ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Research Article

# Vitamin C and Hip Fractures-Review

**Ray Marks***

*Department of Health and Behavior Studies, Teachers College, Columbia University, NY, United States*

***Corresponding Author**: Marks Ray, Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY, United States.

**Received:** April 08, 2020; **Published:** April 20, 2020

## Abstract

**Introduction:** Disabling or life-threatening hip fractures, which are highly prevalent among older populations remain highly challenging to prevent and treat effectively.

Objectives: This mini-review strove to examine whether: 1) vitamin C, a powerful antioxidant potentially involved in many physiological processes, such as bone maintenance, may possibly influence the risk of hip fracture and/or reduce its adverse consequences, and 2) more research in this realm is warranted and should be undertaken.

**Methods:** A comprehensive scan and narrative review of available relevant English language research reports published over the last 40 years (1980 - 2020) and located in key data bases was undertaken. Reviewed specifically were the selected study conclusions, approaches, sampling methods, study sample, and hip fracture vitamin C associations.

**Results:** Along with very few studies on the present topic, no clear conclusion as regards the nature of any clinically relevant association between vitamin C and hip fractures was evidenced among the diverse published works. More recent works are however, alluding to more favorable mediating or moderating effects on hip fracture injuries than not, especially in the context of prevailing vitamin C deficiencies.

**Conclusion:** More research to delineate a possible clinically important mediating role for vitamin C in the context of hip fractures, which remain largely impervious to current modes of prevention and long-term intervention is strongly indicated to advance this potential area of salience for reducing the hip fracture burden.

***Keywords:*** *Ascorbic Acid; Bone Health; Hip Fractures; Intervention; Prevention; Surgery; Vitamin C*

## Introduction

According to Dizdarevic., *et al.* [1], hip fractures, which are common in the elderly population, are both painful and costly, as well as disabling, in the event the patient survives the initial traumatic event and ensuing surgery. But preventive programs that mostly focus on falls prevention, including balance and strength training, plus drug assessments and various environmental management strategies do not commonly discuss the role of vitamin C status, as a possible important determinant of bone status [2,3], as well as overall health status post hip fracture [4].

## Aims of the Review

Since hip fractures, which are increasing prevalence are strongly associated with physical disability challenges and many associated and emergent forms of chronic disability, such as depression [5], this mini review aimed to examine whether vitamin C, previously termed, ascorbic acid, is a possible overlooked factor in the context of hip fracture prevention, and recovery strategies, plus second or recurrent hip fracture prevention strategies. In light of the magnitude of disability and morbidity incurred post-hip fracture, which extends to social costs such as low life quality and frequent hospitalizations, the article specifically examines if this topic is of possible high clinical relevance in this regard, and if so, whether further study and examination of this issue is warranted or not.

### Methods

To examine whether vitamin C has a relevant association with hip fractures, including second and recurrent fractures, and fracture recovery, an extensive scan of available documents housed in PUBMED, Scopus, and WEB of SCIENCE CONSOLIDATED, including most publications published as full length articles in English from 1980 up until March 31, 2020 using the key terms Vitamin C and Hip Fractures, or Ascorbic Acid and Hip Fractures was conducted.

After scanning the available article listings found on these websites for potential inclusion in this current mini-review, those that addressed some aspect of the current topic of interest were selected, downloaded and scrutinized in more depth by the author without regard to research design. After reviewing the available data in this way, it was clear that no systematic overview of such a limited diverse data base was likely to prove of sufficient value for definitively advancing practice. Hence, while it is acknowledged the 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 would arguably still highlight any tentative conclusions and ideas on this topic. To this end, a narrative overview of the material deemed to meet the basic review criteria was undertaken, rather than any aggregated review as outlined below.

