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Research Article

Vitamin E and Hip Fractures: An Underused Prevention Strategy?

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Abstract

Background: Hip fractures and their causative mechanisms and treatments have been topics of great interest for many years. However, when compared to the plethora of research endeavors on vitamin D and hip fractures, very little research has been forthcoming as regards a role for vitamin E in this regard.

Aim: This mini review sought to examine whether vitamin E is a potentially important but somewhat overlooked hip fracture determinant whose properties might be mobilized to offset hip fracture risk, as well as for enhancing fracture healing among aging adults.

Methods: A scoping review of the available literature housed in key data bases of PUBMED, Scopus, and Web of Science Consolidated over the past decades including all years of publication in each instant was conducted using the key words: hip fracture and vitamin E.

Results: This search revealed a generally sparse data set of less than 20 pertinent studies prevails on this topic, regardless of data base examined.

Conclusion: Despite this obvious limitation in teasing out valid conclusions concerning the present topic, when considering that more data point to possible links between vitamin E deficiency and hip fracture risk than not, it seems more research in this realm will be highly valuable in the context of improving primary care strategies for older adults susceptible to hip fractures and their oftentimes life threatening and disabling consequences.

Keywords: *Bone; Hip Fractures; Intervention; Muscle; Prevention; Vitamin E*

Background

Hip fractures, which remain a highly prevalent debilitating health concern, particularly among aging adults [1], are potentially preventable, to some degree, despite very limited efforts in this respect when compared to the magnitude of reported tertiary prevention efforts post hip fracture. A condition that fosters extremely high direct costs, plus a potential array of highly aversive social and personal costs, as well as other highly disabling health conditions such as hip joint osteoarthritis, it is believed more efforts to examine all correlates of hip fracture risk, especially those amenable to primary prevention efforts are highly desirable [2-4].

However, even though it is now 30 years since Cummings and Nevitt [5] advocated for a better understanding of the various physical factors that underlie hip fractures, it is increasingly apparent that efforts to identify salient modifiable factors in this respect are poorly studied, and even if they are, are non-conclusive at best. It is possible however to accept a fairly well-supported role exists for deficient muscle mass and strength losses [6], as well as bone loss associated with aging, along with suboptimal antioxidant related nutritional practices as important factors in mediating hip fracture risk [7].

Other hip fracture determinants that cannot be overlooked but may be ameliorated to some degree through insightful interventions in their own right include a variety of chronic health conditions such as cardiovascular disease, and diabetes [8] along with fall-related risk-factors [2,3].

In this mini review, we elected to specifically examine the evidence base in support of vitamin E, a fat-soluble antioxidant that is an established correlate of bone, muscle, and general health, as one factor that might influence hip fracture risk and/or its manifestation and ensuing severity, as well as the possible onset of recurrent, second or third hip fractures given its potential to reduce the formation of free radicals and oxidative stress that can impact the rate of bone loss and muscle wasting during aging [7,9]. In addition, vitamin E appears helpful for reducing the extent of chronic health conditions associated with aging and that might underpin hip fracture risk. Coupled with its protective properties as regards muscle and bone health, vitamin E may indeed prove worthy of attention in its own right in efforts to improve our ability to offset hip fracture risk among the older population.

In the belief that much more can be done to reduce the incidence of hip fractures among older adults, the present report focuses predominantly on examining whether there is a possible independent, mediating or moderating role for vitamin E supplementation or maintenance that might be harnessed in the realm of efforts to protect against primary hip fracture injuries, as well as secondary hip fractures, and post hip fracture outcomes. With very few intervention approaches that can be safely recommended to prevent or delay the onset of hip fractures, and the fact that a primary fracture often leads to a second fracture or recurrent fracture of the hip, among other debilitating health issues, plus a strong rationale for examining vitamin E in this regard as discussed by Adamo., *et al.* [10], it was hypothesized that evidence in support of vitamin E as one underutilized hip fracture prophylactic and post hip fracture intervention approach would emerge.

