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Effects of Isoflavones on Bone Health across the Lifespan: A Systematic Overview of Meta-Analyses and Clinical Trials

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Abstract

Background: Isoflavones are soy-derived phytoestrogens that may influence bone remodeling differently according to age, sex, hormonal status, dosage, and metabolism. This study evaluated their effects on bone mineral density (BMD), bone mineral content (BMC), and bone turnover markers in children, adolescents, and adults to clarify their potential role in bone health and osteoporosis prevention.

Materials and Methods: In this systematic overview, PubMed, Scopus, Web of Science, the Cochrane Library, and Google Scholar were searched through December 2025 for meta-analyses and comparative studies of soy isoflavones reporting bone mineral outcomes or turnover markers. Quality was assessed using AMSTAR and Jadad scales; substantial heterogeneity required narrative synthesis.

Results: Eight studies, comprising six meta-analyses and two comparative trials, were included. Among postmenopausal women, isoflavone supplementation was generally associated with modest improvements in BMD at the lumbar spine, femoral neck, and total hip, along with favorable changes in bone-resorption markers, particularly pyridinoline and C-terminal telopeptide of type I collagen. Subgroup analyses suggested that effects may be greater at doses below 90 mg/day. However, effect estimates varied across syntheses, and no study demonstrated a reduction in fracture risk. In infants and children, soy-based formula was not associated with significant differences in BMC compared with control formulas. In adolescent boys, short-term isoflavone supplementation did not significantly affect bone turnover markers or growth-related outcomes, despite evidence of systemic isoflavone exposure.

Conclusion: Soy isoflavones may modestly preserve bone density in postmenopausal women as adjuncts but cannot replace established osteoporosis therapies. No skeletal benefits were evident in infants or adolescent boys, and evidence in populations remains limited. Future trials should assess fracture outcomes and account for equol-producer status.

Key Words: Bone mineral density, Bone turnover markers, Isoflavones, Phytoestrogens, Postmenopausal women.

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1- INTRODUCTION

Osteoporosis is a major global health challenge characterized by the systemic deterioration of bone microarchitecture, resulting in increased skeletal fragility and susceptibility to low-trauma fractures (1). In addition to its substantial clinical impact on morbidity, osteoporosis imposes a considerable socioeconomic burden on healthcare systems, accounting for approximately 3.8% of total healthcare expenditures. In European countries, direct fracture-related costs exceed €1.8 billion annually (2). These costs include acute hospitalization and long-term rehabilitation, highlighting the importance of early, proactive, non-pharmacological prevention strategies (3).

The clinical trajectory of osteoporosis is strongly influenced by early skeletal development and cumulative bone mineral accrual. Approximately 60% of adult peak bone mass (PBM) is determined during childhood, adolescence, and early adulthood (4). During these critical developmental periods, rapid skeletal growth occurs through coordinated ossification processes regulated by endocrine pathways and nutritional factors (5). Longitudinal studies suggest that optimized nutritional interventions during early life can enhance bone mineral density (BMD) and bone mineral content (BMC) accrual, thereby establishing a skeletal reserve that may delay osteoporotic fractures later in life (4, 6). Therefore, identifying safe, tolerable, and effective nutritional interventions to support skeletal development throughout the life course remains an important public health priority.

Phytoestrogens, particularly soy-derived isoflavones such as genistein and daidzein, have attracted considerable clinical interest because of their structural similarity to endogenous 17β-estradiol (7). These compounds may exert tissue-specific estrogen-like effects through interactions with estrogen receptors, particularly ERα and ERβ, and are among the phytoconstituents proposed to contribute to potential health benefits (8). At the cellular level, isoflavones may promote osteoblastogenesis, upregulate osteoprotegerin (OPG) expression, and suppress receptor activator of nuclear factor-κB ligand (RANKL), thereby inhibiting osteoclast-mediated bone resorption (9). Molecular and animal studies have shown that low-dose isoflavone supplementation may enhance longitudinal bone growth and improve cortical and trabecular microarchitecture during active growth phases (5, 10). However, translation of these findings to pediatric and adolescent populations has yielded inconsistent results, with clinical trials reporting minimal effects on BMC and growth parameters in infants and adolescent males (11, 12).

In adults, particularly postmenopausal women, the skeletal effects of isoflavones appear to follow a different clinical pattern. Because conventional hormone replacement therapy (HRT) is associated with long-term safety concerns, isoflavones have been extensively investigated as a potentially safer, naturally derived alternative for mitigating postmenopausal bone loss (13). Systematic reviews and meta-analyses involving postmenopausal women suggest that isoflavones may help preserve BMD at the lumbar spine and femoral neck by reducing biochemical markers of bone turnover (BTMs), including pyridinoline and C-terminal telopeptide (14–16).