## Results and their Analysis

### General observations

As of March 31, 2020, the data examined revealed only a small number of relevant studies, if compared to other themes in related research (See table 1).

| | Data Base | | |
|---|---|---|---|
| **Key Words** | **PUBMED** | **SCOPUS** | **Web of Science** |
| Hip Fractures | 37421 | 81725 | 69406 |
| Vitamin C | 64555 | 81725 | 252002 |
| Hip Fracture Prevention Strategies | 517 | 737 | 1324 |
| Vitamin C + Osteoporosis | 230 | 2195 | 4251 |
| Ascorbic Acid + Hip Fractures | 22 | 102 | 69 |
| Vitamin C + Hip Fractures | 30 | 381 | 1028 |
| Vitamin C Deficiency + Hip Fractures | 7 | 99 | 303 |
| Vitamin C Supplementation + Hip Fractures | 3 | 108 | 276 |

***Table 1:*** *Summary of numbers of articles posted at key data bases as of March 31, 2020 showing variations across and within databases as regards topics of current focus and related themes.*

A further examination of the available studies showed that regardless of data base, very few relevant clinical studies on the current topic actually prevailed, and most that were, had been represented on the PUBMED data base, despite the numbers listed above. Moreover, among the available clinical studies, very few prospective studies with robust designs were observed, regardless of data base employed. In all data bases too, themes that emerged from the search were highly diverse., ranging from deficiency effects of vitamin C in the context of bone health and fractures, to its possible pain-relieving or provoking supplementary effect, its anti- oxidant or pro-oxidant effects, despite attempts to narrow the topic and topic keywords. As well, challenges in attempts to aggregate findings in the clinical realm were numerous, including the lack of unified efforts to verify the intake of dietary sources of vitamin C as discussed in some clinical studies, as well as the failure to employ similar measures of either dietary and/or serum vitamin C across studies, or utilize similar samples, and bone status measures, where implemented.

However, it seems hard to refute a general consensus that vitamin C, an important antioxidant and co-factor for numerous biochemical reactions, may be an especially important compound in the synthesis and maintenance of bone tissues [2,6,7]. Vitamin C is also an important factor in mediating general wellbeing, such as cardiovascular, muscle, and neurological health [7-10], often found impaired in people who fall and fracture a hip. As well, pain states that impair function, reflex responsiveness, and desirable protective reflexes, may be heightened in the face of deficient vitamin C [11]. Other research shows skeletal muscle, highly implicated in hip fracture injuries is an important storage site of vitamin C [12].

**Research observations**

Based on the belief that vitamin C sufficiency may help prevent osteoporosis and fractures by mediating osteoclastogenesis, osteoblastogenesis, and bone collagen synthesis, Finck., *et al.* [13] elected to examine whether dietary intakes and plasma concentrations of vitamin C would be found to be associated with estimate measures of heel ultrasound and hip and spine fracture risks in older men and women. Examined were eligible cases who were part of a European study and who completed a 7-day diet diary vitamin C intake estimate survey along with having their vitamin C plasma concentrations assessed. A random subset (4000/25,639 subjects) underwent ultrasound testing, which during a second health examination. This prospective study examined a case-cohort sample of all participants with a fracture up to March 2009 in a random subset (n = 5319). Assessed were associations between quintiles of vitamin C intake and plasma status with and adjusted ultrasound values. Results showed positive associations between ultrasound measures and all quintiles of vitamin C intake, but not plasma status. Higher plasma vitamin C concentrations were significantly associated with reduced fracture risk only in men only. Thus, the idea that vitamin C being linked to hip fracture risk was not confirmed to any degree.

Hart., *et al*. [14] however, noted vitamin C is an essential micronutrient with an adult requiring a daily recommended intake of 75 mg for nonsmoking women and 90 mg for nonsmoking men. In this regard, this group used observational data to support the hypothesis that high dietary intake and supplementation with vitamin C may reduce hip fracture risk in postmenopausal women. According to this group, results of two high quality trials support use of vitamin C 500 mg daily for 50 days as prophylaxis against complex regional pain syndrome after wrist fractures treated conservatively and operatively, as well as similar evidence collected post surgically after foot and ankle surgery precluded any recommendations for offsetting hip fracture risk.