We also noted that when we examined the history of 42 cases with hip fracture histories reported in a prior study, that only 1 patient had an osteoporosis history-often the target of intervention to offset hip fractures, which may have reflected this approach, but almost all or 86% had fallen prior to fracturing their hip, suggesting other factors raise the hip fracture risk. In this respect, of these hip fracture cases, 32/42 or 72% had one or more chronic health conditions, approximately 55% (23/42) had some type of neuromuscular related problem, while a further 36% or 15/42 cases had evidence of poor nutritional exposures, and 13 or 30% cases had both neurological, as well as nutritional deficits. We also found vitamin D intake was not a strong factor in explaining hip fracture outcomes in a related early analysis, when compared with muscle strength losses at the knee [11].

Since vitamin E has been shown to have a largely favorable bearing on bone and muscle health [7], as well as health status in general [12] and mindful that both other intrinsic factors as well as multiple extrinsic factors interact to determine hip fracture risk, the extent of any association of vitamin E levels with hip fracture incidence and recovery that might be harnessed therapeutically was specifically sought.

Aim of the Study

Given the strong global need to improve upon prevailing preventive and treatment strategies to counteract hip fracture disability and morbidity, as well as premature mortality, the key aim of this present mini review was to examine the extent of support for vitamin E as having a positive role to play in the realm of protecting older adults against primary and secondary hip fractures. The key question driving the review was whether hip fracture incidence can be mediated or moderated in some way by vitamin E, for example by adherence to a diet containing the desired daily level of vitamin E nutrients, and/or rendering key vitamin E containing foods available to those at risk for hip fractures, as well as those who have already sustained one or more hip fractures. On the other hand, if vitamin E is deemed to be harmful to bone, or muscle, efforts to reduce or eliminate vitamin E intake would appear reasonable to contemplate. A second aim was to examine if hip fracture outcomes can be favorably affected by vitamin E and whether further research in this realm is indicated or not, and if so, in what respect.

Methods

To address the review aims, related documents published predominantly over the past five years i.e. September 2014-December 2019 were specifically sought, even though no restrictions were placed on years examined in any of the data bases. The present search terms used were: Vitamin E and Hip Fractures. Databases explored were: PUBMED, Web of Science, Medline, and Scopus. After careful screening of available studies, those studies that examined any form of vitamin E in the context of hip fracture prevention were elected for in depth review, regardless of research design. No abstracts or foreign non-English articles or studies examining the topic, not surgically referred to vitamin E usage in arthroplasty contexts, and no preclinical or cellular based studies were analyzed.

After selecting all relevant articles, the downloaded references were carefully examined, and classified as being supportive of efforts to assess and intervene upon deficiencies in vitamin E or not in the context of hip fracture prevention and intervention. After a cursory examination of the available data it appeared that only a very basic narrative overview would be suitable for examining the present issue, and that it would be impossible to apply any scoring method for quality to provide more objective criticism with such diverse limited data. However, despite the possibility of type II errors given the small sample of available studies, it was felt that by including most of the findings published to date on this topic, a broad picture of the issues and conclusions needed to guide further thoughts on this topic would emerge.

For consistency the terms used to describe the vitamin E substrate being discussed in the research were those reported by the authors, even though these were not necessarily strictly comparable across studies. While some studies may have been overlooked, it is believed this ensuing review is inclusive of almost all, if not all, currently relevant studies and reviews on the topic of vitamin E and hip fracture prevention.

Results

Despite a fair number of preclinical animal related studies in the context of efforts to understand the role of vitamin E in a variety of fracture, bone and muscle health contexts, this current search of the literature revealed very few contemporary or past clinically-oriented studies focusing on the implications of vitamin E as related to either hip fracture prevention, or fracture healing or recovery, if compared to literature, for example on vitamin D and hormonal drugs or calcium supplements that are advocated for enhancing bone mass and strength (See table 1). Moreover, many articles accessed from the data bases using the key words notes above were not focused on the prevailing topic at all, and most that were related were not current, were attained via observational data, or were conducted in venues other than the United States. As well, of the 19 related studies examined, vitamin E isoforms assessed in the various studies were not uniform, were frequently assessed using surveys, or by dissimilar assays, and study approaches, time periods and samples varied highly. Most addressed differing research questions or confounding issues, such as the role of several vitamins including vitamin E and their combined effects on factors related to hip fractures.