Nevertheless, the available evidence remains fragmented. Clinical outcomes may vary according to dosage, age-related changes in estrogen-receptor sensitivity, sex-related biological factors, and interindividual differences in gut microbiota metabolism—particularly the capacity to metabolize daidzein into equol, a biologically active metabolite (17–19).

To date, no comprehensive systematic synthesis has mapped skeletal responses to isoflavones across the life course, from infancy to older adulthood.

Therefore, this study aimed to evaluate the effects of soy isoflavones on BMD, BMC, and BTMs across pediatric, adolescent, and adult populations and to clarify their age- and sex-specific roles in osteoporosis prevention and management.

2- MATERIALS AND METHODS

2-1. Study Design and Reporting

This systematic overview was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to enhance transparency and reproducibility in the study-selection and reporting processes (20).

2-2. Ethical Considerations

This study synthesized secondary evidence exclusively from previously published studies reporting de-identified, aggregate-level data. No new primary data were collected from human participants, and no primary animal experiments were conducted by the authors. Therefore, institutional review board approval, animal ethics approval, and informed consent were not required.

2-3. Search Strategy and Information Sources

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar from database inception through December 31, 2025. The search was designed to identify systematic reviews with meta-analyses and primary comparative studies evaluating the effects of soy-derived isoflavones and related phytoestrogens on skeletal outcomes across the life course.

The search strategy was structured around two core concepts: (1) exposure to soy isoflavones or phytoestrogens and (2) bone-related outcomes. Bone-related outcomes included bone mineral density (BMD), bone mineral content (BMC), bone mass, osteoporosis, bone metabolism, and biochemical bone turnover markers (BTMs). The representative search concepts and terms are presented in **Table-1**.

The PubMed/MEDLINE search strategy combined Medical Subject Headings (MeSH) with free-text terms searched in the title and abstract fields. The strategy was adapted for Scopus, Web of Science, the Cochrane Library, and Google Scholar using database-specific syntax, indexing terms, truncation symbols, Boolean operators, and field codes. The complete PubMed/MEDLINE search strategy is presented in Supplementary **Table S1**.

The reference lists of all included studies and relevant systematic reviews were manually screened to identify additional eligible records. The study-selection process is summarized in the PRISMA 2020 flow diagram (**Figure 1**).

Table-1: Search concepts and representative search terms.

Search concept	Representative search terms
Isoflavones and phytoestrogens	isoflavone*; soy; soya; soybean*; genistein; daidzein; glycitein; phytoestrogen*; ipriflavone
Bone density and mineral content	bone; osteoporosis; “bone mineral density”; BMD; “bone mineral content”; BMC; “bone mass”
Bone metabolism and turnover	“bone turnover”; “bone metabolism”; osteocalcin; pyridinoline; deoxypyridinoline; osteoprotegerin; OPG; “C-terminal telopeptide”; CTX; “N-terminal telopeptide”; NTX; “bone-specific alkaline phosphatase”; BAP

Note: Search syntax, field tags, truncation symbols, and Boolean operators were modified according to the requirements of each database.

Supplementary **Table S1:** Full electronic search strategy used in PubMed/MEDLINE.

Database	Search strategy
PubMed/MEDLINE	**Soy isoflavones/phytoestrogens:** (“Isoflavones”[Mesh] OR “Soybeans”[Mesh] OR “Phytoestrogens”[Mesh] OR isoflavone*[tiab] OR soy[tiab] OR soya[tiab] OR soybean*[tiab] OR genistein[tiab] OR daidzein[tiab] OR glycitein[tiab] OR phytoestrogen*[tiab] OR ipriflavone[tiab])
PubMed/MEDLINE	**Bone health outcomes and biomarkers:** (“Bone and Bones”[Mesh] OR “Osteoporosis”[Mesh] OR “Bone Density”[Mesh] OR “Osteocalcin”[Mesh] OR “Alkaline Phosphatase”[Mesh] OR bone[tiab] OR osteoporosis[tiab] OR “bone mineral density”[tiab] OR BMD[tiab] OR “bone mineral content”[tiab] OR BMC[tiab] OR “bone mass”[tiab] OR “bone turnover”[tiab] OR “bone metabolism”[tiab] OR osteocalcin[tiab] OR pyridinoline[tiab] OR deoxypyridinoline[tiab] OR osteoprotegerin[tiab] OR OPG[tiab] OR “C-terminal telopeptide”[tiab] OR CTX[tiab] OR “N-terminal telopeptide”[tiab] OR NTX[tiab] OR “bone-specific alkaline phosphatase”[tiab] OR BAP[tiab])
PubMed/MEDLINE	**Final search string:** (“Isoflavones”[Mesh] OR “Soybeans”[Mesh] OR “Phytoestrogens”[Mesh] OR isoflavone*[tiab] OR soy[tiab] OR soya[tiab] OR soybean*[tiab] OR genistein[tiab] OR daidzein[tiab] OR glycitein[tiab] OR phytoestrogen*[tiab] OR ipriflavone[tiab]) AND (“Bone and Bones”[Mesh] OR “Osteoporosis”[Mesh] OR “Bone Density”[Mesh] OR “Osteocalcin”[Mesh] OR “Alkaline Phosphatase”[Mesh] OR bone[tiab] OR osteoporosis[tiab] OR “bone mineral density”[tiab] OR BMD[tiab] OR “bone mineral content”[tiab] OR BMC[tiab] OR “bone mass”[tiab] OR “bone turnover”[tiab] OR “bone metabolism”[tiab] OR osteocalcin[tiab] OR pyridinoline[tiab] OR deoxypyridinoline[tiab] OR osteoprotegerin[tiab] OR OPG[tiab] OR “C-terminal telopeptide”[tiab] OR CTX[tiab] OR “N-terminal telopeptide”[tiab] OR NTX[tiab] OR “bone-specific alkaline phosphatase”[tiab] OR BAP[tiab])

