osteology

MDPI

Review

Depressive Symptoms as Potential Mediator between Physical Activity and Bone Health—A Scoping Review

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Abstract: Depression constitutes a risk factor for osteoporosis (OP). Increasing physical activity might mitigate this risk, although intensive exercising may lead to opposing effects in depressed patients. The purpose of this scoping review was to summarize the evidence regarding the influence of exercise on bone health in depressed patients, divided into two sections: (1) Which bone markers are affected by depression? (2) How does exercise affect bone health in patients with depressive symptoms? A search of the literature was conducted in PubMed and Web of Science between August 2020–2022. Studies were included based on predetermined criteria for each sub-question. Regarding sub-question 1, eight studies revealed the following bone markers to be influenced by depression: P1NP, BAP, CTX, OC, RANKL, OPG, DPD, and PYD. Regarding sub-question 2, one study found a correlation between depression and bone health in an exercising population, and other studies detected improvements in bone health (n = 4) and depressive symptoms (n = 4) after exercise interventions. The current review shows the potential of exercise as a treatment form to improve bone health in depressed patients. Future trials are needed to assess the influence of exercise intervention on bone health in depressed patients.

Keywords: bone mineral density; HPA-axis; allostatic load; bone markers; exercise

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1. Introduction

Osteoporosis (OP) is a metabolic bone pathology characterized by a decrease (T-score ~≤2.5 SD) in bone mineral density (BMD) caused by an imbalance in osteoblast and osteoclast activity, making the bone more susceptible to fractures [1–5]. It is estimated that over 200 million people suffer from OP worldwide [6,7], with the pathology occurring more often in women but prevalent in men as well [4,8,9]. In the United States, OP leads to approximately one and a half million fractures per year [10], which can lead to various negative consequences, such as decreased mobility, chronic pain, and impaired quality of life [9,11–13]. Common biological risk factors for OP are aging, gender, low body mass index, and previous fractures, as well as endocrine (e.g., hyperthyreosis), immunological (e.g., Crohn's disease), or metabolic (e.g., diabetes) diseases [2,14–16]. Behavioral risk factors consist of malnutrition (e.g., decreased calcium and vitamin D intake), medication (e.g., anti-depressant), and a lack of physical activity (PA) [1,8,17].

In addition to the risk factors already mentioned above, depression also constitutes a risk factor for OP by negatively impacting BMD and bone markers [18–25]. Major depressive disorder (MDD) is a severe (stress-related) mental disorder that impacts the functionality of the whole body [26,27]. In healthy people, stress leads to a process of adaptation of the body by releasing stress hormones (e.g., cortisol) and other mediators through the hypothalamic-pituitary-adrenal (HPA)-axis to maintain homeostasis [27]. This process of adaptation is called allostasis, related to the allostatic load concept first introduced by McEwen and Stellar (1993) [26–28]. However, mental disorders such as depression can arise if the stress demands become too high for a prolonged time. This could lead to a dysregulation of the HPA axis, followed by a state of allostatic overload [26–29].

For this reason, both allostatic overload and/or MDD can affect bone health through biological and behavioral mechanisms, including the use of medications [15,25]. However, the mechanisms and pathways behind the influence of depression on bone metabolism are multifactorial, highly complex, and not completely understood [15,23,30]. The MDD-related dysregulation of the HPA-axis can lead to an increased release of glucocorticoids, inflammatory cytokines (e.g., Interleukin-6), and a reduction of growth hormones and brain-derived neurotrophic factors (BDNF) (indirect growth factors for osteoblasts) [4,14,18,23,31]. Pro-inflammatory cytokines (e.g., Interleukin-6), which are permanently heightened in many depressed patients, result in osteoclast activation, with subsequent degradation of bone and, therefore, a reduction in BMD. Furthermore, depression is associated with oxidative and nitrosative stress (due to the production of reactive oxygen species in mitochondria), a sedentary lifestyle, and premature aging, eventually leading to damaged/changed mitochondrial activity/function [32–35]. The allostatic mediators glucocorticoids and IGF-1 also influence bone metabolism and can cause an imbalance in osteoblast and osteoclast activity, leading to decreased bone health [14,32,36,37]. This illustrates how depression and increased allostatic load or overload can lead to catabolic bone metabolism [31]. On the other hand, regular PA (a possible treatment form of OP) can mediate these negative effects (Figure 1).