In an early study by Simon., *et al.* [15] that examined the relation vitamin C and bone mineral density and the prevalence of self-reported fractures, the authors analyzed data collected from 13,080 adults enrolled in the Third National Health and Nutrition Examination Survey (NHANES III) that took place between 1988 - 1994. Because they identified three-way interactions among smoking, history of estrogen use, and dietary and serum ascorbic acid in postmenopausal women, they analyzed these relations stratified by smoking and estrogen use. The researchers found that dietary ascorbic acid intake was independently associated with bone mineral density among premenopausal women ($p = 0.002$). Among men, serum ascorbic acid was associated in a nonlinear fashion with bone mineral density ($p < 0.05$) and dietary ascorbic acid intake was associated in a nonlinear fashion with self-reported fracture ($p = 0.05$). Among postmenopausal women without a history of smoking or estrogen use, serum ascorbic acid was unexpectedly associated with lower bone mineral density ($p = 0.01$). However, among postmenopausal 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 ($p = 0.001$). Dietary and serum ascorbic acid measures were associated inconsistently with bone mineral density and self-reported fracture among adult participants in NHANES III, suggesting that it has no universal or generic effect, but that gender and age are related mediating or moderating co variables. Pasco., *et al.* [16] did however, find an association in nonsmoking women between vitamin C and osteoporosis, which was suggestive of an effect on bone resorption due to its antioxidant properties.

In an earlier study by Falch., *et al.* [17] who examined the serum concentration of vitamin C in 40 elderly patients with a recently fractures hip and compared these values to those measured in 102 home-living elderly, concentrations of $37 \pm 22$ µmol l vs $50 \pm 29$ µmol l ($p < 0.01$) were noted. Among the patients admitted from home-living conditions and controls, 20 pairs that could be matched with respect to age, sex and season for the test showed serum vitamin C concentration was significantly lower in the hip fracture patients. Based on their findings the researchers proposed that the reduced serum concentration of vitamin C might reflect a general nutritional insufficiency that prevails in at least some hip fracture cases.

In addressing the issue as to whether vitamin C has any bearing on hip fracture risk, Malmir., *et al.* [18] elected to conduct a systematic review that examined data on the association between vitamin C intake and bone mineral density, as well as the risk of fractures and osteoporosis. Subgroup analysis was applied to define possible sources of heterogeneity among the available studies published before

2017. Results showed, greater dietary vitamin C intake was positively associated with bone mineral density at the femoral neck and lumbar spine, however, significant between-study heterogeneity was found at the femoral neck site. In addition, the authors found a non-significant association between dietary vitamin C intake and the risk of hip fracture.

Greater dietary vitamin C intake was associated with a 33% lower risk of osteoporosis, plus a lower risk of hip fracture and osteoporosis, as well as higher bone mineral density at femoral neck and lumbar spine.

In an earlier related study, Martinez-Ramirez., *et al.* [19] analyzed whether serum vitamin C or dietary vitamin C intake, among other factors, are related to osteoporotic fractures in the elderly. To this end, this group carried out a hospital-based case-control study (167 cases, 167 controls) of patients aged 65 or older with low-energy fractures. Controls were adults without fractures, matched for age and sex with cases. Diet was assessed by a semi-quantitative food frequency questionnaire. Serum vitamin C was measured using high- performance liquid chromatography. Multivariable analyses fitted to adjust for confounding variables showed astatistically significant difference between cases and controls for vitamin C blood levels, being higher for controls ($p = 0.01$). Analysis of the association between serum vitamin C and fracture risk showed a linear trend ($p = 0.03$) with a significantly reduced risk for the upper quartile. The intake of vitamin C was not related to fracture risk. However, it was concluded that serum vitamin C levels were lower in cases with osteoporotic fractures than in controls.

Michaelsson., *et al.* [20], on the other hand who investigated the association between dietary intake and the risk of proximal femoral fractures in a case-control study nested in a cohort of women born in 1914 - 1948 who were asked to fill out a food frequency questionnaire found unexpected results. After surveying more than 65,000 women who participated in the enquiry and subsequently examining those who sustained a first hip fracture, versus four individually matched controls for each fracture case, by age and county of residence, a second questionnaire concerning confounding factors was mailed to controls and cases. In all, 247 cases and 893 controls could finally be included and their monthly intake of foods and daily intake of nutrients were calculated and found to be independent risk factors for hip fracture, while postmenopausal hormone replacement therapy protected against hip fracture.

