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The Effect of Oxytocin on Osteoporosis Improvement: A Systematic Review

Seyed Mohammad Mohammadi[1], Samaneh Karimi[2], Nadia Saniee[3], Naser Kamyari[4], Esmat Radmanesh[5]*

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Abstract

Background: Osteoporosis, a chronic skeletal disorder leading to decreased bone density and increased fracture risk, predominantly affects postmenopausal women and the elderly. Current treatments have limitations due to long-term side effects, highlighting the need for new therapeutic approaches. Recent research suggests oxytocin (OT) may play a role in bone formation and density, providing a potential novel treatment avenue.

Methods: This systematic review was conducted based on the PRISMA 2020 statement in 2023. PubMed, Scopus, Web of Science, and grey literature resources (ProQuest, and Google Scholar) were searched with oxytocin and osteoporosis keywords and their synonyms in the MeSH database without time limitation. Inclusion criteria encompassed experimental studies on humans and animals that examined the relationship between oxytocin and osteoporosis, with available full texts in English. The quality assessment of the studies was done based on the CAMARADES checklist, ARRIVE guideline, and NHLBI.

Results: Out of 880 records, 30 studies met the inclusion criteria, comprising 19 animal studies and 11 human studies. The animal studies primarily indicated that oxytocin promotes bone formation, inhibits bone resorption, and may serve as a diagnostic marker for osteoporosis. Human studies showed a positive correlation between oxytocin levels and bone mineral density (BMD), particularly in postmenopausal women, suggesting oxytocin's protective role against osteoporosis.

Conclusion: Oxytocin demonstrates anabolic effects on bone, enhancing bone regeneration and reducing resorption. The findings support oxytocin's potential as a treatment for osteoporosis, though clinical trials are necessary to confirm its efficacy and determine optimal dosing. Further research is needed to explore oxytocin's preventive role and effects on different populations.

Keywords: Osteoporosis, Oxytocin, Bone

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Introduction

Osteoporosis is a chronic and systemic skeletal disorder characterized by increased bone resorption that leads to decreased bone density, and it mainly affects postmenopausal women and the elderly. Osteoporosis is characterized by an imbalance between bone resorption and bone production (1, 2) that leads to decreased bone density. A decrease in bone mineral density and, as a result, a decrease in bone mass leads to an increased risk of fracture (2). If osteoporosis is not treated, repeated fractures occur, which can lead to disability and early death, so treatment with effective anti-fracture drugs can prevent fractures in these patients (3). Drug treatments that strengthen bone

Corresponding author: *Dr Esmat Radmanesh, e.radmanesh@abadanums.ac.ir*

1. Department of Orthopedics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2. Department of Anatomical Sciences, School of Medicine, Abadan University of Medical Sciences, Abadan, Iran
3. Department of Basic Sciences, Asadabad School of Medical Sciences, Asadabad, Iran
4. Department of Public Health, School of Health, Abadan University of Medical Sciences, Abadan, Iran
5. Department of Physiology, School of Medicine, Abadan University of Medical Sciences, Abadan, Iran

↑What is "already known" in this topic:
An imbalance between bone resorption and bone production characterizes osteoporosis.. The anabolic effect of oxytocin on bone has been proven, and bone cells express oxytocin receptors.

→What this article adds:
→What this article adds:
Oxytocin strengthens ossification, bone regeneration, and repair, helps to induce osteoblasts, inhibits bone resorption, and prevents bone resorption by mature osteoclasts. The removal or reduction of oxytocin causes osteoporosis. The findings support oxytocin's potential as a treatment for osteoporosis.

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formation, prevent bone loss, or do both are available, but due to long-term use, they can be associated with common side effects (4). In preclinical studies, several new therapeutic targets are being studied and investigated, which could open more avenues for the treatment of osteoporosis in the future. Advances in molecular knowledge, especially in the mechanisms of bone cell activity, have led to the discovery of new therapeutic agents for osteoporosis (5).

Oxytocin (OT) is a peptide that has a wide range of mental and physical activities in the body, some of which are different in reproductive women and men (6). The anabolic effect of oxytocin on bone has been proven, and bone cells express oxytocin receptors. Oxytocin enhances the differentiation and function of osteoblasts and leads to increased bone formation without affecting bone resorption and improving bone microarchitecture (7). Hence, oxytocin might serve as a promising anabolic therapy for preventing premature osteoporosis (8).

The systematic review aims to examine the results of all studies that express the relationship between oxytocin and osteoporosis. Significant clinical gaps and knowledge challenges prompted this review, including a limited understanding of oxytocin's role in bone metabolism, a scarcity of clinical trials, variability in study results, and the need for new therapeutic approaches due to the limitations of current treatments. Existing studies use different methodologies, dosages, and outcome measures, making it difficult to draw definitive conclusions. By systematically reviewing and synthesizing these studies, we aim to identify consistent patterns, clarify mechanisms, highlight areas where clinical trials are needed, and provide a basis for future research into alternative osteoporosis treatments. This study can motivate clinical studies investigating the therapeutic role of oxytocin and its analogs for osteoporosis.