Data Base	Number of Hip Fracture Related Reports		
	Vitamin E	Vitamin D	% vit E:D Reports
PUBMED	14	1788	0.8%
SCOPUS	224	4237	5.2%
WEB OF SCIENCE 5 data bases	360	4813	7.4%

Table 1: *Web based search results comparing key words vitamin E and hip fractures versus vitamin D and hip fractures for all years covered by data base.*

However, of the 19 somewhat relevant clinical papers retrieved, what is published does appear more promising than not even if hip fractures are not the specific focus of several of these published studies. Shen., *et al.* [13] for example, who applied a form of vitamin E

over a 12-week period to 89 postmenopausal women with osteopenia, age 59.7 ± 6.8 found the tocotrienol supplementation to reduce the degree of bone resorption significantly, while improving the bone turnover rate, which could play a favorable role in preventing structural bone changes that occur with age that are susceptible to falls injuries and hip fractures. A study by Magremanne., *et al.* [14] further showed the possible dual usage of alpha tocopherol alongside Pentoxifylline improved lesions attributed to osteoradionecrosis, which may be valuable to other patients who are at risk for osteonecrosis due to chemotherapy or corticosteroid usage, as are considerable numbers of hip fracture cases [4].

Other data related to the present topic are highlighted in table 2 and 3.

Study type + Research group	Key results
Cross-sectional or observational studies	
Mata-Granados., *et al*. [15]	Lower vitamin E serum levels and osteoporosis appeared to be related in healthy early postmenopausal women
Michaelson., *et al*. [9]	Low vitamin E intake + serum levels appear to increase fracture rates in the elderly, while α-tocopherol-containing supplement use was associated with a reduced rate of hip fracture (HR: 0·78; 95% CI: 0·65, 0·93) Compared with the highest quintile of α-tocopherol intake in ULSAM (follow-up: 12 y), lower intakes (quintiles 1-4) were associated with a higher rate of hip fracture (HR: 3.33; 95% CI: 1.43, 7.76); vitamin E insufficiency is associated with higher fracture risk The HR for hip fracture in men for each 1-SD decrease in serum α-tocopherol was 1.58 (95% CI: 1.13, 2.22) and for any fracture was 1.23 (95% CI: 1.02, 1.48)
Pasco., *et al*. [16]	Vitamin E may suppress bone resorption in nonsmoking postmenopausal women randomly selected wherein the duration of antioxidant supplements including vitamin E appear to negatively correlate with a valid bone resorption marker
Shi., *et al*. [17]	Bone mineral density at the hip and other sites in 2178 adult Chinese women was positively related to greater vitamin E consumption + serum vitamin E levels, but this associate on was not found to be the case in 1025 Chinese men
Yang., *et al*. [18]	Based on 2 cross-sectional studies, increasing quartiles of ỳ-tocopherol were associated with increasing femoral neck bone density, and marginally with **α**-tocopherol associated with dietary intake when adjusted for all covariates
Case-control studies	
Holvik., *et al*. [19]	Low serum concentrations of α-tocopherol were associated linearly with increased risk of hip fracture in older Norwegians, with a 51% higher risk in the lowest compared to the highest quartile.
Sun., *et al*. [20]	Higher dietary vitamins E intake levels are associated with a lower hip fracture risk in elderly Chinese adults. After adjustment for potential covariates, dose-dependent inverse associations were observed between the dietary intake of vitamin E, and the risk of hip fracture (P for trend ≤ 0·005). The OR of hip fracture for the highest (v. lowest) quartile of intake for vitamin E was 0·51 (95 % CI 0·36, 0·73)
Ter Berg., *et al*. [21]	Sarcopenic older adults had 10-18% lower intake of vitamin E and other nutrients compared to nonsarcopenic older adults
Torbergsen., *et al*. [22]	Low vitamin E concentrations were associated with an increased risk of hip fracture, possibly mediated through bone turnover mechanisms

