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The Probable Impact of Soy Isoflavones in Bone Fracture Downturn: A Systematic Review

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ABSTRACT

Background: There is a direct relationship between taking soy isoflavones and higher bone density, but there is a paucity of studies examining the relationship between flavonoid consumption and fracture risk. This study aimed to assess the bone fracture and its relationship to soy product intake by performing a systematic review. **Methods:** Scopus, PubMed, and Web of science were searched to find studies on the effect of soy isoflavones on bone fracture, without any time and language of publication restrictions. Key words of SoyMilk, soymilk, soybeans, soybean, soy, soya, Isoflavones, Isoflavone, ipriflavone, equol, genistein, daidzein, glycitin, fractures, and broken bone were used. **Results:** From a total of 1675 articles, 27 studies (cross-sectional studies (n=1), case-control studies (n=1), cohort (n=11), and randomized control trials (n=14)) were identified, and their quality was assessed. Eighteen studies highlighted mainly positive results in preventive influence of soy bone fractures. Two papers reported a positive effect was observed in men with cancer. No significant association was found between soy intake and bone prevention fracture in eight distinct papers. **Conclusion:** Intake of soy isoflavones can make a significant preventive effect on bone fracture; however, the results of some studies are controversial. Therefore, it is necessary to survey more studies to identify the relationship between isoflavones and bone fracture.

Keywords: *Isoflavones; Bone; Fracture*

Introduction

Bone with frequent renovation during the lifespan is an active tissue (Shetty *et al.*, 2016). Bone renovation contains two stages including formation of new bone tissue and reabsorption of the old bone tissue (Eastell and Szulc, 2017). During growth, the amount of new bone tissue formation surpasses that of reabsorption of old bone tissue, but with age, this trend is reversed. Augmented and non-stop bone reabsorption in aging causes osteoporosis. Osteoporosis is categorized by decreased bone mass related to augmented bone fragility and vulnerability to fracture (Shetty *et al.*, 2016).

Pelvic fractures increase the financial burden by

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20 percent due to long-term care of the elderly and in some cases even death (Bunout *et al.*, 2006). Isoflavone soy is classified as phytoestrogens, because of its similarity with estrogen herbal mixtures that can attach to estrogen receptors, and performs the same function as estrogen (Taku *et al.*, 2011). Isoflavones are found in abundance in soy, so in the case of estrogen deficiency (menopause), they can prevent bone loss and bone fracture (Taku *et al.*, 2011, Zhang *et al.*, 2005, Zheng *et al.*, 2016).

Soybean production and dietary consumption have increased within Western nations with postulated health benefits by increasing bone health, especially in women (Xiao, 2008). There has also been an association between the use of phytoestrogens and increased bone density (Greendale *et al.*, 2002, Zhang *et al.*, 2005); however, studies in Caucasian people are incomplete due to lower habitual consumption of phytoestrogens.

In a study in Shanghai, the average soy isoflavone intake in postmenopausal women was 38 mg / day, which was associated with a reduction in bone fractures (Zhang *et al.*, 2005). Even though genetic factors affect the peak bone mass, regimen is one of the risk factors for osteoporosis (Chan *et al.*, 2011). Natto is a kind of fermented soybean that is taken. This food is rich in menaquinone-7and comprises 100 times more menaquinone-7 than numerous types of cheese (Katsuyama *et al.*, 2002). Based on the present evidence, the consequences of epidemiological studies are still controversial about the effect of soy isoflavone on bone fraction. To the best of the authors' knowledge, this systematic review is the first to survey the effect of soy isoflavone on preventing bone fraction in patients. Bone fracture, especially in menopause women is an important problem worldwide, so in this systematic review, literature was searched to investigate the probable effect of soy isoflavones on bone fracture to reveal the positive effect of soy products on ameliorating fracture of bone in human to help them enjoy their life better. Thus, the main aim of this study was to survey the efficiency of soy isoflavone on fraction in patients by searching randomized controlled trials (RCTs), cohort studies, and case report studies. The study also aimed to examine which type, quantity, and duration of soy isoflavone is more effective for preventing bone fraction.

