

Vitamin A and its derivatives effect on bone mineral density, a systematic review

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ABSTRACT

Background: Even though vitamin A (Vit A) is one of the essential vitamins required for bone growth and development, it is still uncertain whether its effect on bone mineral density (BMD) is beneficial or harmful. **Aim:** To assess Vit A's effect and its derivatives on BMD and the risk of developing osteoporosis. **Data sources:** PubMed, Cochrane Library, Science Direct, Embase, and Google Scholar were searched in February 2019 and updated in November 2020. **Methods:** Conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. **Results:** A total of 13 studies were included in this report out of 9,124 citations. Five of them were cross-sectional studies, and nine were cohort studies. Three out of five cross-sectional studies showed an increase in BMD, while two showed a decrease in BMD. Four out of eight cohort studies found an increase in BMD; two studies found no association between vitamin A level and BMD; one showed an inverse U-shape association of vitamin A with BMD, suggesting that both the increase or decrease levels of vitamin A affect BMD, while only one study showed a decrease in BMD. **Conclusion:** Although most of the included studies showed a favorable effect of Vit A on BMD, Vit A's role or its derivatives on BMD change remains unclear.

Keywords: Bone mineral density (BMD), osteoporosis, Vit A, vitamin A derivatives, vitamin A supplements vitamin

Introduction

Vitamin A (Vit A) plays a role in bone growth and development,^[1] influencing osteoclast and osteoblast. It is one of the fat-soluble vitamins and an antioxidant. It is an essential nutrient required to maintain many biological activities.^[2] The daily required need for Vit A for adults is 900 micro g/d in males and 700 micro g/d in females.^[3] Our diet is found in two forms, either as retinal esterase/retinol, which is found in eggs, milk, fortified cereals, and liver or as carotenoids/beta-carotene, which is found

in vegetables. It is also found in over-the-counter multivitamins and some medications as Isotretinoin.^[2]

There is a debate over whether increased consumption of Vit A is linked to skeletal fragility promotion. Since the 1920s, this relationship was demonstrated in different clinical animal and observational human studies.^[3] M. Mata-Granados found that women with higher retinol levels were more at risk of osteoporosis than women with low retinol levels.^[4]

On the other hand, some studies have shown Vit A to be beneficial for bone health by promoting osteoblasts differentiation and bone formation.^[3] In an Italian case-control study of 75 women with osteoporosis and another 75 women without osteoporosis,

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a positive correlation between femoral neck BMD and plasma retinol level has been found.^[5]

Other studies showed no link between increased Vit A intake and osteoporosis or fractures.

A recent meta-analysis of the prospective cohort studies about dietary intake of vitamins: A, C, E and the subsequent fracture risk at various sites found that increased Vit A intake did not increase the risk.^[6] On the other hand, a 2017 systematic review and meta-analysis suggested that Vit A intake and level may differentially influence the risks of total and hip fractures.^[7]

Since the significance of knowledge about Vit A's role on bone health in dealing with patients with increased risk of osteoporosis and fractures in primary care and the current knowledge about its role on bone health is inconclusive, we aim in this study to assess the evidence of the effect of Vit A on BMD and the risk of developing osteoporosis.

Method

This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to explore the association of vitamin A use and BMD change.^[8]

Study strategy

We performed a comprehensive literature search in February 2019 and an updated one in November 2020. The searched databases were PubMed, Cochrane Library, Science Direct, Embase, and Google Scholar using Vit A, Retinol, Fracture, Osteoporosis, BMD, bone health as the keywords. All published articles (cohort, case-control, cross-sectional, and randomized control trials [RCTs]) discussing the influence of oral Vit A or its derivatives on bone tissue health were extracted. Unpublished literature was searched by looking into the clinical trial registry.^[9]

Inclusion and exclusion criteria

All studies fulfilled the inclusion criteria: (1) Population: Adolescents and adults, males and females. Animal studies were excluded (2) Exposure: Circulating levels of Vit A and retinol in the blood (either from supplements or diet), but all treatment forms were excluded (3) Outcomes: BMD and the osteoporosis risks were detected by radiological evidence. (4) Study type: Cross-sectional, case-control, cohort studies and RCTs (5) Timing: Studies published after 2000. All languages were included.

Study selection

Two reviewers (SR and QK) separately scanned the titles and abstracts, and when required, the full text was recovered and reviewed to identify all the relevant articles. A third author (GR) resolved the disagreements.