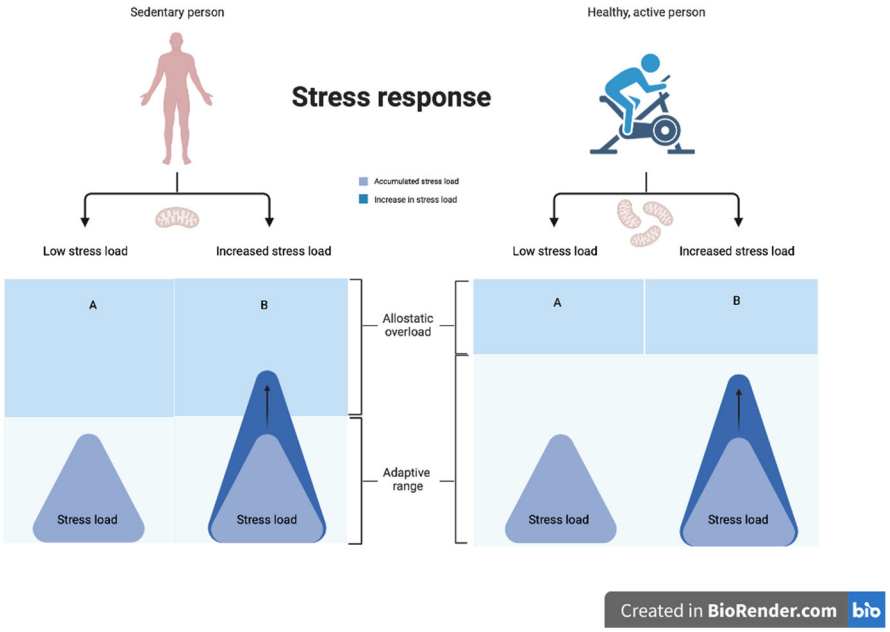

Figure 1. A representation of how the same stressor can lead to different stress responses depending on the physical activity level of the affected person, according to the allostatic load concept first introduced by McEwen and Stellar (1993). On the left side, a person presenting sedentary behavior, which is one of the contributing factors to osteoporosis and common in people with depression [38,39],

is represented with low mitochondrial content. In case of a low-stress load (A), the body of this person is still able to adapt to the stress load, whereas with an increased stress load (B), which is also common in depressed patients, the accumulated stress exceeds the adaptive capacity of the body and can lead to allostatic overload [26,37]. Regular physical activity promotes the multiplication of mitochondrial content and increases mitochondrial function, increases resilience of the cells, and therefore diminishes the chance of allostatic overload. Hence, in a person who is physically active, a similar stress load as in situation B of the sedentary person does not lead to allostatic overload, and homeostasis of the body is maintained. Revised figure of Picard et al. (2014; Figure 2 [33]). Created with biorender.com.

Current treatment forms for OP include supplemental vitamin D and calcium intake, adapting hormone intake to influence the effects of menopause, stem cell therapy, biophosphonates, and increasing physical activity (PA) levels [5,40,41]. Unfortunately, treatment with medications such as biophosphonates and hormonal therapy comes with side effects [41]. Increasing skeletal loading through PA can have a positive influence on BMD and bone metabolism markers, such as collagen cross-links (CTx), osteocalcin (OC), bone alkaline phosphatase (BAP), and Procollagen-1 N-terminal propeptide (P1NP) in osteoporotic patients [10,21,42–47]. Therefore, exercise interventions are considered an important treatment component for OP [18]. Previous reviews have investigated the effect of various types of training programs on bone health. Overall, multicomponent exercise programs (combined aerobic/impact and resistance training) were perceived as most successful in improving bone health [42,48–53].

In addition to the positive effects of exercise on bone health, regular PA can also mitigate the detrimental effects of psychological stress on the body by increasing mitochondrial volume, thus improving cellular resilience against disturbances (Figure 1) [29,33,34,54] and protecting against the negative consequences of stress, including osteoporosis. On the other hand, an acute strenuous exercise bout can also function as a physical stressor. Therefore, exercise could lead to allostatic overload in patients with an already high allostatic load, eventually generating detrimental effects on bodily processes and bone health [14,55]. Consequently, the physiological responses to PA may be different in depressed patients with a high-stress load compared to healthy people. In addition, there are initial indications that bone metabolism can change during a depressive phase [37], thus requiring an adaptation of training intensity. This means that whether MDD is present in a patient may have to be considered when prescribing exercise programs as a treatment to improve bone health.