Methods

Literature search

This systematic review was done to investigate the effect of oxytocin on osteoporosis based on the Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 statement (9). The search was conducted in PubMed, Scopus, web of Science, and the grey literature resources (ProQuest and Google Scholar) without time limitation on 5 January 2023.

Inclusion and exclusion criteria

The inclusion criteria were all experimental studies with human or animal subjects and observational studies, including cross-sectional research that investigates the effect of oxytocin on osteoporosis and bone density, having access to the full texts, and without time limitation. Review articles, case studies, qualitative studies, discussion papers, meta-analyses, dissertations and thesis, book chapters, perspective and opinion articles, and conference abstracts were excluded from the study.

Study selection

The screening involved searching for the following terms: "osteoporosis," "oxytocin," and "bone loss".Duplicates were identified and removed. The studies which had the inclusion criteria and adequate methodological quality were eligible for inclusion in the review. All associations of oxytocin and osteoporosis and low BMD were considered in each study. Two reviewers independently conducted title and abstract screening, quality assessment, and data extraction. A consensus meeting with a third reviewer was used to resolve disagreements. Finally, the reference list and citations of eligible articles were manually screened for further relevant studies.

Data extraction and quality assessment

The research team designed a data extraction form in Excel 2016.Information including author, sex, model, OT dose/duration, groups, year of publication, and main findings were extracted from each animal study. In the human studies, Information including author, year of publication, sex, age, type of study, OT Dosage/ duration, participants, and main findings were extracted. The risk of bias for the animal studies was assessed by the CAMARADES checklist (The quality of each study was evaluated based on a set of criteria, including the statement of temperature control, peer-reviewed publication, use of anesthetic without significant neuroprotective properties, random allocation to treatment or control groups, sample size calculation, appropriate animal model, compliance with animal welfare regulations, blinded assessment of outcomes, and declaration of potential conflicts of interest. Each study was given a quality score out of 10, and the median score for the group was calculated) (10), and in vivo experiments (ARRIVE) guidelines (11). The human studies were apprised using the NHLBI checklist which has a set of 14 criteria as outlined in the Standard Quality Assessment Criteria (Questions for assessing the quality of studies included the research question, groups recruited from the same population and uniform eligibility criteria, study population, sample size justification, sufficient timeframe to see an effect, exposure assessed before outcome measurement, different levels of the exposure of interest, outcome measures, exposure measures, and assessment, repeated exposure assessment, blinding of outcome assessors, follow up rate, and statistical analyses). The quality rating can be categorized as Good, Fair, or Poor. Quality was rated as 0 for poor (0–4 out of 14 questions), I for fair (5–10 out of 14 questions), or II for good (11–14 out of 14 questions) (12).

Results

Results of study selection

The initial search retrieved 880 records (PubMed=131, Scopus=459, Web of science=190, and grey literature resources (ProQuest=27 and Google scholar=73), of which 314 were duplicates. Titles and abstracts of the remaining 566 studies were screened, and 473 articles were excluded that did not meet the inclusion criteria. After reviewing 93 full texts, 63 articles were excluded, leaving 30 articles for data extraction and qualitative assessment, as indicated in the PRISMA flow chart (Figure 1). (9).