Zhang., *et al*. [23]	Antioxidant intake was associated with reduced risk of osteoporotic hip fracture in a cohort of 1215 hip fracture patients and 1349 controls over age 50, and the effect was strongly modified by smoking status. Among ever smokers, participants in the highest quintile of vitamin E intake (vs. the lowest) had a lower risk of hip fracture after adjustment for confounders (odds ratio = 0.29, 95% confidence interval (CI): 0.16, 0.52; p-trend < 0.0001)
Randomized or prospective studies	
Chuin., *et al*. [24]	Vitamin E may protect against bone loss in elderly women that is comparable to resistance training
D'Adamo., *et al*. [25]	High functioning hip fracture cases have higher vitamin E concentrations than low functioning cases; vitamin E may represent a potentially modifiable factor in realm of post hip fracture recovery of function
Melhus., *et al*. [26]	After adjustment for major osteoporosis risk factors, the odds ratio for hip fracture among current smokers with a low intake of vitamin E was 3.0 (95% confidence interval 1.6-5.4); insufficient dietary intake of vitamin E may increase hip fracture risk in current smokers, but more adequate intake appears protective
Hantikainen., *et al*. [27]	Higher dietary non enzymatic antioxidant intake is associated with lower risk of hip fracture in the elderly
Ostman., *et al*. [28]	In elderly men high oxidative stress is associated with reduced bone mineral density, which is more pronounced in individuals with low serum levels of the antioxidant vitamin E
Samierii., *et al*. [29]	A "south-western French" pattern rich in Ca, P, vitamins D and B12, retinol, alcohol, proteins, and fats-including unsaturated fats; poor in vitamins C, E, and K, carotenes, folates, and fibers; and related to a higher consumption of cheese, milk, and charcuterie and a lower consumption of fruits and vegetables was related to a 33% lower risk of hip fractures (95% CI 3-39%, P = 0.03).
Shen., *et al*. [13]	12-weeks of tocotrienol supplementation improved bone remodeling among osteopenic women

Table 2: *Clinically oriented studies demonstrating a possible linkage of vitamin E with hip fracture risk and recovery.*

Researcher group	Study type	Key findings
Ilesamni-Oyelere., *et al*. [30]	Cross-sectional	High nutrient vitamin E α-tocopherol intake of post- menopausal women is negatively associated with hip + trochanter bone mineral density measures
Zhang., *et al*. [31]	Cross-sectional	There is a negative correlation between serum - tocopherol levels and femoral neck bone mineral density

Table 3: *Studies implying detrimental vitamin E effects on hip fractures.*

Discussion

Bone requires a variety of nutrients throughout life in order to develop and assume an array of optimal structural and functional properties [32]. Conversely, the idea that bone loss leading to an increased fracture and disability risk among many older individuals may be significantly affected by a variety of nutritional factors, such as vitamin E has been put forth [13]. Muscle is also key to bone health as well as bone protection and is affected favorably as far as data base shows by optimal vitamin E, rather than deficient levels of vitamin E [33]. Based on current research to examine a role for vitamin E in reducing hip fracture risk, this review not only noted insufficient numbers of any study, especially well-designed hypothesis testing studies in this regard, but somewhat divergent conclusions among those that have been conducted clearly preclude any definitive implications for clinical practice. That is, despite a fairly robust health-associated role for vitamin E, the body's most important antioxidant [34] and one found to mediate a variety of antioxidative processes that could potentially

affect bone and muscle status, and hence hip bone injury vulnerability adversely, the question of whether suboptimal vitamin E intake levels or availability or uptake or all of these factors has a bearing on hip joint fractures, is promising, but still, inconclusive. Indeed, even though several reasonably favorable investigative reports on this topic have been generated in a number of animal models [1], as well as more clinical studies than not (See table 2 and 3), no specific report to date has yielded any irrefutable evidence for regarding vitamin E intake as a crucial antiosteoporotic and/or hip fracture moderating agent via other mechanisms despite a strong case for its possible role in light of its established bone building, and muscle protective roles. Also problematic is the fact that we were not able to conduct any sound systematic quality analysis of any article. However, on balance, since more research is showing a possible link between vitamin E and hip fracture risk, this association should be explored further and reflected upon critically from the standpoint of experimental design in our view. As well, the influences of lifestyle, comorbid illnesses, pain status, inflammation, and obesity, possible hip fracture determinants that can be favorably impacted by vitamin E should be investigated. In the meantime, while the use of calcium is often advocated for bone building in aging adults, calcium alone does not reduce hip fracture incidence significantly [35].