In another study, Sahni., *et al.* [21] evaluating the 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, as part of the Framingham Osteoporosis Study, 366 men and 592 women (mean age 75+5 years) who completed a food frequency questionnaire at baseline were followed to detect emergent hip fractures for about 7-8 years. Tertiles of vitamin C intake created from estimates obtained using the Willett Food Frequency Questionnaire, were used in the hazard's regression analysis, while adjusting for covariates. Results of over 100 hip fractures occurrences showed subjects with the highest tertile values of total vitamin C intake had significantly fewer hip fractures ($p$ trend $= 0.04$) compared to subjects in the lowest intake tertile. Subjects in the highest category of supplemental vitamin C intake had significantly fewer hip fractures ($p = 0.02$) compared to non-supplement users. Dietary vitamin C intake was not associated with fracture risk (all $p > 0.22$), but a possible protective effect of vitamin C on bone health in older adults was suggested. The results were partly, but not totally in line with those of Sun., *et al.* [21] who concluded that a higher dietary intake of vitamins C is associated with a lower risk of hip fracture in elderly Chinese. Dietary intake of vitamin C may also help to counteract the negative effect of inflammatory diets on hip fracture in white women younger than 63 years of age [22].

Kim., *et al.* [24] who studied the association between the dietary intake of postmenopausal Korean women using a semiquantitative questionnaire, and measures of bone mineral density at the lumbar spine, femoral neck and total hip using dual-energy X-ray absorptiometry found vitamin C intake was positively associated with the femoral neck T-score. Vegetable intake showed a positive association with the femoral neck and total hip T-scores, a finding taken to imply a favorable impact of vitamin C on bone health in this sub- group.

More recently, Hill-Mundel., *et al.* [4] found that vitamin C levels monitored during hospitalization of patients with a proximal femoral fracture using high performance liquid chromatography, were significantly lower preoperatively in this group compared to elderly pa-

tients without an acute fracture. A significant decrease of 33.8% in vitamin C plasma level was measured on the day after surgery with a significant recovery up to the time of discharge. Although the preoperative vitamin C status did not have any significant effect on clinical outcome, inadequate levels (< 50 µmol/L) upon discharge significantly increased the incidence and the severity of postoperative complications. Further support for a favorable vitamin C role in the hip fracture context comes from a current review by Sun., *et al.* [25] who conducted a meta-analysis that suggested that dietary vitamin C does vary inversely with the risk of hip fracture (overall OR = 0.73, 95% CI = 0.55 - 0.97, $I^2$ = 69.1%). In addition, an increase of 50 mg/day vitamin C intake, can reduce the risk of hip fracture by 5% (OR = 0.95, 95% CI 0.91 - 1.00, P = 0.05). Torbergsen., *et al.* [26] too concluded that low vitamin C concentrations among other factors may increase the risk of sustaining a hip fracture, possibly as a result of its effect on bone turnover mechanisms.

In an additional review, Zeng., *et al.* [27] who examined the association between dietary intake of vitamin C and the risk of hip fracture, osteoporosis, and bone mineral density loss, concluded that an adequate dietary intake of vitamin C decreases the risk of hip fracture, osteoporosis, and bone mineral density loss. A total of 13 eligible articles (including 17 studies) with 19,484 subjects were identified for the present meta-analysis. The pooled relative risk of hip fracture for the highest vs. lowest category was 0.66 (95% CI, 0.47 - 0.94) for dietary vitamin C intake, i.e. people with a greater frequency of Vitamin C uptake had a 34% (95% CI, 6%-53%) lower prevalence of hip fracture. In subgroup analyses stratified by study design, gender, and age, the negative associations were statistically significant. Furthermore, the statistical analysis of the association between vitamin C intake and the risk of osteoporosis (RR, 0.66; 95% CI, 0.48 - 0.92), plus bone mineral density at the lumbar spine and femoral neck showed beneficial vitamin C intake effects. Table 2 below summarizes the aforementioned findings and study conclusions.