Note: PubMed/MEDLINE was searched from database inception to December 31, 2025. The search strategy was developed using Medical Subject Headings (MeSH) and free-text terms searched in the title and abstract fields.

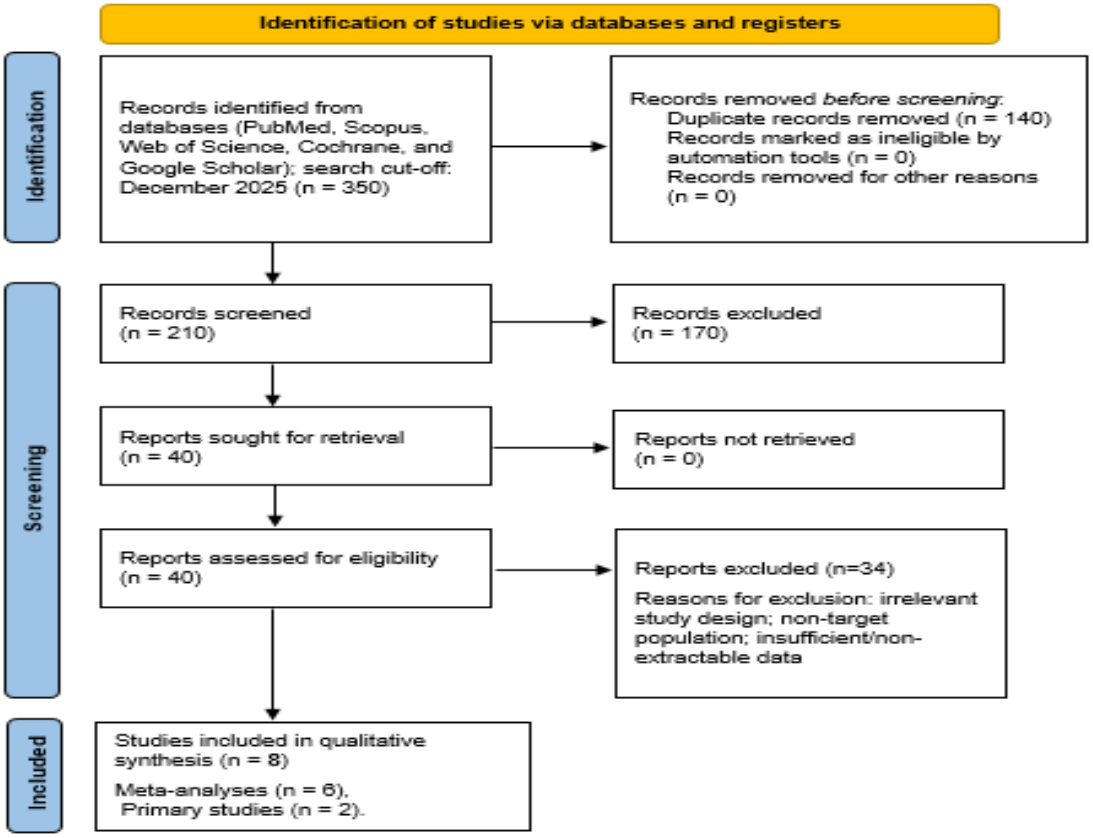

Fig.1: PRISMA 2020 flow diagram of the study-selection process.

2-4. Eligibility Criteria: PICOS Framework

Eligibility criteria were defined a priori according to the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework.