Risk of bias and quality assessment

The Newcastle–Ottawa scale (NOS) is a scale used for evaluating the quality of nonrandomized studies involved in a systematic review and/or meta-analyses.^[10,11] Three factors were evaluated for scoring the quality of the studies, selection, comparability and outcome. The studies' quality was graded by awarding stars in each subset with a total score of 9. The studies that scored seven or more were considered high quality. In contrast, those that scored lower than seven were considered low quality.^[10,11] QK and SR, two independent reviewers, assessed the quality of the included studies using NOS. A third reviewer resolved the disagreements.

Data extraction

For the selected studies, we used Covidence software,^[12] a systematic review production tool for the title, abstract and full-text screening.^[13] After searching, using the keywords, two reviewers (SR, QK) extracted the data separately using pretested data extraction form; any conflicts were resolved by a third reviewer (GR). The extracted information included author, year, study design, setting, patient's age, sample size, confounders, and exposure. The outcomes including osteoporosis (a common skeletal disorder characterized by decreased bone density, compromised bone strength, and increased fracture risk^[14]) were based on the BMD measures for the two groups, exposed and nonexposed.

Dealing with missing data

The mean, *P* values, standard deviations (SD) of the mean difference were missing in the selected studies. Consequently, we contacted the authors of each study with no response received, so we could not pool the results. The present study was approved after review under the ethical standards by King Abdullah International Medical Research Center (KAIMRK) IRB Committee on Feb 3, 2019 (research number RC19/024/R).

Results

Literature search

A total of 9,124 citations were identified by searching the databases and manual search of references. After screening the titles and abstracts, 1,644 duplicates and 7,414 irrelevant studies were removed. Sixty-six studies met our criteria; after full article reviews and assessment for eligibility, 53 studies were excluded. A total of 14 studies are included in this report. Figure 1 shows a PRISMA flowchart depicting the process of selection and exclusion.

Quality of evidence

The overall quality of evidence on the association between Vit A and its derivatives was moderate and high. Most studies were graded seven points or above on the nine-point Newcastle–Ottawa scale for quality. Only two studies had lower grades.^[14,15]