| Researchers | Key findings |
|---|---|
| Ahmadiah., *et al.* [31] | Vitamin C deficiencies compromise bone health |
| Falch., *et al.* [17] | A vitamin C nutrient deficiency might be linked to hip fracture risk in some cases |
| *Finck., *et al.* [13] | Vitamin C intake is not associated with fracture risk, but high levels may significantly lower the risks of hip fractures in men |
| Hart., *et al.* [14] | High dietary vitamin C intake and supplementation may reduce hip fracture risk in postmenopausal women |
| *Lu,mbers., *et al.* [39] | Hip fracture cases had higher plasma vitamin C levels than controls with no fracture attending a day center |
| Malmir., *et al.* [18] | Vitamin C is potentially beneficial, and warrants consideration by orthopaedic surgeons in the treatment of a variety of musculoskeletal injuries |
| *Martinez-Ramirez., *et al.* [19] | Vitamin C intake was not related to osteoporotic fractures |
| *Michaelson., *et al.* [20] | High levels of vitamin C intake increase hip fracture risk |
| *Nieves., *et al.* [40] | No association between vitamin C and hip fractures as examined in cases versus controls who were interviewed |
| Sahni., *et al.* [21] | There is a possible protective effect of vitamin C on bone health in older adults |
| Schnitzer., *et al.* [38] | Vitamin C deficiency contributes to bone resorption and osteoporotic bone status in blacks Africans with femoral neck fractures |
| *Simon., *et al.* [15] | Dietary and serum levels of vitamin C were inconsistently associated with self-reported fractures |
| Sun., *et al.* [22] | A higher dietary intake of vitamins C, among other nutrients, is associated with a lower risk of hip fracture in elderly Chinese |
| Sun., *et al.* [25] | Meta-analysis supporting the view that increasing dietary vitamin C intake can decrease hip fracture risk |
| Torbergsen., *et al.* [26] | Low vitamin C concentrations are associated with an increased hip fracture risk, possibly through its impact on bone turnover |
| Yilmaz., *et al.* [42] | Vitamin C presence may speed up fracture healing |
| Zhang., *et al.* [41] | Vitamin C had a bearing on hip fracture risk in smokers rather than non-smokers |
| Zeng., *et al.* [27] | Vitamin C in diet positively reduces hip fracture risk |

***Table 2:*** *Table showing possible benefits of attaining optimal daily vitamin c levels in efforts to ameliorate hip fracture correlates in some studies, but not others*.*

## Discussion

Hip fractures, an important costly health concern in aging populations commonly lead to disabling hip osteoarthritis, and/or premature death. The associated disability may also severely restrict mobility and independence, thus impacting life quality markedly. Since proximal femur fractures show a high prevalence in elderly patients and are associated with an elevated risk of multimorbidity and early mortality, and recovery is impaired by malnutrition and oxidative stress, which is affected by antioxidants such as ascorbic acid [4], continued efforts to improve preventive strategies against hip fracture injuries, including secondary and tertiary preventive approaches as outlined recently by Choi., *et al*. [28], LeBlanc., *et al*. [29], and Marks., *et al*. [30] are clearly indicated. In addition, rehabilitation strategies capable of maximizing the functional recovery process, and of preventing secondary injuries to offset this current and projected burden are not universally acceptable or demonstrated clearly.

This seems unfortunate because vitamin C has been studied for many years, from many perspectives in its own right, and as a result, several authors have noted a potentially valuable role for considering the possible role of vitamin C in mediating or moderating bone health that may serve as a potent hip fracture determinant [2,25]. The possibility of vitamin C as an adjunct for alleviating, minimizing, ameliorating, or treating hip fractures after they occur must also be considered relevant here [4]. In addition to that, it appears increasing dietary vitamin C intake is likely to decrease the risk of fracturing a hip, at least in some cases, and this association should be more intensely verified [25]. As well, vitamin C may serve as a safe form of analgesic therapy [14], versus medications that may produce dizziness and other falls related risk factors that could be valuable in protecting against primary as well as second or recurrent hip fractures [10].

However, to more ably validate the idea that vitamin C should not be neglected in the course of efforts to prevent hip fracture, the value of vitamin C in preventing frailty, cardiovascular dysfunction, osteoporosis, neural deficits [7,31-34] and osteoarthritis [10] warrants specific study.