- **Population:** Human populations across the life course, including infants, children, adolescents, premenopausal adults, and postmenopausal women. Preclinical rodent models representing active skeletal growth were eligible only for exploratory developmental comparisons and were analyzed separately from human evidence.
- **Intervention:** Soy-derived isoflavones, including genistein, daidzein, and glycitein, as well as structurally related phytoestrogens. Interventions could include dietary supplements, isoflavone-enriched formulas or foods, and isolated or standardized extracts.
- **Comparator:** Placebo, no intervention, standard diets or formulas without isoflavone enrichment, or active comparative therapies, as specified in the original studies.
- **Outcomes:** Primary outcomes were changes in BMD and BMC, particularly at the lumbar spine, femoral neck, and total hip. Additional outcomes included BTMs, such as bone-formation markers—bone-specific alkaline phosphatase (BAP) and osteocalcin—and bone-resorption markers, including pyridinoline (PYD) and C-terminal telopeptide of type I collagen (CTX). Secondary outcomes included safety outcomes and treatment-related adverse events.

- **Study design:** Eligible studies included peer-reviewed systematic reviews with meta-analyses of randomized controlled trials (RCTs), individual double-blind or single-blind RCTs, controlled clinical trials, and controlled preclinical comparative studies. Dissertations, conference abstracts, narrative reviews without systematic methods, editorials, commentaries, and non-peer-reviewed reports were excluded.

2-5. Study Selection and Screening

Retrieved records were exported to reference-management software, and duplicate records were removed before screening. Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion and consensus or, when necessary, consultation with a third reviewer.

The final evidence base comprised eight studies: six systematic reviews with meta-analyses and two primary comparative studies. The characteristics of the included meta-analyses and primary studies are summarized in **Tables 2 and 3**, respectively.

2-6. Data Extraction

Two reviewers independently extracted data using a standardized, pilot-tested data-extraction form. Extracted variables included the first author, publication year, country or study setting, study design, participant or animal characteristics, sample size, intervention type, dose, duration, comparator, attrition or dropout information, adverse events, and principal findings. Discrepancies were resolved through discussion and consensus.

2-7. Methodological Quality Assessment

Methodological quality was independently assessed by two reviewers. Systematic reviews with meta-analyses were evaluated using the 12-item A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist, with total scores ranging from 0 to 12. Primary clinical trials were assessed using the Jadad scale, which evaluates randomization, blinding, and reporting of withdrawals and dropouts, with scores ranging from 0 to 5 (21).

Because the study by Ahn and Park (2017) was a preclinical animal experiment, the Jadad scale was not considered a validated risk-of-bias tool for this study. Its methodological features were therefore described separately and interpreted cautiously. Quality ratings for systematic reviews and the human clinical trial are presented in **Tables 2 and 4**, respectively. Any disagreements were resolved through consensus.

2-8. Data Synthesis and Heterogeneity Analysis

A quantitative meta-analysis was not conducted because of substantial clinical and methodological heterogeneity across the included evidence. Sources of heterogeneity included differences in participant characteristics, intervention formulations and doses, treatment durations, comparator conditions, outcome definitions, and skeletal measurement sites.

Accordingly, findings were synthesized narratively and stratified by life stage and clinical population. This approach enabled structured comparisons of age- and sex-specific skeletal responses to isoflavone and phytoestrogen exposure.

Table-2: Characteristics and Methodological Quality of Included Meta-Analyses (n=6).

Author (year)	Included studies/participants	Target population	Intervention and outcomes	Main findings	AMSTAR score
Vandenplas et al. (2014) (12)	6 studies; NR	Infants and children	Soy-based formulas; BMC	No significant difference in BMC compared with control formulas (P=0.54)	11/12
Akhlaghi et al. (2020) (22)	52 trials; NR	Adults aged >18 years	Soy isoflavones; BMD and BTMs	Favorable effects on bone loss were reported, including improved BMD in normal-weight individuals and reduced bone resorption in overweight individuals	11/12
Sansai et al. (2020) (19)	63 RCTs; 6,427 participants	Postmenopausal women	Isoflavones; BMD	Genistein at 54 mg/day and ipriflavone at 600 mg/day significantly improved BMD and showed a favorable safety profile	11/12
Kanadys et al. (2021) (16)	63 RCTs; 6,427 participants	Postmenopausal women	Soy isoflavones; BTMs	Isoflavone supplementation was associated with favorable changes in biochemical markers of bone metabolism	10/12
Barańska et al. (2022) (14)	18 RCTs; NR	Postmenopausal women	Soy isoflavones; BMD and BTMs	Isoflavone supplementation appeared to preserve BMD and slow the rate of postmenopausal bone loss	11/12
Inpan et al. (2024) (15)	63 RCTs; 9,026 participants	Postmenopausal women	Isoflavones; BMD	Isoflavone supplementation, particularly genistein at doses of ≥54 mg/day, significantly increased BMD	11/12

Abbreviations: AMSTAR, A Measurement Tool to Assess Systematic Reviews; BMC, Bone mineral content; BMD, Bone mineral density; BTMs, Bone turnover markers; NR, Not reported; RCT, Randomized controlled trial.

