/day). Exercise and placebo group received 60 min of resistance training three times/week and placebo (lactose) and exercise and vitamin group received 60 min of resistance training three times/week and ascorbic acid (1000 mg/day) and a-tocopherol (600 mg/day). Lumbar spine (LS) BMD decreased significantly by 1 % in the placebo group but remained stable in the other three intervention groups. Taken together, evidence from these two trials investigating vitamin C's effect

on bone density loss is unclear. While these two studies show promising results for vitamin C intake (at dosages much higher than usual dietary intake), they did not examine the effect of vitamin C alone and the study by Chuin et al. was not double blinded. The studies had small sample size and limited duration of treatment. Future trials are needed to examine interventions of vitamin C supplementation in larger studies of longer duration. Such good-quality double blinded randomized controlled trials will aid in confirming the epidemiological findings reported thus far and will help in ascertaining optimal intakes for osteoporosis prevention.

Vitamin C and Fracture Risk

As noted above, several studies have examined dietary vitamin C's effect on bone density but relatively fewer studies have examined effects on fracture. Most of the studies with fracture outcomes had either cross-sectional or case-control designs. Some fracture studies also reported significant interactions with smoking or estrogen use (Table 8.3). In a case cohort study from the Swedish Mammography Cohort [17], Melhus et al. examined 247 cases (44 current and 42 former smokers) and 873 controls (93 current and 127 former smokers) aged 40–76 years. Significant interaction between current smoking status and both dietary vitamin E ($P=0.02$) and vitamin C ($P=0.03$) intake was reported. Among current smokers, hip fracture risk increased with low intake of vitamin E [3.0 (95 % CI: 1.6–5.4)] or vitamin C [3.0 (1.6–5.6)]. In contrast, the OR decreased to 1.1 (0.5–2.4) and 1.4 (0.7–3.0) with high intakes of vitamin E and C, respectively. Current smokers with a low intake of both vitamins E and C, the risk of hip fracture was much higher; OR = 4.9 (2.2–11.0).

The only prospective cohort study on this topic was from the Framingham Osteoporosis study. This study evaluated associations of vitamin C intake (total, dietary, and supplemental) with incident hip fracture and non-vertebral osteoporotic fracture, over a 15- to 17-year follow-up [40]. 366 men and 592 women (mean age 75 ± 5 years) completed a food frequency questionnaire (FFQ) in 1988–1989 and were followed for non-vertebral fracture until 2003 and hip fracture until 2005. Tertiles of vitamin C intake were created after adjusting for total energy (residual method). Over follow-up 100 hip fractures occurred and 180 non-vertebral osteoporotic fractures occurred. Among men and women in this study, subjects in the highest tertile of total vitamin C intake (median = 313 mg/day) had a significantly lower risk of hip fracture as compared to subjects in the lowest tertile of intake (median = 94 mg/day) (HR T3 = 0.56, 95 % CI = 0.31–0.98, P = 0.04, HR T2 = 0.73, 95 % CI = 0.44–1.20, P = 0.21, P for trend = 0.04, Global test P value = 0.0001). Similarly, subjects in the highest tertile of total vitamin C intake (median = 308 mg/day) had lower risk of non-vertebral osteoporotic fracture as compared to subjects in the lowest tertile of intake (median = 95 mg/day) (HR T3 = 0.66, 95 % CI = 0.43–1.01, P = 0.06, HR T2 = 0.93, 95 % CI = 0.65–1.36, P = 0.73, P for trend = 0.05, Global test P value < 0.0001). Subjects in the highest category of *supplemental vitamin C* intake (median = 260 mg/day) had significantly lower risk of hip fracture as compared to non-supplement users (HR T3 = 0.31, 95 % CI = 0.13–0.73, P = 0.007, HR T2 = 0.50, 95 % CI = 0.20–1.24, P = 0.13, P for trend = 0.02, Global test P value < 0.0001). Similarly, subjects in the highest category of supplemental vitamin C intake (median = 260 mg/day) tended to have lower risk of non-vertebral osteoporotic fracture as compared to non-supplement users, but this only approached significance (HR T3 = 0.58, 95 % CI = 0.30–1.11, P = 0.10, HR T2 = 0.80, 95 % CI = 0.38–1.71, P = 0.57, P for trend = 0.07, Global test P value < 0.0001). Dietary vitamin C intake was not associated with fracture risk (all $P>0.22$).