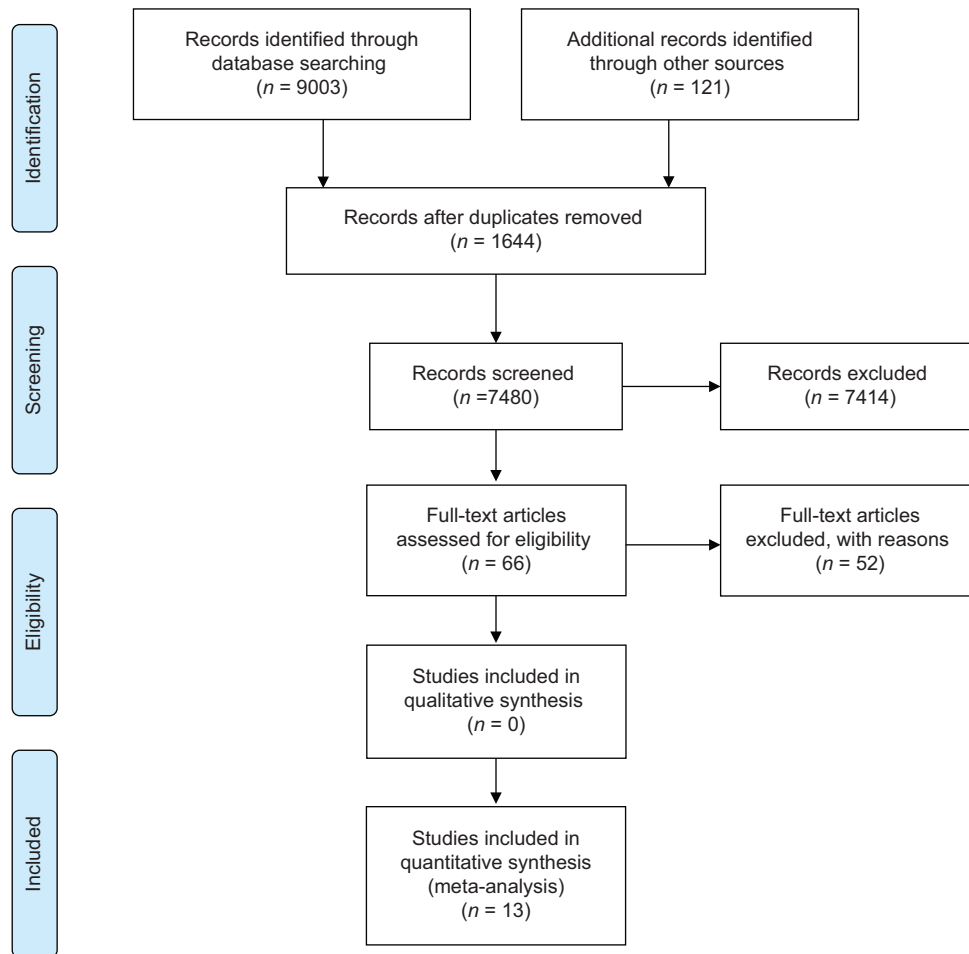


Figure 1: A PRISMA flowchart depicting the process of selection and exclusion (<http://prisma-statement.org/prismastatement/flowdiagram>).

Study characteristics

The 14 included studies were a mixture of cross-sectional and cohort studies, which reported the association between Vit A or its derivatives' use and change in BMD, and these were in English. The studies were conducted in the USA, Brazil, Denmark, Korea, Spain, Norway, China, Thailand, and the Netherlands. Overall, the data for 71,078 participants, including adults, age groups ranging between 20 and 80, were used in this systematic review. Half of the included studies used both genders; the other half included females only, three of which were postmenopausal. The enrolled articles either study the effect of Vit A, retinol, or beta-carotene on BMD. The BMD change was measured by DXA. Most of the included studies' results were adjusted for age, sex, and BMI [Table 1].^[4,15,16-20]

Primary outcomes

Five of the included studies were cross-sectional to look for the relation between dietary Vit A and BMD. Four of those showed an increase in BMD, while one showed a decrease in BMD in all sites (lumbar spine, femoral neck, and trochanter).

The eight cohort studies used supplemental Vit A derivatives (retinol or retinal esterase or beta-carotene). Of them, four found an increase in the BMD with greater levels of supplementary Vit A.

While only one study showed a decrease in BMD, two studies found no association between these levels and BMD; another one showed an inverse U-shape association of Vit A with BMD, suggesting that both increased or decreased levels of vitamin A affect BMD.

Discussion

This systematic review of observational studies that aimed to explore the association between Vit A and its effect on BMD revealed mixed results. Although most of the incorporated studies revealed a favorable effect, uncertainty remains over Vit A's role or its derivatives on BMD change.

Most of the included studies have confirmed that a higher Vit A intake may increase BMD in all positions, which can be explained by the fact that Vit A acts as an antioxidant that reduces bone resorption by decreasing oxidative stress.^[27] However, the exact underlying mechanism remains unclear as hypervitaminosis A is associated with adverse bone effects by disrupting the calcium-regulating hormone metabolism and decreasing vitamin D activity.^[7]

A recent meta-analysis by Zhang *et al.*^[7] found that a higher beta-carotene intake may increase total fracture risk. They also