Table-3: Characteristics and Findings of Included Primary Comparative Studies (n=2).

Author (year), reference	Study population or model	Sample size	Intervention and dosage	Duration	Main findings
Jones et al., (2003) (11)	Adolescent boys; mean age, 16.8 years	n=128 (intervention, 69; control, 59)	Isoflavone equivalents, 50 mg/day, versus placebo	6 weeks	Supplementation at levels typical of a traditional Japanese diet had no significant effect on BTMs or short-term growth
Ahn and Park, (2017) (5)	Three-week-old female Sprague–Dawley rats	n=32 (four groups)	Low-dose isoflavones, 10 mg/kg; high-dose isoflavones, 50 mg/kg; or 17β-estradiol, 10 μg, versus vehicle	8 weeks	Low-dose soy isoflavone supplementation significantly improved longitudinal bone growth and bone microarchitectural quality in growing female rats

Abbreviations: BTM, Bone turnover marker; n, Sample size.

Table-4: Methodological Quality Assessment of Primary Studies (n=2).

Author (year)	Study type	Randomization	Blinding	Withdrawals and dropouts	Total score	Quality assessment
Jones et al., (2003) (11)	Human randomized controlled trial	2	2	1	5/5	High
Ahn and Park, (2017) (5)	Preclinical animal study	Not applicable	Not applicable	Not applicable	Not applicable	Descriptive assessment only

Note: The Jadad scale evaluates randomization (0–2 points), blinding (0–2 points), and reporting of withdrawals and dropouts (0–1 point), with a total score ranging from 0 to 5. A score of ≥3 was considered indicative of sufficient methodological quality for synthesis. Because Ahn and Park (2017) was an animal study, the Jadad scale was not applied as a validated quality-assessment tool. Its methodological characteristics were interpreted descriptively.

3- RESULTS

3-1. Study Characteristics and Methodological Quality

The study-selection process is summarized in the PRISMA 2020 flow diagram (**Figure 1**) (20). Following database searching, duplicate removal, title and abstract screening, and full-text eligibility assessment, eight studies were included in the final evidence synthesis. These comprised six systematic reviews with meta-analyses and two primary comparative studies. The included evidence encompassed infants and children, adolescent boys, postmenopausal women, and a preclinical model of growing female rats (5, 11, 12, 14–16, 19, 22).

The six systematic reviews were conducted by Vandenplas et al. (12), Barańska et al. (14), Inpan et al. (15), Kanadys et al. (16), Sansai et al. (19), and Akhlaghi et al. (22). Detailed

characteristics of the included systematic reviews and primary studies are presented in **Tables 2 and 3**, respectively. Methodological quality assessments are summarized in **Tables 2 and 4**.

Substantial clinical and methodological heterogeneity was observed across the included studies with respect to participant characteristics, isoflavone formulations and dosages, intervention durations, outcome definitions and assessment methods, and comparator conditions (12, 14–16, 19, 22). In addition, several meta-analyses included overlapping randomized controlled trials, limiting the statistical independence of their pooled estimates. Therefore, the findings were synthesized narratively rather than quantitatively.

3-2. Effects in Pediatric and Adolescent Populations

Evidence from pediatric and adolescent populations was limited and did not demonstrate consistent skeletal benefits (11, 12). Among infants and children receiving soy-based formula, the included systematic review reported no significant difference in bone mineral content (BMC) compared with control formulas (P=0.54) (12).

Similarly, in a randomized controlled trial involving adolescent boys, six weeks of isoflavone supplementation at a dose of 50 mg/day significantly increased urinary genistein and daidzein concentrations, confirming systemic exposure. However, the intervention did not significantly affect bone-specific alkaline phosphatase, the urinary pyridinoline-to-creatinine ratio, or short-term anthropometric growth parameters (11).

In contrast, the included preclinical study of three-week-old female Sprague–Dawley rats found that eight weeks of low-dose isoflavone supplementation (10 mg/kg/day) significantly improved longitudinal bone growth and bone microarchitectural quality compared with the control condition (5). Because this finding was derived from an animal model, it was considered exploratory and was not interpreted as equivalent to evidence from human pediatric or adolescent populations.

Overall, the available human evidence did not support a significant effect of isoflavone exposure on BMC, bone turnover, or short-term growth in infants or adolescent boys (11, 12). Evidence regarding adolescent girls and premenopausal women was insufficient to support definitive conclusions.