Unfortunately, data regarding the effectiveness of exercise on bone health in depressed patients, in general, is very limited [14]. Therefore, this scoping review aims to provide an overview of the currently available knowledge regarding the influence of exercise on bone health in depressed people and to identify the gap(s) of knowledge which should be addressed in future research [56]. For that purpose, two sub-questions were investigated: Firstly, even though BMD, measured through DEXA scans [57], is the outcome used for the diagnosis of osteoporosis, bone markers can provide additional and earlier information about alterations in bone metabolism. Therefore, bone markers can possibly be used as diagnostic markers for the early prediction of OP [58,59]. Hence, the question 'Which bone markers are affected by depression?' (SQ1) was assessed. Second, the sub-question 'How does exercise affect bone health in patients with depressive symptoms?' (SQ2) was addressed.

2. Materials and Methods

This scoping review was conducted according to the recommendations of Pham et al., (2014) and the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [60,61]. Since this review aimed to answer two sub-questions, two systematic searches consisting of keywords and Medical Subject Headings (MeSH)terms were performed in PubMed and Web of Science between August 2020 and August 2022. For sub-question 1, the following search string was entered in the online databases: ("bone turnover markers" OR "bone markers" OR "bone metabolism" OR "bone homeostasis" OR "bone alterations") AND (stress OR

depression). The following inclusion criteria were applied: Randomized controlled trial, clinical trial, cross-sectional study, observational study, pre-post study, the outcome of bone markers, published between 2010 and 2022, and full-text in English, German or Dutch. Exclusion criteria consisted of animal studies, reviews, case reports, study protocols, and letter(s) to the editor or no included bone markers for analysis (e.g., solely inclusion of fractures or BMD).

Regarding sub-question 2, the search word combination of (exercise OR "physical activity" OR "physical exercise") AND (osteoporosis OR bone) AND (depression OR "allostatic load" OR stress) was entered into the two online databases. Inclusion criteria consisted of a randomized controlled trial, clinical trial, cross-sectional study, observational study, pre-post study, outcomes regarding bone health and depressive symptoms, participants 18 years or older, published in 2000–2022, participants with low and/or normal BMD or OP, and published in English, German or Dutch. Exclusion criteria contained study protocols, case reports, letters to the editor and reviews, participants with additional pathologies (e.g., cardiovascular diseases, cancer), animal population, and studies including additional interventions (e.g., weight loss).

After the online search, results from both PubMed and Web of Science were accumulated, and duplicates were removed. Afterward, studies were screened for eligibility for this review based on the title. The remaining articles were screened for eligibility based on inclusion and exclusion criteria identified in the abstract and full text. The study selection process is shown for each sub-question in Figure 2 (PRISMA diagram) [62].