At the same time, preclinical studies aimed at developing testable hypotheses deserve more attention in this author's view, as do studies that examine vitamin C serum levels among differing types of hip fracture and hip fracture severity. The role of comorbid health conditions, age, gender, and ethnicity, among other factors, in this regard also warrants careful study. Moreover, whether vitamin C impacts fatigue, muscle aches and pains, mood and healing that can independently contribute to the overall magnitude of hip fracture disability warrants study. Since the bone building and/or antioxidant properties of vitamin C may only emerge after prolonged administration [35], studies of sufficiently long durations to permit changes to be revealed are recommended as well.

Meantime, even though the diverse aspects of vitamin C utilization and pharmokinetics is poorly understood and researched more evidence than not, implies the presence of a persistent vitamin C deficiency found to be debilitating generally speaking, may be one factor that inadvertently raises the risk for hip fractures directly or indirectly, even though conflicting results prevail. To generate more insight into this issue and others, and to foster more adequate translation of prevailing data to the clinic however, the possible linkages presented in figure 1 applied to carefully selected samples might serve as a reasonable starting point. After that, meticulously and rigorously designed studies to rule out competing hypotheses, and to avoid cross sectional inferences that do not take into account the fact that reported vitamin C intake may not be the same as actual plasma levels, and that its effects may be both disease specific, as well as dose-dependent and take weeks or months to unfold [35] are advocated. The efficacy of tailoring doses for purposes of reducing hip fracture risk, and disability should also be examined.

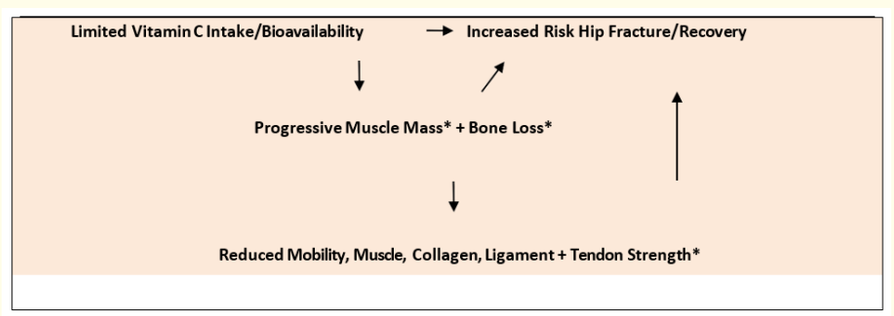


***Figure 1:*** *Points* at which vitamin C or a lack thereof may influence the hip fracture risk cycle.*

## Conclusion

Hip fractures, which produce high levels of mortality and morbidity remain a major challenge to treat and prevent. While laudable programs are in place that address multiple risk factors proven to heighten hip fracture risk, very little attention is given to vitamin C and its adjunctive or its potentially adverse potential effect. Based on this current mini-review, and in agreement with LeBlanc., *et al*. [29] and Malmir., *et al*. [18] the observation that having a hip fracture heightens the risk for hip fracture reoccurrence and/or additional fractures [36] and that bone mineral density appears to be positively affected by vitamin C [37], it seems reasonable to conclude that this factor and its possible physiological and pharmakinetic impact on the quality of bone health as this pertains to hip fractures should be studied further [34].

Indeed, a daily intake of vitamin C in sufficient quantities may yet be sufficiently suitable for minimizing bone resorption processes associated with aging, thus helping to safely reduce or minimize hip fracture risk, while speeding up hip fracture healing [42] due to its additional anti-oxidant and anti- inflammatory attributes, even though some studies have reported vitamin C to heighten hip fracture risk.

However, since the data are not robust, regardless of study conclusion, more research in this realm is clearly desirable. In the mean-time, those who are hospitalized with a hip fracture should be examined for vitamin C status, and treated accordingly to limit poor fracture outcomes, plus secondary fractures. Preventive programs should not overlook the utility of emphasizing the daily use of adequate vitamin C dietary sources, and make these available, if necessary. Educators can be helpful by expanding on the importance of vitamin C, to high risk individuals, as well as the dangers of excess supplementation, and directing people accordingly.