The influence of isoflavones on bone metabolism

Phytoestrogens are derivatives of plant compounds that have both antiestrogenic and estrogenic properties. Soy contains large amounts of isoflavones with a structure of 17 b-estradiol. Isoflavones bind to estrogen-binding receptors and function similarly to estrogen (Kuiper *et al.*, 1997). Genistein and daidzine are key isoflavones found in soy (Anderson *et al.*, 1999).

Isoflavones are involved in the formation of the bone tissue by binding to osteoblast receptors through a genomic mechanism involved in inhibiting the function of nuclear estrogen receptors (Blair *et al.*, 1996). Its receptor osteoprotein (OPG) and receptor activator of nuclear factor kappa beta (RANKL) are involved in tissue analysis and hemostatic bone resorption. Postmenopausal women receiving genistein have lower sRANKL levels, indicating a possible mechanism of the phytoestrogens in the bone (Marini *et al.*, 2008). Excessive consumption of animal protein increases the urinary excretion of calcium which is effective in the process of osteoporosis, while this trend has not been observed in the consumption of soy protein (Breslau *et al.*, 1988).

Materials and Methods

Search strategy: Systematic search of studies was performed in PubMed, Scopus, and ISI web of science from the initial record up to July 2021 by means of the MESH terms and keywords compromising: Soy Milk" "soymilk" or "Soybeans" or "soybean" or "soy" or "soya" or "Isoflavones" or "Isoflavone" or "ipriflavone" or "equol" or "genistein OR "daidzein" OR "glycitin" AND "Fracture" or "fractures" or "broken bone" to find the pertinent studies for this study by two independent reviewers (Hamidian Shirazi M and Hejazi M). Also, to confirm that all relevant

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articles were included, the reviewers evaluated the reference lists of the studies. For screening the studies, all the articles were imported to the Endnote X9 (Bld 12062). Then, duplicated articles were omitted and the suitability of the remaining essays was evaluated based on the title, abstract, and full text.

Search strategies exist as the supplementary file (the search was processed by the Web of science as: (“Soy Milk” or soymilk or Soybeans or soybean or soy or soya or "Isoflavones" or "Isoflavone" or "ipriflavone" or "equol" or genistein OR daidzein OR glycitin) AND (Fracture or fractures or “broken bone”), by PubMed as: (((((SOY[Title/Abstract]) OR ("Soy Foods"[Mesh] OR "Soy Milk"[Mesh] OR "Soybeans"[Mesh] OR "Soybean Proteins"[Mesh])) OR ((((("Isoflavones"[Mesh]) OR "Genistein"[Mesh]) OR "Equol"[Mesh]))) OR ((((((isoflavone*[Title/Abstract]) OR Genistein*[Title/Abstract]) OR Equol*[Title/Abstract]) OR ipriflavone*[Title/Abstract]) OR daidzein*[Title/Abstract]) OR glycitin[Title/Abstract]))) AND ((("Fractures, Bone"[Mesh]) OR bone* fracture*[Title/Abstract]) OR bone* broken[Title/Abstract]), and by scopus as: (“Soy Milk” or soymilk or Soybeans or soybean or soy or soya or "Isoflavones" or "Isoflavone" or "ipriflavone" or "equol" or genistein OR daidzein OR glycitin) AND (Fracture or fractures or “broken bone”)).

Eligibility criteria: The articles were selected based on inclusion and exclusion criteria. The inclusion criteria were clinical trial studies, observational studies, case reports, cohort patients of all ages with fractions in a database, international journals, and domestic scientific journals. The exclusion criteria comprised books, theses, research reports, animal studies, such as red clover or synthetic isoflavones, curments with isoflavones from origins other than soy, and review articles.