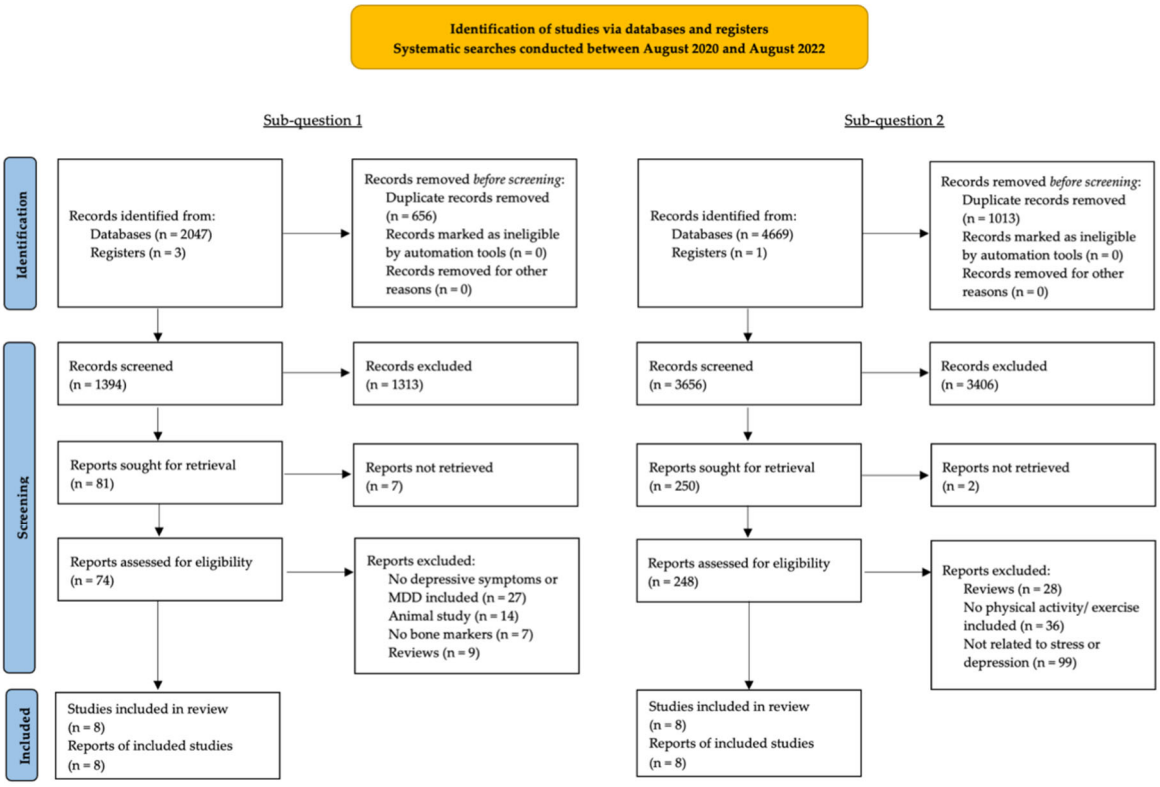

Figure 2. PRISMA flow chart.

Data regarding authors, year of publication, study type, population, intervention type, and the effects of exercise interventions on bone health and depression-related parameters (e.g., BMD, osteoclasts, allostatic load, depression questionnaires) were collected and presented in tabular form.

Two researchers independently assessed the quality of studies for sub-question 1 and 2. In case of conflicting answers on the various criteria, the differences were discussed, possibly with a third researcher, and eventually, a consensus was reached. The quality

of studies for sub-question 1 was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute [63]. The quality of studies for sub-question 2 was assessed using the PEDro scale [64,65] for RCTs and the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group from the National Heart, Lung and Blood Institute for the studies with a pre-post study design [66].

3. Results

In total, 6720 articles were initially identified through the systematic search process on PubMed and Web of Science. After removing duplicates, 5050 publications remained. The full-text eligibility of 168 articles was assessed, and finally, a total of 16 articles were included to answer the two sub-questions (Figure 2). Many articles were excluded after the initial screening step due to the broad scope of the search string, which could not be narrowed due to the possibility of missing relevant literature.

3.1. Sub-Question 1: Which Bone Markers Are Affected by Depression?

Eight articles (N = 926 participants) were included in this part (Table 1). Depression was assessed through different methods, including psychiatrist assessment and questionnaires, such as the Beck Depression Inventory (BDI), Psychological General Well-Being Schedule (PGW), Children's Depression Inventory (CDI), Children's Depression Rating Scale-Revised (CDRS-R), Hamilton Depression Rating Scale (HDRS), Mini-International Neuropsychiatric Interview (MINI), Inventory for Depressive Symptomatology (IDS), Beck Anxiety Inventory (BAI) and Montgomery–Asberg Depression Rating Scale (MADRS).

Table 1. Study characteristics included for sub-question 1.