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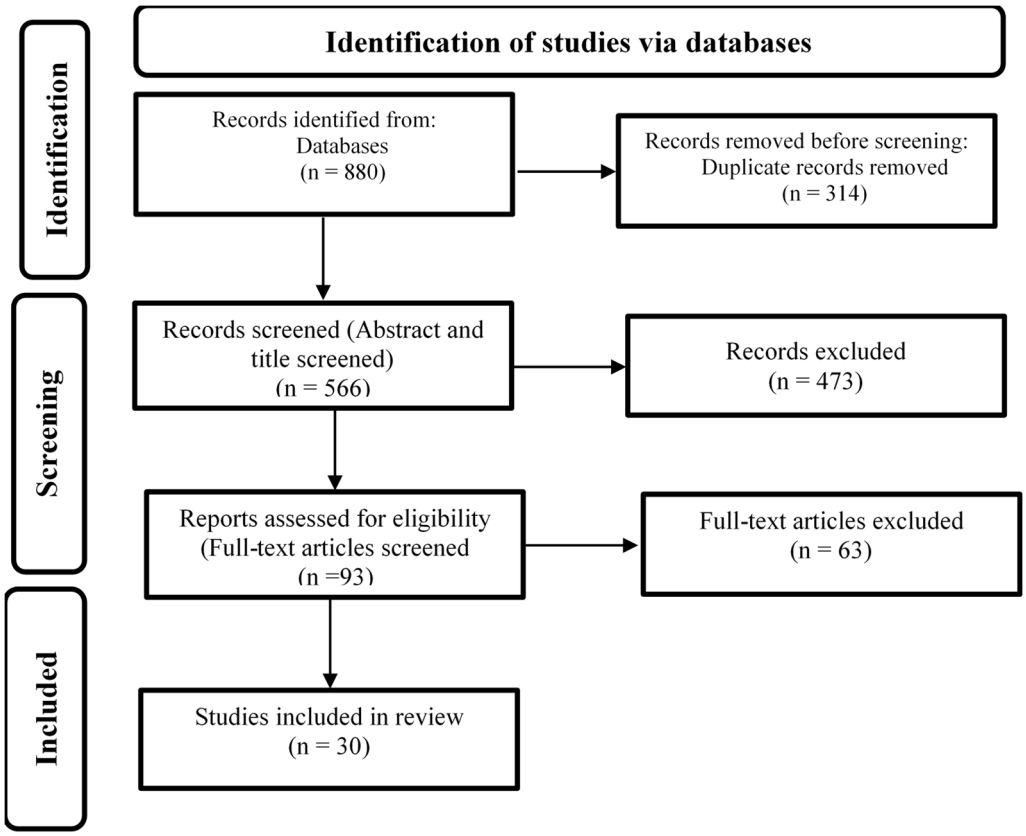

Figure 1. The diagram of the literature search and selection process was limited to studies that investigated the relationship between osteoporosis and oxytocin

Overview of included studies

Characteristics of the included studies are reported in Tables 1 and 2. Among the included studies, 19 studies are animal studies, which are reported in Table 1, and 11 studies are human studies, which are listed in Table 2. None of the studies were clinical trials. These studies have been conducted in 8 different countries. Most studies have been conducted in the United States of America (n=6), France (n=6), Brazil (n=5), Iran (3), China (n=4), Italy (n=3), Turkey (n=2), and Korea (n=1).

The included human studies are from 2002 to 2022, which consist of cross-sectional studies (n=6), a cohort study (n=2), and cell culture studies (n=3). Most of the human studies have been conducted on women, except two cross-sectional studies that have been conducted on men, and two cell culture studies have been conducted on both groups of women and men. Most of the human studies (n=8) measured the level of oxytocin in the participants' blood and studied its relationship with BMD.

The included animal studies are from 2008 to 2022, in which 14 studies on females, 3 studies on males, and two studies on both males and females were examined. These studies were conducted on rats (n=10), mice (n=6), rats and mice (n=1), and rabbits (n=2). In all included animal studies, the interventional effect of oxytocin was measured.

Dosage amounts, and routes of administration and measurement of oxytocin varied widely among the included studies, and there were no restrictions on daily dosing regimens or routes of administration or measurement methods of oxytocin.

Relationship between oxytocin and osteoporosis in the animal study

Of the fourteen animal studies included, ten studies were exclusively conducted on female animals, in which it was observed that oxytocin facilitates the intergenerational transfer of calcium ions from pregnant mothers to infants. To prevent excessive skeletal loss, oxytocin inhibits bone resorption by mature osteoclasts (13). Oxytocin plays an important role in regulating bone regeneration (14) and has an anabolic effect on bones (8, 15), enhancing bone formation and inhibiting bone loss (16). It was also observed in these studies that the anabolic effect of estrogen on bones could be through the production of oxytocin by bone osteoblasts, and with the increase in the concentration of estrogen, the increase in the release of oxytocin is observed, which causes rapid skeletal recovery (17). In aged female rats, oxytocin plays a role in inducing the differentiation of osteoblasts (18). In ovariectomized mice, oxytocin has an anti-osteoporosis role (19). Osteopenia was observed in mice lacking oxytocin receptors (20). In these studies, it was observed that oxytocin can be used as a new diagnostic marker for osteoporosis and oxy-

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Table 1. Characteristics of published animal articles on the relationship between oxytocin and osteoporosis