Data extraction: Associated data on the effect of soyisoflavone consumption on bone fracture were extracted by two reviewers (Hamidian Shirazi M and Hejazi M). The information was extracted from the selected articles and collected in a sheet containing the first authors’ name, article’s name, publication year, study design (parallel or crossover), intervention duration, blinding, randomization, number of participants in each group, form of treatment (e.g., isoflavones, soy, or soy milk), dosage of isoflavones, and the substance used as placebo.

Study quality: The Jadad Quality Assessment (Peterson *et al.*, 2011) Scale was used to assess the quality of interventional studies. This scale consisted of three variables including randomization methods (1 point), blinding (1 point), and inclusion of participants (1 point) for a total score of 3 points. Studies that received 3 points or more were identified as high quality (Clark *et al.*, 1999). On the other hand, Newcastle-Ottawa Quality scale was used to assess quality of observational studies. Papers were evaluated based on selection (4 questions), outcome (3 questions), and comparability (1 question) for a total score of 10 points. In this scale, studies obtaining 3-10, 3-6, and 0-3 points were ranked as high, moderate, and low quality (Penson *et al.*, 2013, Piekarz and Ward, 2007) (**Tables 2** and **3**).

Study selection: First, by studying titles and abstracts of articles based on inclusion and exclusion criteria, the papers were reviewed (**Figure 1**), and then the articles on the effect of soy isoflavones on bone fraction were excluded from this study.

Results

After studying the related articles, the titles and abstracts were cautiously screened to find the effect of soy isoflavones on bone fraction (**Figure 1**). The researchers investigated 1675 articles in Scopus (n=861), Web of science (n=703), and PubMed (n=111). After omitting duplicates (n=502), the remaining articles (n=1046) were screened. Full texts of 102 articles were assessed and 3 studies were not available; moreover, 99 studies were excluded based on the criteria or had nothing to do with the subject of the study, so 27 articles were selected. The articles contained cross-sectional studies (n=1), case-control studies (n=1), cohort (n=11), and randomized control trials (n=14). All the studies showed the effect of soy isoflavone on the bone fraction. Based upon the jadad Scale among 12 interventional studies, eight studies were identified as high quality and four studies as low quality. Among observational studies, 11 studies were categorized as and the others as low quality.

Outcome characteristics of participants with bone fracture: The baseline characteristics of the studies are displayed in **Table 1**. The studies were printed from 1997 to 2020. The geographic place of each study was different. In 23 studies, the study population consisted of females and mostly postmenopausal and also in 5 studies, they were both sexes. The age range of participants in the studies was between 6 months and 75 years. The length of time of the studies was different, ranging from 1 month to 10 years. The amounts of soy product were different (36mg/day to 200mg/day).

Effect of soy isoflavones on bone fracture: In 18 out of 27 studies, the preventive effect of soy and other soy products was observed on bone fractures. In 2 studies, only a positive effect was observed in men with cancer, and no effect was seen in women with cancer. In 8 studies, there was no association between other soy products and bone fractures.