Authors	Study Type	# Participants	Gender (M/F)	Age Range	Depression Duration	Quality [63]
Atteritano et al., (2013)	Cross-sectional	100	0/100	49–58 years	2–12 years mean 7.33 ± 3.05 years	8/12
Calarge et al., (2017)	Prospective study and cross-sectional	264	105/159	15–20 years	N.M.	10/14
Fazeli et al., (2013)	Cross-sectional	65	32/33	12–18 years	Boys: 2.6 ± 2.6 years Girls: 1.9 ± 1.2 years	8/12
Govender et al., (2010)	Cross-sectional	45	0/45	20–40 years	N.M.	5/11
Malik et al., (2013)	Cross-sectional	50	13/37	22–59 years	1–16 years Mean 4.9 ± 5.2 years	9/13
Skowrońska-Jóźwiak et al., (2020)	Cross-sectional	144	63/79	46.9 ± 11 years	6.9 ± 5.5 years	8/12
Sommerhage et al., (2013)	Cross-sectional	50	0/50	29–70 years	N.M. (Mean of 4.6 previous episodes)	9/13
Wippert et al., (2019)	Cross-sectional and longitudinal	208	51/157	18–65 years	Acute episode	10/13

N.M. Not mentioned.

The bone markers assessed regarding their link to depression were Osteocalcin (OC; n = 5), Procollagen type 1 N-terminal propeptide (P1NP; n = 2), Carboxy-terminal collagen crosslinks (CTX; n = 6), Bone (specific) alkaline phosphatatse (B(S)AP; n = 3), Pyridinoline (PYD; n = 2), Deoxyridinoline (DPD; n = 2), Osteoprotegerin (OPG; n = 2) and Receptor activator of nuclear kappa-B ligand (RANKL; n = 2). Additionally, BMD was assessed

in seven out of the eight included studies. The up- or downregulation as a consequence of depression or conflicting results is provided in Table 2. The quality of studies ranged from 5/11 to 10/13 points on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute [63].

Table 2. Concentrations (elevated, decreased, or conflicting levels) of bone markers and bone mineral density influenced by depression.

Bone Marker	# Studies	Concentrations		
Bone formation		↑	↓	↔
Osteocalcin (OC)	5 [7,37,67–69]	1×	1×	3×
P1NP	2 [24,37]			2×
Bone-specific alkaline phosphatase (BAP)	3 [67,68,70]	2×		1×
Bone resorption				
(beta-)CTX	6 [7,24,37,68,69,71]	2×		4×
Pyridinoline (PYD)	2 [67,70]	2×		
Deoxypyridinoline (DPD)	2 [67,70]	2×		
Bone regulation				
Osteoprotegerin (OPG)	2 [69,70]	1×	1×	
RANKL	2 [69,70]	1×		1×
Diagnostic outcome				
BMD	7 [24,37,67–71]		5×	2×

#: number, ↑: Upregulated, ↓: Downregulated, ↔: within normal range or conflicting results.

3.1.1. Bone Formation

In the included studies, osteocalcin (OC), procollagen type 1 N-terminals (P1NP), and bone alkaline phosphatase (BAP) were discussed as bone formation markers. Regarding OC (n = 5), the following results were found: one study found a reduced concentration [7], one study detected normal OC concentrations, varying to both the reduced and increased sides [69], one study showed an increased OC concentration during a depressive episode, but a reduced concentration in participants who had a high allostatic load [37], one study showed increased OC concentrations in depressed patients [67], and lastly one study showed a decreased OC/CTx ratio in males [68]. Two studies assessed the influence of depression on P1NP: one study found reduced levels of P1NP in MDD patients compared to controls; however, this difference was only significant in girls, and after adjusting for BMI, there were no significant differences in P1NP concentrations in either gender [24]. Another study showed that P1NP concentrations increased with depression severity but showed lower levels in patients with a high allostatic load and decreased concentrations in participants with allostatic overload [37]. BAP concentrations were assessed in three studies, were elevated in two studies [67,70] and increased depending on gender in one study [68].

3.1.2. Bone Resorption

Regarding bone resorption, the markers collagen crosslinks (CTX), deoxypyridinoline (DPD), and pyridinoline (PYD) were assessed. The marker CTX (n = 6) showed either elevated [7,71], normal [24,69] higher or lower concentrations dependent on allostatic load [37], or increased BAP/CTX and OC/CTX ratios in depressed patients [68]. Two studies assessed DPD and PYD concentrations and showed elevated concentrations for both [69,70].

3.1.3. Bone Regulation

Furthermore, the concentrations of bone regulation markers OPG and RANKL in depressed patients were assessed. The study of Malik et al., (2013) showed increased OPG levels and RANKL concentrations within a normal range [69], whereas Atteritano et al. (2013) showed decreased OPG levels and higher RANKL concentrations [70], leading to a lower OPG/RANKL ratio.