Authors	Year	Country	Sex	Model	OT Dosage/ duration	Groups	Main Finding	Score
Elabd et al. (21)	2008	France	F	OVX mice and Wistar rats/ Cell Culture	with 1 mg/kg OT for 8 weeks	ovariectomy or sham surgery	Plasma oxytocin level can be a new diagnostic marker for osteoporosis and oxytocin administration can be used as a treatment for this disease.	6
Liu et al. (13)	2009	USA	F	pregnant mice	25 lg/mouse, thrice weekly, for 5 weeks	control versus 18-day pregnant female mice	To prevent excessive skeletal loss, oxytocin inhibits bone resorption by mature osteoclasts, and oxytocin facilitates the transfer of calcium ions from the expectant mother to the pups.	7
Tamma et al. (22)	2009	USA	F/M	Mice/ ex vivo bone marrow cell cultures	OT (0, 0.01, 0.1, 1, 10, 100 nM)/ at different times	OT- and Oxtr deficient mice (displayed profound osteoporosis) against wild-type littermates (n 8 mice/group)	Deletion of oxytocin or oxytocin receptor in male or female mice causes osteoporosis due to decreased bone formation.	5
Colli et al. (16)	2012	Brazil	F	Wistar rats	OT (45 mg/rat) Two ip injections were given with a 12 h interval between them.	Sixteen female Wistar rats (24-month-old)	Oxytocin promotes bone formation and also inhibits bone resorption in aged, non-cycling female rats.	8
Colaianni et al. (17)	2012	USA	F	Mouse Models—OTR/ mice/ Cell Experiments	17-estradiol (E2; 108 M) for 21 days/ absence of OT receptors (OTRs) in OTR-/- osteoblasts	Osteoblasts were isolated from wild-type (OTR+/+) or OTR-/- bone marrow stromal cells in female mice from calvarias of 5-day-old pups	The anabolic action of estrogen in mice can be done through oxytocin produced by osteoblasts in the bone marrow, as a result of the release of oxytocin in the bone marrow by increasing the concentration of estrogen, it can cause rapid skeletal recovery in the last stages of lactation.	8
Park et al. (25)	2014	Korea	M	Sprague–Dawley rats/ subcutaneous ectopic bone formation model	A High initial OT dose (250 µg) / lower OT dose (50 µg)	Forty-five 16-week-old adult male Sprague–Dawley rats	Oxytocin promotes new bone formation through an osteoinductive mode of action.	6
Beranger et al. (26)	2014	France	F	OVX mouse as a model for postmenopausal osteoporosis	different doses of OT (0.1 or 1 mg/kg;IP	groups of mice(n 6–12); Sham-Ve, Sham-OT (1 mg/kg), OVX-Ve, OVX-OT (0.1 mg/kg), OVX-OT (1 mg/kg)	Oxytocin can restore bone homeostasis after OVX and thus has great therapeutic potential in the field of osteoporosis.	8
Beranger et al. (23)	2015	France	F/M	mice	OT (1 mg/kg)/IP/ 8 weeks	Ten-week-old C57Bl/6J mice	Treatment with oxytocin led to the normalization of bone parameters in ovariectomized mice, but this did not happen in orchidectomized mice. As a result, oxytocin can be an interesting alternative to estrogen treatment in postmenopausal women, but it is not able to compensate for the decrease in androgen levels.	7
Sun et al. (20)	2016	Italy	F	Mice (murine lactation model)	Oxtr was deleted specifically in osteoblasts	The generation of wild-type mice, Oxtr−/−, Avpr1α−/−, and Col2.3Cre:Oxtrfl/fl (n = 6 mice)	Oxytocin and vasopressin have opposite effects on the skeleton. The results showed that Oxtr-/- mice developed osteopenia, but Avpr1α-/- mice had a high bone mass phenotype.	7

tocin can be an effective treatment for osteoporosis (21).

Two studies on male and female mice showed that the elimination of oxytocin or the oxytocin receptor caused osteoporosis due to reduced bone formation (22). It was also observed that although oxytocin treatment led to the normalization of bone parameters in ovariectomized rats, this did not happen in orchidectomized rats. Oxytocin is unable to compensate for decreased androgen levels. Oxytocin seems to be an interesting alternative to estrogen therapy in postmenopausal women (23).

Two of the animal studies were exclusively conducted on males, and it was found that systemic administration of oxytocin increases new bone formation and bone repair (24). Oxytocin promotes new bone formation through