Taken together, these studies suggest that vitamin C intake may be protective against hip fracture as well as other fractures. These protective effects were more evident among current smokers and estrogen using women. Larger prospective cohort studies are required to further clarify

Table 8.3 Studies of vitamin C and relative risk of fractures of the hip and other sites

Type of Fracture/Study	Study design	Sample	Results
Hip fracture			
Michaelsson et al. (1995) [42]	Case-control study, the Swedish Mammography Cohort	247 cases and 893 matched controls aged 40–75 years	Higher vitamin C intake was associated with increased hip fracture risk compared to low intake (adjusted OR = 1.9, 95 % CI: 1.2–3.1)
Melhus et al. (1999) [17]	Case cohort study, the Swedish Mammography Cohort	247 cases (44 current and 42 former smokers) and 873 controls (93 current and 127 former smokers) aged 40–76 years	Effect modification by smoking. Among current smokers, low dietary vitamin C was associated with a higher hip fracture risk; OR = 3.0 (1.6–5.6). No association was seen with high dietary vitamin C; OR = 1.4 (0.7–3.0). Effect modification by vitamin E. Current smokers with a low intake of both vitamins E and C, had increased risk of hip fracture; OR = 4.9 (2.2–11.0)
Zhang et al. (2005) [12]	Case-control	1215 male and female cases aged ≥50 years and 1349 age- and sex-matched controls without hip fracture	Effect modification by smoking. Ever smokers: Vitamin C intake did not have a significant linear association with hip fracture. Never smokers: Protective trends seen with higher intake (5th quintile, OR = 0.65 (95 % CI, 0.38–1.13), P trend = 0.02
Sahni et al. (2009) [40]	Prospective cohort, the Framingham Osteoporosis Study	366 men and 592 women (mean age 75 years)	Over follow-up 100 hip fractures occurred. Subjects in the highest tertile of total vitamin C intake had significantly fewer hip fractures (P trend = 0.04) compared to those in the lowest tertile of intake. Subjects in the highest category of supplemental vitamin C intake had significantly fewer hip fractures (P trend = 0.02) compared to non-supplement users. Dietary vitamin C intake was not associated with fracture risk (all P > 0.22)
Any fracture			
Simon and Hudes, (2001) [11]	Cross-sectional, third National Health and Nutrition Examination Survey (NHANES III)	3778 pre-menopausal women, 3165 post-menopausal women and 6137 men aged 20–90 years	Effect modification by smoking and history of estrogen use in post-menopausal women. Among ever smokers with a history of estrogen use, a standard deviation increase in serum ascorbic acid was associated with a 49 % decrease in fracture prevalence
Sahni et al. (2009) [40]	Prospective cohort, the Framingham Osteoporosis Study	366 men and 592 women (mean age 75 years)	Over follow-up, 180 non-vertebral osteoporotic fractures occurred. Subjects in the highest tertile of total vitamin C intake had significantly fewer non-vertebral fractures (P trend = 0.05) compared to subjects in the lowest tertile of intake. Subjects in the highest category of supplemental vitamin C intake had significantly fewer non-vertebral fractures (P trend = 0.07) compared to non-supplement users. Dietary vitamin C intake was not associated with fracture risk (all P > 0.22)

these interactions with hip fracture as well as other fractures.

Conclusion

Dietary and lifestyle factors have important contributions to skeletal health. Higher vitamin C intake appears to be associated with higher BMD and lower bone loss. These associations seem to be modified by other nutritional and non-nutritional factors. Limited work suggests that usefulness of vitamin C intake in bone loss prevention, particularly in men with concomitant low intakes of calcium or vitamin E. However, more studies are needed to confirm these findings. Vitamin C intake also appears to be protective against hip fractures and other fractures, though there is a dearth of prospective cohort studies in this area. Some studies have suggested that association of vitamin C with bone measures is non-linear. Overall the protective effects of vitamin C have been observed at levels much higher that the dietary recommended intakes. Well designed randomized controlled trials are needed to confirm these epidemiological findings and to ascertain optimal intakes for osteoporosis prevention.

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