3.1.4. Bone Mineral Density

In addition to bone markers, the influence of depression on the diagnostic outcome of BMD was assessed in seven out of the eight included studies for this sub-question. Similar to the bone markers results, the results for BMD were also conflicting. Two studies noted no difference in groups with (a history of) MDD compared to (psychologically) healthy controls [24,69]. However, the other five studies detected a lower BMD in the depressed participants compared to controls [37,67,68,70,71].

3.2. Sub-Question 2: How Does Exercise Affect Bone Health in Patients with Depressive Symptoms?

Eight studies (N = 1.201 participants) were included to assess the associations between depression, OP, and exercise. Two of the studies stemmed from the same intervention, but one assessed the influence of this intervention on bone health and the other on depressive symptoms [9,72]. The characteristics of the included studies are provided in Table 3.

The influence of exercise on BMD was assessed in five included studies (spine, hip, trochanter, femoral neck; Table 3). Three studies found a positive influence of exercise on BMD [5,72]. Pearson et al. (2005) assessed the influence of PA on BMD values and detected an increase of BMD of 0.5% (0.793 $\rightarrow$ 0.797 g/cm^2; NS) at the spine and 3% at the hip (0.873 $\rightarrow$ 0.900 g/cm^2; $p < 0.0001$) after the intervention [5]. The study of Kukuljan et al., (2009) found significant improvements in all their assessed BMD parameters (femoral neck, upper and lower FN, L_1–L_4, total hip, and trochanter) after their exercise intervention. Sen et al., (2020) detected a significant increase in BMD at the femoral neck and L_2–L_4 region in the whole-body vibration exercises group but not in the high-impact exercise group [73]. Milliken et al., (2006) assessed the association between depression and BMD after a 1-year exercise program and found that Beck Depression Inventory (BDI) scores were significantly related to BMD values at the femur neck but not greater trochanter or spine [74]. In the study of Dieli-Conwright et al., (2018), no significant changes in BMD were detected. Two of the five studies that assessed BMD also included the assessment of exercise on bone markers, in addition to BMD [73,75], and both found significant changes in certain bone marker (OC and BAP) concentrations [75]. Two studies solely investigated depressive symptoms before and after an exercise and rehabilitation intervention in OP patients [6,12].

Table 3. Study characteristics and outcomes (BMD, bone markers, and depression scores) of the included studies for sub-question two.