3-3. Effects on BMD in Postmenopausal Women

In postmenopausal women, the evidence was more consistent and generally suggested favorable effects of isoflavone supplementation on bone mineral density (BMD) (14, 15, 19, 22). Across the included meta-analyses, significant improvements in BMD were reported at the lumbar spine (P=0.03), total hip (P=0.04), and femoral neck (P<0.001) (14, 15, 19, 22).

The direction of the effect on lumbar spine BMD was consistent across several meta-analyses. Sansai et al. reported a mean difference of 0.0175 g/cm² (95% CI: 0.0088–0.0263; P<0.0001); Barańska et al. reported a weighted mean difference of 1.63 (P=0.004); and Inpan et al. reported a mean difference of 21.34 mg/cm² (P=0.001) (14, 15, 19).

Comparable findings were observed for femoral neck BMD. Sansai et al. reported a mean difference of 28.88 mg/cm² (P<0.0001), whereas Barańska et al. reported a weighted mean difference of 1.87 (P<0.0001). Inpan et al. also reported a significant improvement, with a mean difference of 0.0172 g/cm² (P=0.0073) (14, 15, 19).

Significant improvements were also reported for BMD at the distal radius (P=0.006) and total hip (P=0.013) (14, 19).

Akhlaghi et al. reported that the effects of soy isoflavones varied according to participant characteristics, with improved BMD observed among normal-weight individuals and reduced bone resorption among overweight or obese individuals (22). Although the magnitude of the reported effects varied across meta-analyses, the overall findings suggest that isoflavone supplementation may help attenuate postmenopausal bone loss, particularly at the lumbar spine and femoral neck (14, 15, 19, 22). These findings should be interpreted cautiously because of differences in dosage, intervention duration, baseline skeletal status, outcome measurement, and potential overlap among primary trials included in the meta-analyses (14, 15, 19, 22).

3-4. Effects on Bone Turnover Markers

The effects of isoflavones on biochemical bone turnover markers suggested a predominantly antiresorptive pattern in postmenopausal women (16, 22). Urinary pyridinoline levels were significantly reduced in some analyses; however, the magnitude and consistency of the effect varied across comparisons, with reported PPP values ranging from <0.001 to 0.07. The most favorable findings were generally observed at doses below 90 mg/day (16).

Overall, urinary deoxypyridinoline levels did not differ significantly between intervention and control groups (P=0.10). However, subgroup analyses indicated significant reductions among studies with intervention durations of less than one year (P=0.02), doses below 90 mg/day, and participants with a body mass index of ≥25 kg/m² (P=0.03) (16).

These findings suggest that intervention dose, treatment duration, and participant characteristics may modify the effects of isoflavones on bone-resorption markers (16, 22). Isoflavone supplementation was also associated with a significant increase in osteoprotegerin (P<0.001) and a significant reduction in C-terminal telopeptide of type I collagen (CTX; P=0.043) (16).

In subgroup analyses, CTX reduction was significant at doses below 90 mg/day (P=0.02) but not at doses of ≥90 mg/day (P=0.31) (16). In contrast, no significant effects were observed for serum bone-specific alkaline phosphatase, osteocalcin, or N-terminal telopeptide, irrespective of intervention dose or duration (16).

3-5. Overall Synthesis of Findings

Overall, the findings suggest age- and sex-dependent skeletal responses to isoflavone exposure (5, 11, 12, 14–16, 19, 22). In postmenopausal women, isoflavone supplementation was associated with improved BMD at clinically relevant skeletal sites and reductions in selected bone-resorption markers, particularly pyridinoline and CTX (14–16, 19, 22). These effects appeared to be more consistent in subgroup analyses involving doses below 90 mg/day (16).

Conversely, the available human evidence from infants and adolescent boys did not demonstrate significant improvements in BMC, bone turnover, or short-term growth (11, 12). Although the positive findings from the growing-rat model provide biological rationale for further investigation, they cannot be directly extrapolated to human populations (5). Evidence regarding adolescent girls and premenopausal women remains insufficient, highlighting an important priority for future clinical research.

4- DISCUSSION

4-1. Principal Findings

This systematic overview identified a life-stage-specific pattern in skeletal responses to soy isoflavones. The most supportive evidence was observed in

postmenopausal women, in whom isoflavone supplementation was associated with modest improvements in bone mineral density (BMD), particularly at the lumbar spine, femoral neck, and total hip, along with favorable changes in selected bone-resorption markers (14, 15, 23). In contrast, the limited human evidence available for infants and adolescent boys showed no significant effects on bone mineral content (BMC), biochemical bone turnover, or short-term growth (11, 12). Positive findings from a growing-rat model (5) provide biological plausibility but cannot be directly extrapolated to pediatric or adolescent populations. Overall, the findings suggest that skeletal responses to isoflavones are age- and sex-dependent and may be influenced by hormonal milieu, intervention characteristics, and interindividual differences in metabolism.