Table 1: Included study results

	Study first author, year (country)	study name	Study design	Setting	Number of patients	Supplement, type, dose	Gender	results/outcomes	summary of the result
1	Thais R. Silva, 2015 (Brazil)	Associations between body composition and lifestyle factors with bone mineral density according to time since menopause in women from Southern Brazil: a cross-sectional study	Cross-sectional	hospital based (Gynecological Endocrinology Unit)	99	dietary vitamin A	Females	vitamin A appears to be less consumed among women with lower bone mass. Considering all sample, vitamin A intake lower than 700 mcg a day, that is the recommended amount for dietary reference intakes	increase BMD
2	Sahni S, 2009 (USA)	Inverse association of carotenoid intakes with 4-y change in bone mineral density in elderly men and women: the Framingham Osteoporosis Study 2009	Cohort	population based	874	a-carotene, b-carotene, cryptoxanthin, lycopene, and lutein/zeaxanthin	both	Carotenoids showed protective role against 4 year BMD loss in older men and women.	increase BMD
3	C Ballew, 2009 (USA)	High Serum Retinyl Esters Are Not Associated with Reduced Bone Mineral Density in the Third National Health and Nutrition Examination Survey, 1988–1994	cohort	population based	68 to 374 for men and from 597 to 602 for women	Retinyl Esters	both	no associations between physiological indicators of potential excess vitamin A intake and either BMD or osteopenia/osteoporosis	No association
4	Kristina L. Penniston, 2006 (USA)	Serum retinyl esters are not elevated in postmenopausal women with and without osteoporosis whose preformed vitamin A intakes are high	Cohort	population based	60	Retinol /Retinyl esters / NS Total VA /Retinyl esters	Females	Serum retinyl esters were not elevated in these postmenopausal women despite intakes of total VA that were nearly two-fold the Recommended Dietary Allowance. However, retinyl ester concentration (percentage of total VA) was marginally associated with osteoporosis	marginal decrease BMD
5	JOANNE H. E. PROMISLOW, 2002 (USA)	Retinol Intake and Bone Mineral Density in the Elderly: The Rancho Bernardo Study	Cohort	population based	958	RETINOL	Both	Both sexes, increasing retinol became negatively associated with skeletal health at intakes not far beyond the recommended daily allowance (RDA), intakes reached predominately by supplement users, inverse U-shaped association of retinol intake with BMD and bone maintenance observed in this cohort raises the concern that either too little or too much retinol may adversely affect bone health	both increase or decrease level of Vitamin A affect BMD
6	L Rejnmark, 2004 (Denmark)	No effect of vitamin A intake on bone mineral density and fracture risk in perimenopausal women	cohort	multicenteric	1869		Females	no associations between intake of vitamin A and BMD of the femoral neck or lumbar spine	No association

Contd...

Table 1: Contd...

7	Nam-Seok Joo,2015(Korea)	Vitamin A intake, Serum Vitamin D and Bone Mineral Density: Analysis of the Korea National Health and Nutrition Examination Survey (KNHANES, 2008-2014)	Cross-sectional	population based	6481 (2907 men and 3574 women)	Dietary vitamin A	both	Total hip and femoral neck BMD in men and lumbar spine BMD in women were both positively correlated with dietary vitamin A intake (Mean dietary vitamin A intakes were 737 and 600 µg RE (Retinol Equivalents) in men and women, respectively) in subjects with serum 25(OH)D >75 nmol/L.	increase BMD
8	J. M. Mata-Granados,2013(Spain)	Vitamin D insufficiency together with high serum levels of vitamin A increases the risk for osteoporosis in postmenopausal women	Cross-sectional		232		Females	Bone density measurements revealed that the risk of osteoporosis was ~8 times higher in women with the highest retinol levels, as compared with women with the lowest retinol levels.	decrease BMD
9	Kristin Holvik,2015(Norway)	No increase in risk of hip fracture at high serum retinol concentrations in community-dwelling older Norwegians: the Norwegian Epidemiologic Osteoporosis Studies	cohort	multicenter population based study	21774	s-retinol	both	inverse association between s-retinol and risk of hip fracture, which was statistically significant in women but not in men	increase BMD
10	GD Chen ,2015(china)	Association of dietary consumption and serum levels of vitamin A and β-carotene with bone mineral density in Chinese adults β-carotene with bone mineral density in Chinese adults	Cohort	population based	3154	Serum levels of retinol and β-carotene	both	greater levels of serum retinol, β-carotene, and the β-carotene-to-retinol ratio were associated with a higher BMD	increase BMD
11	Mi-Ja Choi,2007(Korea)	Relationship of nutrient intakes and bone mineral density of elderly women in	Cross-sectional	clinic center	101	Dietary Vitamin A	Females	Vitamin A, vitamin B1, and vitamin B2 intakes of participants in the osteoporosis group were lower than those in the normal group	increase BMD
12	Chupeerach C , 2011(Thailand)	Decreased retinol transport proteins in Thai postmenopausal women with osteoporosis	Cross-sectional	OBGYN clinic	144		Females	this study showed lower TTR, BMI and serum calcium in osteoporotic patients than controls. Malnutrition is a risk factor for osteoporosis and TTR may be a marker for osteoporosis	decrease BMD
13	de Jonge,2015(Netherlands)	Dietary vitamin A intake and bone health in the elderly: the Rotterdam Study	cohort	Population based	5288	Ditary intake	both	a plausible favourable relation between high vitamin A intake from the diet and fracture risk in overweight subjects, whereas the association between vitamin A and BMD is mainly explained by BMI.	increase fracture

observed a positive influence of lower blood retinol levels on total and hip fracture risk. Additionally, a high intake of Vit A had slightly increased the risk of hip fracture but decreased total fracture risk in their results. The difference in retinol absorption could explain this variability in the fracture risk.^[7] Houtkooper et al.^[27] measured BMD at lumbar vertebrae 2–4, femur neck, Ward’s triangle, and trochanter. A positive association between retinol intake and BMD at all bone sites except for the femoral neck was found.