Publication	Study Type # Participants Sex (M/F) Age	Osteoporosis Depression	Exercise Intervention	Supervised/Home Group/Individual	Duration Follow-Up	BMD		Bone Markers		Depression Scores *Time between Measurements*		Quality [65,66]
Pearson et al. (2005) [5]	Pre-post trial N = 375 (*BMD* n = 155) 8/367 44–90 y *M* = 67 y	Low BMD [1]- 	2 × 2.5 h/week exercise (2 strength training sessions and 30/40 min. of aerobic training + education + consultation staff Encouraged to perform additional training (1 strength training session and aerobic up to 150 min.) at home	2×/week supervised Additional at home-	8 weeks 6 months; 2 years (BMD)	Hip Spine	2-year change 0.793 → 0.797 g/cm^2 (0.5%) t-score: −1.27 → −1.22 SD 0.873 → 0.900 g/cm^2 (3%) t-score: −1.68 → −1.43 SD *		-	CES-D [2] *8 weeks*	8.5 ± 7.7 → 6.8 ± 6.2 *	9/12
Dieli-Conwright et al., (2018) [75]	RCT [3] N = 100 Overweight/obese women + < 6 months breast cancer survivors 53.5 ± 10.4 y 60% postmenopausal	- -	3×/week (moderate–vigorous) Aerobics + Resistance	Supervised Individual	16 weeks 3 months	Whole-body Lumbar spine Total hip Trochanter Femoral neck	1.22 ± 0.1 → 1.27 ± 0.1 g/cm^2 1.16 ± 0.09 → 1.20 ± 0.09 g/cm^2 0.91 ± 0.09 → 0.94 ± 0.09 g/cm^2 0.72 ± 0.07 → 0.74 ± 0.07 g/cm^2 0.88 ± 0.1 → 0.90 ± 0.1 g/cm^2	OC [4] BAP [5] CTX [6] NTX [7] RANK [8] RANKL [9]	12.1 ± 3.1 → 15.0 ± 4.1 ng/mL * 16.1 ± 4.6 → 18.0 ± 5.0 ng/mL * 0.48 ± 0.1 → 0.44 ± 0.2 ng/mL 18.6 ± 3.1 → 17.7 ± 2.8 nM BCE/L 27.4 ± 6.8 → 26.7 ± 6.4 pg/mL 142.5 ± 18.9 → 146.1 ± 16.1 pmol/L	CES-D *16 weeks*	Exercise: 15.1 ± 3.3 → 9.7 ± 2.5* CON: 15.2 ± 3.5 → 16.7 ± 3.4 Between-group diff: 6.6 *	6/10
Solak et al., (2008) [12]	Pre-post trial N = 60 Postmenopausal Women Water (N = 30): 55.8 ± 4.6 y Land (N = 30): 56.0 ± 4.1 y	OP [10] Mix	Water: 5 × 35 min/week Land: 5 × 40 min/week	Water: supervised and group based Land: individual and home-based	3 weeks 2 months		-		-	BDI [11] *3 weeks* *2 months*	water vs. land: rate of people whose BDI scores became normal more in water vs. land exercise group *	6/12
Milliken et al., (2006) [74]	Randomized trial N = 320 (266 completed) Postmenopausal women 40–65 y	Normal BMD- 	3×/week Aerobic, weight-bearing, and lifting	Supervised -	1 year	Femur neck Trochanter Spine	BDI negative predictor for BMD BDI not significantly related to BMD BDI not significantly related to BMD		-	BDI *baseline*	4.52 ± 4.5	3/10
Zhang (2017) [6]	Observational study/pre-post trial N = 162 71/91 Conv. group: 67.5 ± 5.1 y HBM [12] group: 68.2 ± 6.1 y	OP fracture Mild–moderate depression	CON: conventional rehabilitation including psychological care Rehabiliation with Health-Belief Model exercises: education + psychological care	- -	3 months -		-		-	SDS [13] *3 months*	HBM:63.2 ± 9.1 → 50.4 ± 8.4 * CON: 62.3 ± 7.2 → 54.7 ± 8.1 * Diff between HBM and CON *	4/10

Table 3. *Cont.*

Publication	Study Type # Participants Sex (M/F) Age	Osteoporosis Depression	Exercise Intervention	Supervised/Home Group/Individual	Duration Follow-Up	BMD			Bone Markers				Depression Scores *Time between Measurements*			Quality [65,66]
Matthews et al., (2020) [9]	RCT N = 180 Men 50–79 years	Normal–low BMD Mix	3×/week High-intensity progressive resistance training + weight-bearing impact exercise. Groups: 1 = Milk + exercise, 2 = Exercise, 3 = Milk, 4 = Control	Supervised Group based	12 months -	Femoral neck Upper FN Lower FN L_1–L_4 Total hip Trochanter Femoral neck Upper FN Lower FN L_1–L_4 Total hip Trochanter	Exercise + milk 1.4% * 1.6% * 1.3% * 2.0% * 1.1% * 1.1% * Milk −0.4% −0.2% −0.4% 2.1% * 1.2% * 1.6% *	Exercise 1.7% * 1.8% * 1.8% * 2.1% * 1.2% * 1.6% * Control −0.2% −0.5% 0.0% 0.6% 0.5% 0.8%								
Kukuljan et al., (2009) [72]													CES-D *6-months* *12-months* *6 months* *12 months*	Exercise + milk −0.8 −0.5 Milk 1.0 −0.02	Exercise −0.8 −1.4 Control −0.8 −0.1	6/10
Sen et al., (2020) [73]	RCT N = 58 Postmenopausal women 40–65 years	Low BMD–OP -	3 × 20–60 min/week: Whole-body vibration (WBV), high impact (HI), and control group	Supervised Group based	6 months -	Femoral Neck Total Hip L_1–L_4 Spine L_2–L_4 Spine	HI +1.9% g/cm^2 −0.6% g/cm^2 +0.3% g/cm^2 −0.7% g/cm^2	WBV +5.0% g/cm^2 * +1.9% g/cm^2 * +0.9% g/cm^2 +1.3% g/cm^2	OC CTX	HI +48.3% * +11.1%	WBV - 31.3% +4.6%	CON +18.5% +7.8%	BDI *6 months*	HI: 10.9 ± 4.9 → 10.3 ± 5.6 WBV: 15.5 ± 4.1 → 9.0 ± 3.3 * CON: 12.5 ± 6.0 → 15.9 ± 6.5 *		4/10