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Table 1. Continued

Authors	Year	Country	Sex	Model	OT Dosage/ duration	Groups	Main Finding	Score
Santos et al. (18)	2018	Brazil	F	Rat (Rattus norvegicus albinus)	100 nmol/L oxytocin	Multiparous female rats at ages 12 and 24 months were used for BMMSCs isolation.	Oxytocin can act as an aid to induce osteoblastic differentiation of BMMSCs in aged female rats.	8
Fallahnezhad et al. (27)	2018	Iran	F	Wistar rats	OT incubation with optimum dose was performed for 48 h (two times, 10−12 molar)	Twelve 3.5 months-old female Wistar rats	Oxytocin incubation and laser + Oxytocin incubation have a positive effect on OVX-BMMSCs.	8
Qiu et al. (30)	2019	china	F	New Zealand white rabbits	subcutaneous injection of 1 mg/kg of oxytocin daily for 10 days	Seventy-five rabbits / three groups (n = 25 per group): control group; OP group (OVX-vehicle); and OP+ oxytocin group (OVX-oxytocin group.	Early treatment with oxytocin can effectively reduce bone resorption in a rabbit model of osteoporosis.	8
Moghazy et al. (19)	2020	Iran	F	Sprague-Dawley rats	OT (0.1 mg/kg/day)/IP/ eight successive weeks	group I :sham, group II : ovariectomy, and group III : ovariectomy + OT	Oxytocin may have an anti-osteoporosis effect in ovariectomized mice. Thus, maintaining oxytocin levels early after ovarian function decline may act as a protective measure against bone loss.	8
Fernandes et al. (8)	2020	Brazil	F	Rats (Rattus norvegicus albinus)	two OT doses (134 µg/Kg) /IP/ 12-h interval (7:00 AM – 7:00 PM)	Seventeen-month-old healthy female rats (n=10/group)	Due to its anabolic role on bone, oxytocin is a promising solution for the prevention of primary osteoporosis, and its effect in controlling osteopenia indicates the prevention of osteoporosis in the perioperative period.	7
Altay et al. (24)	2020	Turkey	M	New Zealand white rabbits	10 mIU/ kg of OT / IM/ once daily until the end of the distraction phase	28 male New Zealand white rabbits.	Systemic administration of oxytocin increases bone formation and bone repair.	8
Fallahnezhad et al. (28)	2020	Iran	F	Wistar rats	OT (10−12 M, every 24 h, two times)	A total of 12 adult female Wistar rats	Both Oxytocin and PBMT + Oxytocin treatments could promote the mineralization of OVX-BMMSC in vitro at late stages of the osteogenic induction process.	8
Akay et al. (29)	2020	Turkey	M	Wistar rats	Oxytocin in crystalized particulate form (527 IU/mg)	Eighty adults / eight groups (n = 10)	Oxytocin provides accelerated bone regeneration in rat calvaria.	8
Santos et al. (14)	2022	Brazil	F	Wistar rats	OT (134 µg/Kg/IP)/ Two injections	Wistar rats at 19 and 20 months of age.	Endogenous oxytocin plays an important role in regulating bone regeneration during periosteopause, and exogenous oxytocin can be used as a preventive intervention in this period to improve bone quality.	8
Fernandes-Breitenbach et al. (15)	2022	Brazil	F	Wistar rats	(Ot; 134 µg/kg/ip)/two injections	Forty Wistar rats (18 months) with irregular estrous cycle	Strength training and oxytocin together as a promising intervention with anabolic action on bone can be effective for the prevention of osteoporosis in women.	7

osteoinduction (25). Oxytocin can restore bone homeosta-

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sis after ovariectomy when the activities of osteoclasts and osteoblasts are reduced, so oxytocin has therapeutic potential for osteoporosis (26). Oxytocin and laser + oxytocin incubation have a favorable effect on OVX-BMMSCs (bone marrow mesenchymal stem cells) (27). Oxytocin and PBMT + oxytocin can increase the mineralization of OVX-BMMSCs in the process of osteogenesis induction (28), and also oxytocin increases the rate of bone regeneration in rat calvaria (29). In a rabbit model of osteoporosis, bone BMD values had a consistent downward trend, and oxytocin treatment effectively reduced bone loss in these animals (30) (Table 1).

Relationship between oxytocin and osteoporosis in the human study

Of the nine human studies included, six were specifical-

Table 2. Characteristics of published human articles on the relationship between oxytocin and osteoporosis