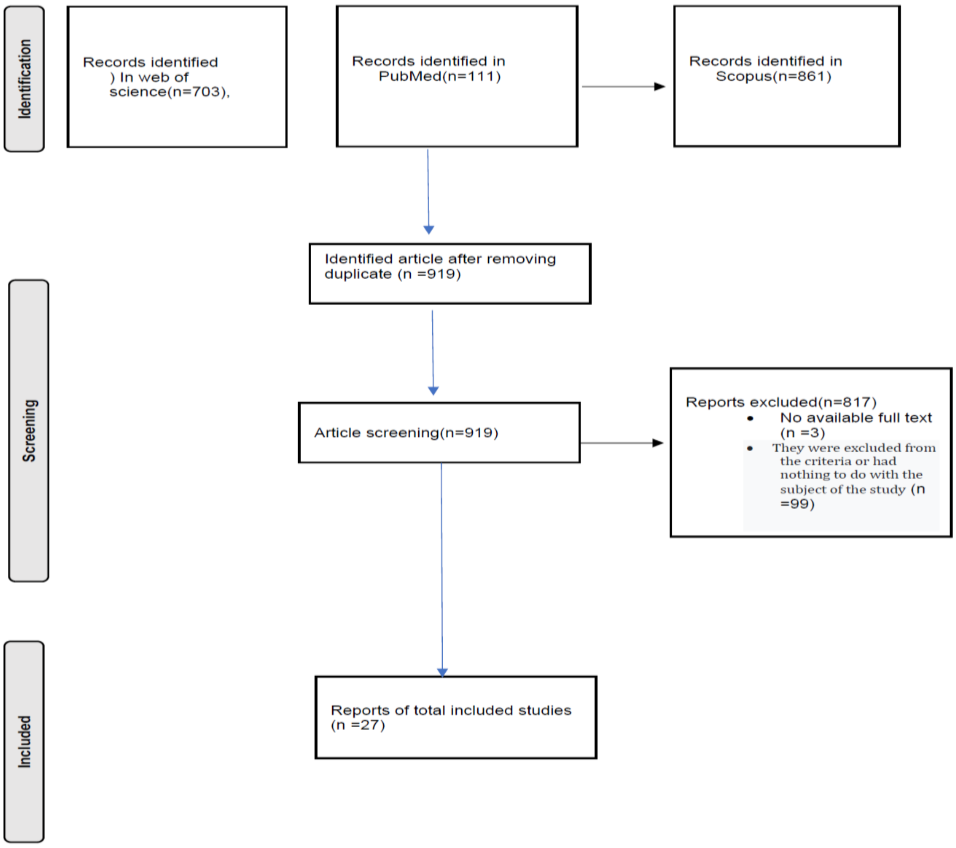

Figure 1. The flowchart of the screening and selection procedure of the studies.

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Table 1. Features of the studies on the effect of isoflavones.

Study	Location	Number	Characteristics	Sex	Age(y)	Interventions and groups	Study design	Outcomes
(Kojima *et al.*, 2020)	Japanese	1417	Postmenopausal	Female	15–79	FFQ of natto, tofu, and another soybean	Prospective cohort	Decrease the risk of hip fracture
(Zheng *et al.*, 2019)	China	N1=4139 N2= 1987 N3=2152	N1= stage 0–III breast cancer patients N2= pre-/perimenopausal N3= postmenopausal patients	Female	20-75	Consume soy using Frequency questionnaire	Prospective	Decrease the risk of hip fracture
(Nayeem *et al.*, 2019)	America	99	Healthy premenopausal women	Female	30-42	Isoflavones (136.6 mg) and placebo	Clinical trial	Decrease the risk of hip fracture
(Yoshikata *et al.*, 2018)	China	74	Menopause	Female	44–74	Per oral equol-containing supplement, 10 mg/day	A Prospective Observational Study	Decrease the risk of hip fracture
(Zhang *et al.*, 2017)	China	1050	Elderly	Male/ female	52-83	Validated 79-item food frequency questionnaire	Case-control study of	Decrease the risk of hip fracture
(Arcoraci *et al.*, 2017)	Italy	121	Postmenopausal	Female	Mean 54.5	With either 1000 mg of calcium and 800 IU vitamin D3 in placebo group and vitamin D3,calcium, and Genistein aglycone (54 mg/day in intervention group	Clinical trial	Decrease the risk of hip fracture
(Myers *et al.*, 2015)	Australia	1188	Postmenopausal	Female	Mean 80.0	A validated food-frequency questionnaire	Prospective cohort	Decrease the risk of hip fracture
(Baglia *et al.*, 2015)	China	1,587	Breast cancer diagnosis	Male and female	20 - 75	Food frequency questionnaire	Cohort	Decrease the risk of hip fracture
(Dai *et al.*, 2014)	Singapore Chinese	63,257	Both pre- and postmenopausal	Male and female	45–74	A validated food-frequency questionnaire	Prospective population-based cohort	Decrease the risk of hip fracture
(Lappe *et al.*, 2013)	USA	70	Postmenopausal	Female	Mean age 54.8	Case: genistein (30 mg/days), vitamin K1 (150 µg/days) vitamin D3 (800 IU/days), vitamin K1 (150 µg/days) and	Clinical trial	Decrease the risk of hip fracture