## Bibliography

1. Dizdarevic A., *et al.* "A comprehensive review of analgesia and pain modalities in hip fracture pathogenesis". *Current Pain Headache Reports* 23. 10 (2019): 72.

2. Chin KY. and Ima-Nirwana S. "Vitamin C and bone health: evidence from cell, animal and human studies". *Current Drug Targets* 19.5 (2018): 439-450.

3. Aghajanian P., *et al.* "The roles and mechanisms of actions of vitamin C in bone: new developments". *Journal of Bone and Mineral Research* 30.11 (2015): 1945-1955.

4. Hill-Mündel K., et al. "Preoperative ascorbic acid levels in proximal femur fracture patients have no postoperative clinical impact, while ascorbic acid levels upon discharge have a major effect on postoperative outcome". *Journal of Clinical Medicine* 9.1 (2019): E66.

5. Veronese N and Maggi S. "Epidemiology and social costs of hip fracture". *Injury* 49.8 (2018):1458-1460.

6. Zheng LZ., *et al.* "Magnesium and vitamin C supplementation attenuates steroid-associated osteonecrosis in arat model". *Biomaterials* 238 (2020): 119828.

7. Lykkesfeldt J., *et al.* "Vitamin C". *Advances in Nutrition* 5.1 (2014):16-18.

8. Takisawa S., *et al.* "Vitamin C deficiency causes muscle atrophy and a deterioration in physical performance". *Science Reports* 9.1 (2019): 4702.

9. Guo YE., *et al.* "Vitamin C promotes oligodendrocytes generation and remyelination". *Glia* 66.7 (2018): 1302- 1316.

10. Ripani U., *et al.* "Vitamin C may help to reduce the knee's arthritic symptoms. Outcomes assessment of nutriceutical therapy". *Medical Archives* 73.3 (2019): 173-177.

11. Shaik-Dasthagirisaheb YB., *et al.* "Role of vitamins D, E and C in immunity and inflammation". *Journal of Biological Regulatory Homeostatic Agents* 27.2 (2013): 291-295.

12. Savini I., *et al.* "Vitamin C homeostasis in skeletal muscle cells". *Free Radical Biology Medicine* 38.7 (2005): 898-907.

13. Finck H., *et al.* "Cross-sectional and prospective associations between dietary and plasma vitamin C, heel bone ultrasound, and fracture risk in men and women in the European Prospective Investigation into Cancer in Norfolk cohort". *American Journal of Clinical Nutrition* 102.6 (2015): 1416-1424.

14. Hart A., *et al.* "The role of vitamin C in orthopedic trauma and bone health". *American Journal of Orthopedics* 44.7 (2015): 306-311.

15. Simon JA., and Hudes ES. "Relation of ascorbic acid to bone mineral density and self-reported fractures among US adults". *American Journal of Epidemiology* 154.5 (2001): 427-433.

16. Pasco JA., *et al.* "Antioxidant vitamin supplements and markers of bone turnover in a community sample of nonsmoking women". *Journal of Womens' Health* 15.3 (2006): 295-300.

17. Falch JA., *et al.* "Low levels of serum ascorbic acid in elderly patients with hip fracture". *Scandinavian Journal of Clinical and Laboratory Investigation* 58.3 (1998): 225-228.

18. Malmir H., *et al.* "Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: a systematic review and meta-analysis of observational studies". *British Journal of Nutrition* 19.8 (2018): 847-858.

19. Martínez-Ramírez MJ., *et al.* "Vitamin C, vitamin B12, folate and the risk of osteoporotic fractures. A case- control study". *International Journal of Vitamin Nutrition Research* 77.6 (2007): 359-368.

20. Michaëlsson K., *et al.* "Diet and hip fracture risk: a case-control study. Study Group of the Multiple Risk Survey on Swedish Women for Eating Assessment". *International Journal of Epidemiology* 24.4 (1995): 771- 782.

21. Sahni S., *et al.* "Protective effect of total and supplemental vitamin C intake on the risk of hip fracture--a 17- year follow-up from the Framingham Osteoporosis Study". *Osteoporosis International* 20.11 (2009): 1853-1861.