4-2. Pediatric and Adolescent Bone Health

Evidence supporting skeletal benefits in pediatric populations remains insufficient. Soy-based infant formula was not associated with significant differences in BMC compared with control formulas (12). Although this finding is reassuring regarding skeletal safety, it does not indicate that soy formula enhances bone accrual. Furthermore, the available studies were not designed to determine whether early-life isoflavone exposure influences peak bone mass or later fracture risk. Short-term assessments of BMC and growth may fail to capture delayed effects that could emerge during pubertal maturation or early adulthood.

Similarly, short-term supplementation with isoflavone equivalents in adolescent boys increased urinary isoflavone metabolites but did not significantly affect bone-specific alkaline phosphatase, pyridinoline excretion, or growth (11). The confirmation of systemic exposure in the absence of measurable skeletal effects suggests that poor adherence or inadequate absorption is unlikely to fully explain the null findings. More plausible explanations include the short intervention duration, limited statistical power, the relatively weak estrogenic activity of dietary isoflavones, and the distinct endocrine environment of male adolescence. In addition, bone-turnover markers measured over a few weeks may be insufficiently sensitive to detect changes in bone mass, which typically require longer follow-up periods.

The favorable effects of isoflavones on longitudinal growth and bone quality in growing female rats (5) suggest potential interactions among isoflavones, sex, and developmental stage. However, differences in metabolism, exposure relative to body size, skeletal maturation, and endocrine physiology limit translation to humans. Importantly, evidence in adolescent girls remains absent despite marked sex-specific differences in estrogen concentrations and pubertal bone accrual. Longitudinal human studies involving adolescent girls and young women are therefore needed before conclusions can be drawn regarding the effects of isoflavones on peak bone mass.

4-3. Postmenopausal Bone Health

The most consistent evidence of benefit was observed in peri- and postmenopausal women. Systematic reviews and meta-analyses suggest that isoflavone supplementation may improve BMD or attenuate estrogen-deficiency-related bone loss, particularly at the lumbar spine; however, effects at the femoral neck and other skeletal sites are less consistent (23–25). This pattern is biologically plausible because estrogen deficiency after menopause accelerates bone remodeling and shifts the balance toward bone resorption. Compounds with selective estrogen receptor activity may therefore exert more detectable skeletal effects in a low-estrogen environment than during

infancy, adolescence, or premenopausal adulthood.

Nevertheless, the observed improvements in BMD should be interpreted as evidence of potential bone preservation rather than proof of fracture prevention. Although BMD is an established surrogate measure of skeletal strength, none of the included evidence demonstrated a reduction in fragility fractures. In addition, the magnitude of effects and reporting formats differed across meta-analyses, limiting direct quantitative comparisons. Accordingly, the current evidence does not support the use of isoflavones as a substitute for established osteoporosis therapies in women at high fracture risk. Instead, they may have an adjunctive nutritional role in selected postmenopausal women, provided that expectations remain modest and long-term outcomes are considered.

The biochemical findings were broadly consistent with a predominantly antiresorptive effect. Reductions in pyridinoline and C-terminal telopeptide of type I collagen (CTX), together with increased osteoprotegerin, support the potential attenuation of osteoclast-mediated bone resorption (16). In contrast, bone-specific alkaline phosphatase, osteocalcin, and N-terminal telopeptide were not consistently altered. This inconsistency may reflect differences in biomarker kinetics, laboratory assays, baseline remodeling activity, intervention duration, and isoflavone formulation. Because bone-turnover markers are subject to biological and preanalytical variability, isolated biomarker changes should not be interpreted independently of BMD or clinically relevant skeletal outcomes (2).

4-4. Dose–Response and Biological Plausibility

Subgroup analyses suggested that doses below 90 mg/day may produce more favorable changes in pyridinoline and CTX than higher doses. However, this apparent non-linear pattern should be considered hypothesis-generating rather than definitive. Subgroup analyses are frequently underpowered and may be confounded by intervention duration, adherence, baseline BMD, dietary background, body mass index, menopausal duration, and product composition. Therefore, the available evidence does not establish an optimal dose or demonstrate that lower doses are inherently superior.

Isoflavones, particularly genistein and daidzein, are structurally similar to 17β-estradiol and may activate estrogen receptor-dependent genomic and non-genomic pathways, with a relative preference for estrogen receptor β. Proposed skeletal mechanisms include promotion of osteoblast differentiation, modulation of the receptor activator of nuclear factor-κB ligand/osteoprotegerin axis, and suppression of osteoclast formation and activity. These mechanisms are consistent with the antiresorptive pattern observed in postmenopausal women.