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						polyunsaturated fatty acids (1 g Controle: calcium		
(Tai *et al.*, 2012)	Taiwan	431	Postmenopausal	Female	45-65	00-mg/day isoflavones (aglycone equivalents) (172.5 mg genistein + 127.5 mg daidzein) and600 mg of calcium and 125 IU of vitamin D3 per day	Clinical trial	The relative risk of bone fracture and its 95% CI for the isoflavone group were 1.64 (0.74, 3.67)
(Hasnah *et al.*, 2012)	Malaysia	125	Postmenopausal	Female	Mean age 60	A dietary history Questionnaire	A cross-sectional study	A diet without dairy increased the risk of bone fractures
(Lousuebsakul Matthews *et al.*, 2011)	Canada	337	Postmenopausal	Female	54-75	Completed a lifestyle and dietary questionnaire and FFQ	Cohort study	BUA measurement related to soy foods intake and history of minor accident fracturesp= 0.25
(Kuhnle *et al.*, 2011)	UK	F=2580 M=4973	Cancer	Male and female	45–75	Survey of soy intake using a newly developed food composition database	Prospective study cohort	Decrease the risk of hip fracture
(Haron *et al.*, 2010)	Malaysia	21	Postmenopausal	Female	55-65	A glass of milk (114 g) or from a meal of tempeh (206 g); each containing 130 mg calcium. At each study of Phase and Phase 2 (mid-August), intravenous 42Ca and oral 44Ca	Clinical trial	No effect
(Koh *et al.*, 2009)	Chinese	63,257	Healthy	Male and female	45–74	Using food frequency questionnaire , lifestyle factors and questions on medical history	Prospective cohort	Decrease the risk of hip fracture
(Newton *et al.*, 2006)	USA	F=13 M=98	Healthy	Male and female	50–80	Soy protein comprising 83 mg isoflavones (45.6 mg genistein, 31.7 mg daidzein), aglycone units; the control group comprising 3mg isoflavones	Clinical trial	No effect
(Ikeda *et al.*, 2006)	Japan	944	Postmenopausal	Female	20-79	Dietary natto intake was assessed by a FFQ on both occasions	Cohort	Reduced risk
(Bunout *et al.*, 2006)	Chile	100	Elderly with femoral osteoporosis.	Male and female	Mean age 70	31 g proteins per and 90 mg isoflavones, 400 IU vitamin D, 800 mg calcium, 60 ug vitamin K day	Clinical trial	No effect
(Zhang *et al.*, 2005)	USA	75,000	Postmenopausal	Female	40-70	FFQ	Cohort	May reduce the risk of fracture

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(Welch *et al.*, 2005)	UK	F=5,379 M=6,369	Cancer	Male and female	42 -82	Individuals were divided into four groups based on soy consumption and vegetarian status and a food frequency questionnaire was used.	Prospective study	Calcaneum BUA in vegetarian men was significantly lower than but in female had no effect
(Harada *et al.*, 2004)	Japan	2035	Elderly	Male and female	Mean age 65	An anonymous survey consisting of 12 questions	Clinical trial	Reduced risk
(Kaneki *et al.*, 2001)	Japan	105	Postmenopausal	Female	50–84	Examined the influence of Japanese fermented soybean, on serum vitamin K	Clinical trial	Reduced risk
(Alexandersen *et al.*, 2001)	Denmark	474	Postmenopausal	Female	45-75	200 mg 3 r placebo all received 500 mg/d of calcium	Clinical trials	No effect
(Sato *et al.*, 2000)	Japan	9	Long-Distance Runners	Female	20-24	1350 g of vitamin K2 and 72 mg of soybean isoflavones	Clinical trial	Reduced risk
(Reginster *et al.*, 1997)	Denmark	460	Menopause	Female	45-75	IP (200 mg, and 500 g oral calcium everyday	Clinical trial	Reduced risk
(Agnusdei and Bufalino, 1997)	Italy	149	Elderly, osteoporotic women	Female	65–79	IP (200 mg, and 1 g oral calcium everyday	Clinical trial	Reduced risk