Authors	Year	Country	Sex	Age	Type of study	OT Dosage/ measurement /duration	Participants	Main Finding	Quality assessment
Colucci et al. (36)	2002	Italy	F	25 to 35 years	In vitro	The anti-oxytocin receptor antibody	Osteoclast precursors from PBMCs collected from healthy female donors aged 25 to 35 years	Treatment with oxytocin increases Ca2i and this hormone can increase the number of pre-osteoclasts, thus it can affect osteoclastogenesis.	Good
Lawson et al. (33)	2011	USA	F	mean age 27.6±1.3 years	cross-sectional study	immunosassay kit from Assay Designs	36 women: 17 with anorexia nervosa (AN) and 19 healthy controls (HC).	Low levels of oxytocin are associated with decreased BMD and body fat and contribute to anorexia nervosa-induced bone loss.	Fair
Breuil et al. (35)	2011	France	F	55 to 85 years	Cross-sectional	OT was measured in duplicate by ELISA	20 postmenopausal women with severe osteoporosis compared to 16 healthy controls	Low serum oxytocin levels are associated with severe osteoporosis, independent of estradiol or leptin.	Fair
Colaianni et al. (41)	2011	Italy	F/M	NR	In vitro	polyclonal anti-OT, monoclonal anti-OTR	Human osteoblasts prepared from trabecular bone biopsies	Oxytocin produced by osteoblasts in the bone marrow in response to estrogen acts on the oxytocin receptor and exerts a strong anabolic effect.	Fair
Breuil et al. (40)	2014	France	F	55–79 years	OPUS cohort	Oxytocin RIA	1097 postmenopausal women	High oxytocin levels were associated with high BMD at the pelvis in women with high serum leptin or low estradiol levels.	Good
Breuil et al. (39)	2015	France	M	50-80 years	The MINOS study	Oxytocin RIA	In 552 men aged 50-80 years	Oxytocin serum level in men is not related to bone density and common fractures.	Fair
Schorr et al. (34)	2017	USA	F	18 to 45 years	Cross-sectional	Serum sampled for integrated overnight oxytocin levels	Fifty-nine women, ages 18 to 45 years: amenorrheic AN (N = 16), eumenorrheic HC (N = 24), eumenorrheic OB (N = 19)	Oxytocin indicates the availability of energy and mediates bone density and strength. Oxytocin may also provide avenues for the treatment of obesity and osteoporosis.	Fair
Ge et al. (37)	2019	China	F/M	12–16 years old	In vitro	10, 50, or 100 nM OT for 1 h.	PDLSC preparation by extracted teeth from eight patients aged 12 to 16 years	Oxytocin-induced osteogenic differentiation could have the potential for use in periodontal regeneration.	Good
Du et al. (31)	2021	China	F	50–90 years	A cross-sectional study	Quantikine ELISA	478 healthy community-dwelling postmenopausal women aged 50–90 years	Postmenopausal women with osteoporosis were more likely to have lower oxytocin levels.	Good
Aulinas et al. (38)	2021	USA	M	20-60 years	cross-sectional study	frequent sampling of blood for assessment of pooled oxytocin levels	37 men (17 CDI and 20 APD)	The relationship between oxytocin levels and BMD and estimated hip strength in hypophyseal subjects with CDI was observed in this study.	Fair
Yu et al. (32)	2022	China	F	a mean age of 51.17 years	A cross-sectional study	Serum OT was measured using ELISA kit	149 healthy female individuals; 74 premenopausal and 75 postmenopausal	A positive correlation between serum levels of oxytocin and BMD was observed, suggesting a protective role and therapeutic use of oxytocin in osteoporosis, especially for premenopausal women.	Fair

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ly conducted on women, and these studies found that oxytocin was associated with osteoporosis and that postmenopausal women with osteoporosis were more likely to have lower oxytocin levels (31). A positive correlation was observed between the serum level of oxytocin and BMD, which can indicate the protective role and therapeutic use of oxytocin in osteoporosis in premenopausal women (32). Low levels of oxytocin are associated with decreased bone density and body fat, contributing to bone loss in anorexia nervosa (33). Oxytocin is an indicator of energy availability and has an impact on bone density, structure, and strength and could be targeted for the treatment of obesity and osteoporosis (34). Low serum oxytocin independent of other factors associated with osteoporosis or regulators of serum oxytocin levels such as estradiol or leptin appears to be associated with severe osteoporosis, strengthening the concept that oxytocin may play a role in the pathophysiology of osteoporosis. Menopause is involved (35). OTR expression was further confirmed on both osteoclasts and their progenitors. Oxytocin treatment increases Ca2i, and this hormone may affect osteoclastogenesis by increasing the number of pre-osteoclasts (36).

One human study involving men and women showed that oxytocin increased the migration, proliferation, and osteogenic differentiation of PDLSCs. Therefore, oxytocin may promote periodontal regeneration (37). Two of the included human studies were conducted exclusively on men, and one study provided evidence for an association between oxytocin levels and BMD and estimated pelvic geometry and strength in hypophyseal with CDI (38). Another study showed that in men, serum oxytocin levels were not associated with bone density, bone turnover rate, or common fractures (39). High oxytocin levels are associated with high BMD in the hip of women with low serum estradiol levels or high leptin levels (40). In the bone marrow, in response to estrogen, oxytocin is produced by osteoblasts and acts on the oxytocin receptor, causing a strong anabolic effect (41) (Table 2).

Quality assessment

Each animal study received a quality score out of 10 points, and the median score for the group was 8.Most of the recommendations of the results of the evaluation of the quality of human studies of this study are fair.

Discussion

This study was conducted to investigate the relationship between oxytocin and osteoporosis. In this study, 29 human and animal studies were included, in which oxytocin was administered in animal studies, and the effect of oxytocin on osteoporosis and BMD was investigated. However, in human studies, oxytocin was not administered, but oxytocin levels were measured in people suffering from osteoporosis or old and postmenopausal people. Studies have shown that oxytocin plays a role in improving osteoporosis.