22. Sun LL., *et al.* "Associations between the dietary intake of antioxidant nutrients and the risk of hip fracture in elderly Chinese: a case-control study". *British Journal of Nutrition* 112. 10 (2014): 1706-1714.

23. Orchard T., *et al.* "Dietary inflammatory index, bone mineral density, and risk of fracture in postmenopausal women: results from the Women's Health Initiative". *Journal of Bone and Mineral Research* 32.5 (2017): 1136- 1146.

24. Kim DE., *et al.* "Relationship between bone mineral density and dietary intake of β-carotene, vitamin C, zinc and vegetables in postmenopausal Korean women: a cross-sectional study". *Journal of Internal Medical Research* 44.5 (2016): 1103-1114.

25. Sun Y., *et al.* "Dietary vitamin C intake and the risk of hip fracture: a dose-response meta-analysis". *Osteoporosis International* 29.1 (2018): 79-87.

26. Torbergsen AC.., *et al.* "Micronutrients and the risk of hip fracture: case-control study". *Clinical Nutrition* 36.2 (2017): 438-443.

27. Zeng LF., *et al.* "Can dietary intake of vitamin C-oriented foods reduce the risk of osteoporosis, fracture, and bmd loss? systematic review with meta-analyses of recent studies". *Frontiers of Endocrinology* 10 (2020): 844.

28. Choi NG., *et al.* "Fall-related emergency department visits and hospitalizations among community-dwelling older adults: examination of health problems and injury characteristics". *BMC Geriatrics* 19.1 (2019): 303.

29. LeBlanc KE., *et al.* "Hip fracture: diagnosis, treatment, and secondary prevention". *American Family Physician* 89.12 (2014): 945-951.

30. Marks R., *et al.* "Hip fractures among the elderly: causes, consequences and control". *Ageing Research Reviews* 2.1 (2003): 57-93.

31. Ahmadieh H and Arabi A. "Vitamins and bone health: beyond calcium and vitamin D". *Nutrition Review* 69. 10 (2011): 584-598.

32. Balboa-Castillo T., *et al.* "Low vitamin intake is associated with risk of frailty in older adults". *Age Ageing* 1.47 (2018): 872-879.

33. Ballaz SJ. and Rebec GV. "Neurobiology of vitamin C: expanding the focus from antioxidant to endogenous neuromodulator". *Pharmacology Research* 146 (2019): 104321.

34. Lykkesfeldt J and Tveden-Nyborg P. "The pharmacokinetics of vitamin C". *Nutrients* 11.10 (2019): E2412.

35. Zollinger PE., *et al.* "Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomized trial". *Lancet* 354.9195 (1999): 2025-2028.

36. Ojo F., *et al.* "History of fractures as predictor of subsequent hip and nonhip fractures among older" Mexican Americans". *Journal of the National Medical Association* 99.4 (2007): 412-418.

37. Liu ZM, *et al.* "Greater fruit intake was associated with better bone mineral status among Chinese elderly men and women: results of Hong Kong Mr. Os and Ms. Os studies". *Journal of the American Medical Directors Association* 16.4 (2015): 309-315.

38. Schnitzler C., *et al.* "Ascorbic acid deficiency, iron overload and alcohol abuse underlie the severe osteoporosis in black african patients with hip fractures - a bone histomorphometric study". *Calcified Tissue International* 76.2 (2005): 79-89.

39. Lumbers M., *et al.* "Nutritional status in elderly female hip fracture patients: comparison with an age- matched home living group attending day centres". *British Journal of Nutrition* 85.6 (2001): 733-740.

40. Nieves JW., *et al.* "A case-control study of hip fracture: evaluation of selected dietary variables and teenage physical activity". *Osteoporos International* 2.3. (1992): 122-127.

41. Zhang J., *et al.* "Antioxidant intake and risk of osteoporotic hip fracture in Utah: an effect modified by smoking status". *American Journal of Epidemiology* 1.163 (2006): 9-17.

42. Yilmaz C, *et al.* "The contribution of vitamin C to healing of experimental fractures". *Archives of Orthopaedic and Trauma Surgery* 121.7 (2001): 426-428.

**Volume 11 Issue 5 May 2020**