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Table 2. Jadad scale quality assessment for RCTs.

Study	Randomization	Blinding	An account of all patients	Total	Quality
(Nayeem *et al.*, 2019)	2	2	1	5	High
(Arcoraci *et al.*, 2017)	2	2	0	4	High
(Lappe *et al.*, 2013)	2	2	1	5	High
(Tai *et al.*, 2012)	2	2	1	5	High
(Haron *et al.*, 2010)	1	1	1	3	Low
(Newton *et al.*, 2006)	2	2	1	5	High
(Bunout *et al.*, 2006)	1	1	1	3	Low
(Kaneki *et al.*, 2001)	1	1	1	3	Low
(Alexandersen *et al.*, 2001)	2	2	1	5	High
(Sato *et al.*, 2000)	1	1	1	3	Low
(Reginster *et al.*, 1997)	2	2	0	4	High
(Agnusdei and Bufalino, 1997)	2	2	0	4	High

Table 3. Newcastle-Ottawa quality assessment for cohort, case control, and cross sectional studies.

Study	Selection	Comparability	Outcome	Total	Quality
(Kojima *et al.*, 2020)	3	1	3	7	Good
(Zheng *et al.*, 2019)	3	1	2	6	Fair
(Yoshikata *et al.*, 2018)	2	1	2	5	Fair
(Zhang *et al.*, 2017)	3	1	2	6	Good
(Myers *et al.*, 2015)	3	1	2	6	Good
(Baglia *et al.*, 2015)	2	1	3	6	Good
(Dai *et al.*, 2014)	3	1	2	6	Good
(Hasnah *et al.*, 2012)	3	0	2	5	Fair
(Lousuebsakul Matthews *et al.*, 2011)	3	1	2	6	Good
(Kuhnle *et al.*, 2011)	3	1	2	6	Good
(Koh *et al.*, 2009)	3	1	2	6	Good
(Ikeda *et al.*, 2006)	3	1	2	6	Good
(Zhang *et al.*, 2005)	3	1	2	6	Good
(Welch *et al.*, 2005)	3	1	3	7	Good
(Harada *et al.*, 2004)	2	1	2	5	Fair

Discussion

This study provided a summary of soy isoflavone and its products on bone fracture. By reviewing 27 articles, the relationship between the consumption of soy isoflavone and the risk of bone fractures in individuals was assessed. Results revealed that the intake of soy isoflavones caused a significant preventive effect on bone fracture. Bone repair, which is caused by various diseases and factors, is a complex function that interacts with the cells. Osteoblasts play a role in bone synthesis and collagen deposition outside the cell. Inflammatory cells such as neutrophils, macrophages, and eosinophil go to the fracture site and cause inflammation (Claes *et al.*, 2012). This process leads to absorption of the osteoblasts. Peroxidases also penetrate the affected area. On the other hand, peroxidases and fibroblasts play a role in the extracellular matrix biosynthesis (DeNichilo *et al.*, 2015). Soy-derived peroxidase also builds bone tissue and collagen I and it is also effective in controlling inflammation and regenerating the extracellular matrix (Barker *et al.*, 2021).

In the view of quality, 8 interventional studies had high quality, which makes it possible to draw a causal link between bone fracture prevention and soy isoflavone intake. Moreover, 11 out of 15 studies had high quality and showed beneficial effects for bone fracture prevention.