Oxytocin increases new bone formation and bone repair (24) and has a positive relationship with BMD and a negative relationship with the risk of osteoporosis, as a result of which oxytocin can be a determinant of bone density in postmenopausal women and as a factor. It is protective against low bone mass (32). This association of high serum oxytocin levels with high BMD seems to have a direct effect on bone cells independent of estradiol action in postmenopausal women (40). More extensive new bone formation was observed in rat cranial CSDs with increasing doses of oxytocin, suggesting that oxytocin promotes new bone formation through an osteoinductive mode of action (25). Oxytocin causes skeletal homeostasis by stimulating the formation of osteoblasts and through the mutual modulation of osteoclast formation and function. It has been observed that mice without oxytocin hormone or its receptor suffer from osteoporosis, which increases with age in both sexes (42). A study was shown for the first time the expression of oxytocin receptors in human osteoclasts. Oxytocin receptors are specifically located in wide spots on the membrane of mature multinucleated osteoclasts. The expression of oxytocin receptors was further confirmed by western blot analysis in osteoclasts and osteoclast precursors (36).

In addition to being secreted from the posterior pituitary, oxytocin can also be produced by bone marrow osteoblasts and acts as a regulator of estrogen-mediated bone formation. Oxytocin receptors are expressed in both osteoblasts and osteoclasts, and their stimulation by oxytocin increases bone mass. The potency of the hormone estradiol to increase bone mass depends on oxytocin receptors (43). Consequently, in the bone marrow, oxytocin produced by osteoblasts in response to estrogen acts on its receptor to exert a strong anabolic effect. This effect is by activating the Erk MAP kinase pathway (41). Mice lacking oxytocin receptors have osteogenesis defects and could not show an increase in cortical thickness, trabecular bone volume and bone formation in response to estrogen (17).

Oxytocin levels are significantly reduced in ovariectomized rats and mice that develop osteoporosis, and oxytocin injection can ameliorate bone loss in ovariectomized rats (19, 21). A protective measure against bone loss after reduced ovarian function is maintaining oxytocin levels. Considering that the half-life of oxytocin is short, it is better to study oxytocin analogs that have a longer half-life and are more stable for the development of osteoporosis treatment (19). By acting on osteoclast precursors, oxytocin stimulates osteoclastogenesis, which contributes to maternal skeletal mobility. Oxytocin prevents excessive skeletal loss by inhibiting bone resorption by mature osteoclasts (13). Oxytocin levels may be lower in postmenopausal women with osteoporosis., suggesting that oxytocin's effect on bone is not entirely dependent on sex hormone levels. The relationship between oxytocin and osteoporosis is not influenced by vitamin D and exercise.Oxytocin is a promising candidate as a serum biomarker related to osteoporosis and/or sarcopenia (31).

Oxytocin stimulates the differentiation of osteoblasts to a mineral phenotype by upregulating BMP-2, which controls the expression of osterix, ATF-4, and Schnurri-2. Oxytocin stimulates osteoclast formation through RANK-L up-regulation as well as by activating NF-B and MAP

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kinase signaling. Bone resorption by mature osteoclasts is inhibited by oxytocin, which releases cytosolic synthesis of Ca2 and NO. (22). Oxytocin increased plasma bone biochemical markers, such as osteocalcin and alkaline phosphatase (ALP), and tartrate-resistant acid phosphatase (TRAP) decreased significantly, indicating an antiresorptive effect of oxytocin (16). Administration of oxytocin increases plasma superoxide dismutase and in rat femoral neck, it causes more cortical and trabecular thickness, number of trabeculae, BMD, lower expression of TRAP and higher OCN, bone strength and also decreases porosity of the bone marrow cortex and higher inertia (14). The combination of strength training and oxytocin has anabolic action on bone in females and resulted in a higher maximum load, with higher BV/TV, higher Rankl and Ctsk expression, lower activity of TRAP, and lower Po.N (15). Oxytocin increased the expression of osteogenesis-related genes such as collagen I, alkaline phosphatase, osteopontin, runt-related transcription factor 2, and osteocalcin (OCN). It also increases bone differentiation by activating the phosphorylation of ERK and AKT pathways (37).