In another recent systematic review by Zhou et al.^[6] on the dietary vitamin intake effect on fracture risk, no harmful impact of Vit A was found. They explained their results by their included

study sites of fractures which were not differentiated, and the effect estimates for the fractures in different sites might have been neutralized. The sources of Vit A differ between studies in previous meta-analyses.

These contradictory results regarding vitamin A intake, absorption, and role in fracture risk suggest that an increase in BMD is not a guaranteed protector against fracture risk. Other factors may have a role in increasing such a risk. For example, the Iowa Women’s Health Study followed up over 34,000 postmenopausal women for an average of 9.5 years and found a no-dose-response relationship demonstrated between Vit A and fracture risk at all sites.^[28]

Bone fragility and fracture risk are dependent on bone mass and quality; in animal studies, it has been shown that an excess Vit A has a negative effect on the cortical bone. On the other hand, human epidemiologic studies only used the DEXA scan to assess BMD, which is a two-dimensional technique providing measurements of a real (mg/cm^2) rather than volumetric (mg/cm^3) BMD.^[29,30] DXA fails to assess Vit A's independent changes on the trabecular and cortical bone or the important components of bone microarchitecture.^[31]

All the cross-sectional studies showed a protective role of Vit A on BMD if the participants took the vitamin's daily allowance from the diet. However, the exact level of Vit A either from the diet or supplement to cause a beneficial bone effect or prevent harm, cannot yet be determined from the available evidence. As most of the studies assessed the dietary intake based on a different questionnaire regarding food frequency; the semi-quantitative instrument might have errors classifying that intake. Moreover, concurrent ingestions of other nutritional substances may affect the relationship between Vit A ingestion, absorption, and health outcomes.^[15] For example, fatty meals increase the absorption of Vit A and Vit D as well. Moreover, other antioxidants, vitamins, and minerals consumed from the diet affect bone health.

Most of the included studies were carried over the aging population, and as it is known that aging is a risk factor for a poor diet and weight loss; both may contribute to osteoporosis.

In this review, only observational studies (cross-sectional and cohort) were included because there have been very few RCTs and case-control studies in humans, which did not fulfill our inclusion criteria. All cross-sectional studies showed a protective role on BMD if the participants took the daily allowance of Vit A from the diet. In contrast, the included cohort studies that used supplemental Vit A were not all consistent with this role. This may be assigned to the fact that a healthy balanced diet rich in nutrients, minerals, and antioxidants other than Vit A positively affect bone health.

Our study did not involve a meta-analysis because the pooling of results was not possible due to the missing data. Moreover, we only studied the effect of Vit A on BMD as the previous systematic reviews on the fracture risk did not illustrate this role. Also, their results were inconsistent, which merited further investigation.

Thus, taking Vit A in doses higher than required for bone health benefits cannot be encouraged until a dose-response relationship is further studied where the exact mechanism and possible harms are illustrated. This relationship should be further investigated by large-scale prospective studies considering other confounders. More studies are required to clarify the reasons for the increased hip fracture with increased Vit A intake despite the decrease in all site fracture risk. The effect of Isotretinoin (high-dose Vit A), which is one of

the most common used dermatologic treatment for several conditions, like acne, on BMD should be investigated.

This systematic review has several remarkable strengths, such as the comprehensive search, strict inclusion criteria that focused only on the relationship between the Vit A use and BMD change, and the included studies published with no language restrictions. Nevertheless, only observational studies' involvement carries the possibility of unmeasured residual confounding, which cannot be excluded. Moreover, observational studies cannot clarify if the observation is a causal effect or a result of unmeasured variables.

Conclusion

Our study reviewed the risk and benefit of Vit A on BMD; we revealed a favorable effect, where most of the included studies have shown that a higher Vit A intake may increase BMD in all sites. However, we still have inconclusive evidence of this positive relationship due to a lack of quantitative data. Therefore, well-controlled observational and RCTs are recommended to convey more valuable results. Aging is a risk factor for a poor diet and weight loss; both may contribute to osteoporosis.

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Conflicts of interest

There are no conflicts of interest.

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