Soy products reduce the risk of bone fractures in

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postmenopausal women (Zhang *et al.*, 2005). They also increased bone mineral density (BMD) (Abdi *et al.*, 2016). Soy isoflavones might affect the bone by decreasing bone resorption while motivating bone formation (Arjmandi and Smith, 2002). Soy products stimulate the osteoblastic formation of osteoprotegerin, which prevents bone resorption (Viereck *et al.*, 2002). They also have a function and structure similar to tamoxifen, which can be effective in reducing bone loss after menopause (George *et al.*, 2020). Soy isoflavones, with their antioxidant effect, suppress angiogenesis by inhibiting the protein tyrosine kinase and cell growth by interfering with signal transmission. Isoflavones are also thought to inhibit aromatase and 5α reductase and induce estrogen synthesis (George *et al.*, 2020).

Soy also increases the production of insulin-like growth factor 1, an indicator recognized to increase osteoblastic activity related to bone formation (Arjmandi and Smith, 2002).The amount of IGF-I in both sexes decreases with age, which intensifies in menopause (George *et al.*, 2020). IGF-I, like growth hormone, stimulates bone formation (George *et al.*, 2020). It may also increase the production of 1,25 (OH)2 vitamin D by regulating 1α-hydroxylase activity (George *et al.*, 2020). Soy consumption in postmenopausal women has caused a reduction in urinary excretion of bone indicators (Nikander *et al.*, 2004). Menaquinone-7 (MK-7) enables osteocalcin γ -carboxylation (Shetty *et al.*, 2016), and mineralization (Bruge *et al.*, 2011). In a study in the Caucasus, MK-7 consumption was effective in preventing bone fractures in postmenopausal women (Knapen *et al.*, 2013). Thus, soy products prevent bone fractures by preserving bone mass and bone microarchitecture (Rønn *et al.*, 2016). Soy products can decrease bone loss (Wong *et al.*, 2009) and provoke bone formation (Ma *et al.*, 2008b, Marini *et al.*, 2007); this association was not found in 8 studies. This can be attributed to different types of isoflavones in different soy products (Kojima *et al.*, 2020). Isoflavone aglycones in unfermented soy products, such as tofu, are absorbed faster and have more bioavailability than other soy products (Izumi *et al.*, 2000). The phytoestrogens in soy reduce the process of bone loss (Ma *et al.*, 2008a). The effect of soy in avoiding osteoporosis in men has not been determined (Newton *et al.*, 2006). The exact mechanism of genistein in men is unknown (Piekarz and Ward, 2007). Genistein prevents bone loss by increasing the activity of osteoblasts in male rodents (Khalil *et al.*, 2005). Decreased testosterone is observed in men with age (Orwoll *et al.*, 2006), since testosterone helps maintain bone health in men (Amin *et al.*, 2006). Therefore, isoflavones can be effective in preventing bone fractures in older men and soy products, due to the mentioned properties, can be effective in preventing bone fractures.

Opposing effects

Isoflavones have structures similar to estrogens, so they increase the risk of breast cancer in susceptible individuals or general survival from breast cancer (Qiu and Jiang, 2019, Touillaud *et al.*, 2019).

Limitation

This review study had some limitations. Each study had different interventions, evaluating different results, which made impossible to compare the results. Also, confounding factors such as age, BMI, and dietary calcium intake were not investigated.

Conclusion

Various diseases and factors that affect bone fractures mainly affect the quality of life of people. Therefore, the results of this review revealed that soy consumption may have a beneficial effect on preventing bone fraction. More studies with a longer time of intervention on a larger sample size are recommended to approve these results.

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Author contributions

Hamidian Shirazi M, Mollaei M, Hamidian Shirazi A and Hejazi N. contributed to the research concept; Hamidian Shirazi M, Hejazi N and Ramezani A searched databases, screened articles, and extracted data. All authors contributed to the writing and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

No conflict of interest is declared.

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