Fat, leptin, and oxytocin may share a common signaling pathway, or they may independently signal energy availability. In women with anorexia nervosa, the lack of oxytocin may be a sign of a lack of energy and resources for bone formation (33). In a study, women with osteoporosis had significantly lower serum levels of oxytocin, leptin, and LH and higher CTX and SHBG. Fat mass and lean mass decreased significantly in women with osteoporosis. Serum oxytocin levels were significantly associated with bone mineral density (35). Oxytocin is a marker of energy availability and may mediate bone density, structure, and strength. Oxytocin pathways may provide targets for the treatment of obesity and osteoporosis (34). Mice that lack oxytocin or lack the oxytocin receptor gain weight without increasing food intake, indicating that a lack of oxytocin can cause a decrease in metabolic rate. As a result of oxytocin treatment, late-onset obesity occurs in oxytocin-deficient or oxytocin-receptor-deficient mice, as oxytocin can regulate energy (44). Oxytocin can have an independent negative relationship with menopause and, more strongly, with obesity (45). Plasma oxytocin levels in women are higher than in men and older people have higher plasma AVP levels than young people (46). Oxytocin can increase odontoblast-like cell differentiation, thereby increasing dentin formation, and can also be an important factor for dentinogenesis (47). In a study of older men, serum oxytocin levels were not associated with bone density, bone turnover rate, or frequent fractures, and unlike women, serum oxytocin levels were not associated with BMD or BTM levels. Also, no correlation was found between serum oxytocin and common fractures (39).

The osteogenic medium in female rat BMMSCs, along with oxytocin administration, increased oxytocin and oxytocin receptors, which improved bone differentiation and increased alkaline phosphatase activity, as well as increased gene expression of bone morphogenetic protein 2, osteocalcin, bone sialoprotein and osteopontin, was observed to demonstrate the role of oxytocin as a facilitator of osteoblastic differentiation (18). Intra-abdominal obesity and osteopenia can be improved in the ovariectomized mice model (simulation of menopause) under the influence of oxytocin (26). PBMT + oxytocin treatment can significantly increase the survival of OVX-BMMSC in OIM (osteogenesis induction medium) in laboratory conditions and increase the mineralization of OVX-BMMSC in the culture medium at different stages of the osteogenesis induction process (28). Accelerated bone regeneration in rat calvaria and increased mean bone mineral density were observed under the effect of treatment with oxytocin-loaded sustained-release PLGA microspheres containing thermosensitive hydrogel graft (HCPOM) (29).

Limitations

There were some limitations to our study, including First, clinical trial studies were not conducted in this regard. Second, few studies have been conducted on men. Thirdly, in animal studies, the doses of oxytocin used to improve osteoporosis varied greatly, and it was difficult to determine the effective dose of oxytocin. According to the results and limitations of the study, it is suggested that to confirm the therapeutic role of oxytocin on women's osteoporosis, clinical trial studies should be conducted. There are very few studies on the effect of oxytocin on osteoporosis in men, which requires more animal and human studies in this field. More studies are needed on the preventive role of oxytocin against osteoporosis. Also, studies are needed to determine the effective dose of oxytocin in improving osteoporosis. Considering that most of the studies in this field were conducted on elderly people, it is recommended to conduct studies on young people as well. In this systematic review, various studies were examined, showing heterogeneity such as the inclusion of animal studies, human and laboratory studies, varied study methods, and doses of oxytocin across the articles. Additionally, there were differences in gender and sample sizes among the studies. For example, the various heterogeneities observed in human cross-sectional studies, these variations and limitations affect the interpretation of the relationship between oxytocin levels and bone health. In this systematic review and similar studies, there are several confounding factors such as variations in serum oxytocin levels, gender, and age, which may influence the study results and overall review findings.

Conclusion

Oxytocin has anabolic effects on bone and strengthens ossification, bone regeneration, and repair, helps to induce osteoblasts, inhibits bone resorption, and prevents bone resorption by mature osteoclasts. The removal or reduction of oxytocin causes osteoporosis. The findings support oxytocin's potential as a treatment for osteoporosis, though clinical trials are necessary to confirm its efficacy and determine optimal dosing. Further research is needed to explore oxytocin's preventive role and effects on different populations. Due to the lack of clinical trials in this regard, it is suggested to conduct clinical efficacy studies on the effect of oxytocin in patients with osteoporosis. Also, more studies on the effect of oxytocin on bone are needed in the future to identify the most efficient and ef-

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fective therapeutic dose of oxytocin that has the least complications in elderly patients with osteoporosis.

Authors' Contributions

Conceptualization: Radmanesh E, Mohammadi SM. Data collection: Radmanesh E, Saniee N, Karimi S. Methodology: Radmanesh E, Mohammadi SM, Saniee N, Karimi S, Kamyari N. Writing – original draft: Radmanesh E. Review & editing: all authors (Radmanesh E, Mohammadi SM, Saniee N, Karimi S, Kamyari N).

Ethical Considerations

The ethics code of this study (IR.ABADANUMS.REC.1401.099) was approved by the Ethics Committee of Biological Research of Abadan University of Medical Sciences in Iran.

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Conflict of Interests

The authors declare that they have no competing interests.

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