Interindividual differences in metabolism may further contribute to the variable response to isoflavones. Daidzein can be metabolized by gut microbiota into equol, a metabolite with greater estrogen receptor activity; however, only a proportion of individuals are equol producers. Differences in equol-producer status, gut microbial composition, dietary background, and supplement bioavailability may therefore explain some of the heterogeneity across trials. Although these factors have not been measured consistently enough to support clinical stratification, they should be considered in future research.

A recent systematic review and meta-analysis found no statistically significant estrogenic effects of soy isoflavones on endometrial thickness, vaginal maturation index, follicle-stimulating hormone, or

estradiol levels in postmenopausal women, suggesting that their clinical effects differ from those of systemic estrogen therapy (26). This finding supports a cautious interpretation of isoflavones as selective modulators rather than hormone-replacement therapies. In addition, the National Center for Complementary and Integrative Health reported that soy isoflavones may have beneficial effects on bone density in postmenopausal women, while emphasizing that outcomes vary according to product type and population (27).

4-5. Strengths and Limitations

A major strength of this overview is its life-course perspective, integrating evidence from infancy, adolescence, and adulthood rather than focusing exclusively on postmenopausal women. The inclusion of BMD, BMC, and bone-turnover markers also enabled comparison of structural and metabolic skeletal outcomes. In addition, study selection and narrative synthesis were guided by predefined methods and reported in accordance with PRISMA 2020 (20).

Several limitations should be considered. First, the evidence base was dominated by postmenopausal women, whereas evidence in infants, adolescent boys, adolescent girls, premenopausal women, and adult men was sparse or absent. This imbalance limits conclusions regarding age- and sex-specific effects across the life course. Second, substantial clinical and methodological heterogeneity resulted from differences in isoflavone source, composition, dose, duration, comparators, menopausal status, and outcome measurement. Therefore, statistical pooling across all evidence sources was not appropriate.

Third, the included meta-analyses likely contained overlapping primary trials. Their findings cannot, therefore, be considered independent replications, and repeated inclusion of the same trials may have amplified the apparent consistency of the observed effects. Fourth, the use of aggregate data precluded exploration of participant-level modifiers, including baseline BMD, body mass index, ethnicity, dietary soy intake, menopausal duration, and equol-producer status. Fifth, the animal study differed substantially from the human evidence with respect to species, exposure, and biological context; it should be regarded as mechanistic support rather than clinical evidence. Finally, improvements in BMD and bone-turnover markers do not necessarily indicate reduced fracture risk, and the available evidence remains insufficient to establish long-term antifracture efficacy or comparative effectiveness against standard osteoporosis therapies.

4-6. Implications for Research and Practice

Future randomized controlled trials should prioritize underrepresented populations, particularly adolescent girls, premenopausal women, adult men, and ethnically diverse groups. These studies should include adequately powered samples, longer follow-up periods, standardized reporting of isoflavone composition and aglycone-equivalent dose, and harmonized assessment of BMD at the lumbar spine, femoral neck, and total hip. Bone-turnover markers should be collected under standardized conditions, and adverse events, adherence, background diet, and co-interventions should be reported systematically.

Prospective stratification by equol-producer status and measurement of circulating isoflavone metabolites may help distinguish biological non-response from inadequate exposure. Studies involving younger populations should assess longitudinal bone accrual and peak bone mass rather than relying solely on short-term biomarkers. In postmenopausal women, trials evaluating fracture outcomes

and directly comparing isoflavones with standard preventive strategies are needed before isoflavones can be incorporated into osteoporosis-treatment recommendations. At present, isoflavones may be considered a possible adjunct within a healthy dietary pattern but not a replacement for established osteoporosis therapies.

5- CONCLUSION

This systematic overview suggests that skeletal responses to soy isoflavones vary across the life course. The most consistent evidence was observed in postmenopausal women, in whom supplementation was associated with modest improvements in BMD at the lumbar spine, femoral neck, and total hip, together with favorable changes in selected bone-resorption markers. However, heterogeneity, overlap among trials included in existing meta-analyses, and the absence of fracture outcomes limit the certainty and clinical applicability of these findings.

Current human evidence does not demonstrate skeletal benefits in infants or adolescent boys, and positive findings from animal models cannot be directly extrapolated to pediatric populations. Evidence is particularly limited for adolescent girls, premenopausal women, and adult men. Isoflavones may have an adjunctive role in preserving bone mass after menopause but should not be considered a replacement for established osteoporosis-prevention or treatment strategies. Long-term, adequately powered trials incorporating standardized interventions, clinically relevant skeletal outcomes, safety assessments, and metabolic stratification, including equol-producer status, are needed to determine which populations are most likely to benefit.

6- CONFLICT OF INTEREST: None.

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