Moreover, a variety of novel pharmacologic bone building interventions including hormone therapy have been found to be potentially harmful to the health of the aging adult, while a role for vitamin D in its own right as a fracture risk mediator remains in dispute and is non-conclusive [36].

On the other hand, since vitamin E has potent proven biological effects related to well-established hip fracture determinants, and is available in many food sources that might be used to influence bone health, muscle function, and fracture risk [43] its possible utility in the context of hip fracture prevention surely warrants more attention. Indeed, if averting a possible vitamin E deficiency can reduce hip fracture risk and subsequent fractures of the hip to some degree and can do this safely in the context of at risk men and women, the benefits of this strategy could be far reaching. Research to establish, both favorable vitamin E influences, as well as what dosages of vitamin E if taken as a supplement are possibly helpful versus those that are harmful should be specifically investigated to avoid overlooking a possible cost-effective and effective means of reducing hip fracture disability and death, as well as excess morbidity due to over indulgence in vitamin E and is hence strongly urged. A role for vitamin E post hip fracture should also be explored more intently in the author's view.

Concluding Remarks

Notwithstanding the limited number as well as unexplored quality of the available clinical studies that focus on, or mention, vitamin E and hip fractures, most of the related research in this context shows vitamin E to favorably impact a wide array of health promoting factors including those that influence bone and muscle health [12,37], as well as physical function [38]. Moreover, despite several studies to the contrary [39-41], recent findings by Shen., *et al*. [13], Chin., *et al*. [43] and Adamo., *et al*. [10] indicate a possible set of benefits for vitamin E supplementation or adequate dietary intake in the context of efforts not only to avert hip fractures, but to possibly foster hip fracture recovery rates and enhance more rapid recovery of functional abilities. Research further shows vitamin E may well orchestrate many fundamental bone building mechanisms at the molecular and cellular level that can account for its observed impact on bone [12,42], as well as positively influencing muscle and health status, that could help to reduce any proclivity to falls that produce hip fractures. Indeed, rather than employing pharmaceutical drugs to build bone or prevent its age-associated loss, that may have numerous adverse side effects, vitamin E in various forms may yet serve as an effective natural antiosteoporotic agent in protecting osteopenic women, as well as postmenopausal women [13], along with older men against hip fracture disability [43] effectively and safely. As such, the appropriate application of vitamin E supplements or food intake in this regard, may indeed be projected to have the potential to not only reduce the odds of incurring enormous degrees of morbidity, but also the associated suffering among the elderly, both men and women, and should be studied more intently and comprehensively. Including, but not limited to examining the comparative impact of varying vitamin E homologues on hip fracture prevention and outcomes, as well as its efficacy with respect to calcium and vitamin D, among other nutriceuticals.

The comparative effects of foods that may prevent deficiencies in vitamin E versus supplements, on bone health and related muscle determinants that heighten hip fracture risk should also be explored. These include but are not limited to certain commonplace low cost oil and seed products, which may potentially prove effective not only in a preventive sense, but also after a hip fracture [44]. While many hip fracture risk fractures prevail, targeting adults using steroids, those with malabsorption conditions, along with smokers and alcohol dependent persons, frequent fallers, and those with comorbid illnesses might prove especially valuable. In addition, those who are physically and/or cognitively challenged or unable to prepare meals or shop for foods containing vitamin E along with those unable to afford the required foods/supplements [24] or both, might warrant some specific help in this regard [44]. Efforts to routinely measure vitamin E serum levels in all aging adults, as well as educating the general public, as well as primary care and osteoporosis patients, in particular about the facts of vitamin E, including the use of supplements that are derived chemically from synthetic products, is also indicated, especially in cases with preexisting illnesses, and where either deficient or excess serum vitamin E levels prevail, even if support for this idea is not universal and tentative at best.

In addition to the aforementioned practice perspectives, considering the fact that as in other areas of clinical research, the presence of contradictory evidence may not imply ineffectiveness, but rather unanticipated research design and interpretation issues, and others, more effective research attempts to supplement available clinical results will undoubtedly help to strengthen the credence of the current evidence base and is strongly encouraged.

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