* Significant result ($p < 0.05$); # number of participants; [1] Bone mineral density; [2] Center for Epidemiological Studies Depression Scale; [3] Randomized controlled trial; [4] Osteocalcin; [5] Bone specific alkaline phosphatase; [6] β-CrossLaps/carboxy-terminal crosslinked telopeptide of type 1 collagen; [7] amino-terminal crosslinked telopeptide of type 1 collagen; [8] Receptor activator of nuclear factor κ-B; [9] Receptor activator of nuclear factor κ-B ligand; [10] Osteoporosis; [11] Beck Depression Inventory; [12] Health-Belief-Model [13] Self-rating Depression Scale.

All the included studies investigated the influence of exercise on depressive symptoms through questionnaires (Center for Epidemiological Studies Depression Scale (CES-D); Beck Depression Inventory (BDI); Self-rating Depression Scale (SDS)). In four out of the seven studies, depressive symptoms significantly ($p < 0.05$) improved after the intervention (Table 3) [5,6,12,75]. The quality of studies included for this sub-question ranged from 3/10 to 6/10 on the PEDro scale for the RCTs (n = 6) and 7/12 to 9/12 in the pre-post studies (n = 2) assessed by the Quality Assessment Tool for Before-After (pre-post) Studies With No Control Group from the National Heart, Lung, and Blood Institute [66].

4. Discussion

The overall aim of this scoping review was to provide a summary of the currently available knowledge regarding this topic and to identify the gap(s) of knowledge which should be addressed in future studies.

The goal of the first sub-question was to investigate which bone (turnover) markers are influenced by depression. The current gold standard of bone health assessment is to measure bone mineral density (BMD) through DEXA scans [58,76]. Therefore, many previous reviews assessed the influence of stress-related diseases, such as depression, solely on BMD [76]. Several methods exist to assess bone health, such as DEXA scans for measuring BMD, bone marker concentration evaluation, and imaging techniques (e.g., ultrasound), for which BMD measurement remains the gold standard [77]. Nonetheless, even though bone markers are not recommended as direct diagnostic markers for OP, these markers can predict the risk for osteoporosis and osteoporotic fracture [58,59]. These bone markers could possibly be used as signs of changed bone metabolism due to depression before BMD changes have occurred. Additionally, bone markers could be utilized as a regulation tool to monitor the response to treatment [59].

Eight included studies assessed the influence of depression on bone (turnover) markers, but not all studies included the above-mentioned markers. The detected bone markers were OC (n = 5), P1NP (n = 2), CTX (n = 6), BAP (n = 3), PYD (n = 2), DPD (n = 2), OPG (n = 2), and RANKL (n = 2). In general, concentrations (elevated/normal/decreased) of bone markers varied among studies due to the varying operationalization of depression, age groups, and gender. When comparing the influence of depression on bone markers versus BMD, one study showed altered bone marker concentrations in girls, whereas BMD levels remained unchanged compared to the healthy controls [24], confirming the notion that bone markers can be influenced by depression without an altered BMD.

Two main factors affecting the results are depression severity and stress load. Wippert et al. (2019) investigated the concentrations of OC, P1NP, and CTX during an acute depression episode in patients (N = 145; mean age 46.63 years) with varying levels of allostatic load and life burden. On the one hand, the researchers detected that an acute depressive episode led to an increased expression of bone markers in participants with higher depression scores and symptom severity [31,37]. On the other hand, Wippert et al. (2019) found that this anabolic bone adaption was limited in participants with high life burden and a decreased bone metabolism in participants with high allostatic load, possibly due to accumulated stress in tissues and cells over time and therefore causing the body's inability to adapt to the acute stress situation [37]. This inability to adapt eventually leads to a catabolic bone metabolism [37]. Hence, bone marker concentrations seem to depend on depression severity and allostatic (over)load. Therefore, when assessing bone health through bone markers, depression severity and allostatic load should be taken into account.

In addition to the influence of depression severity and stress load, serotonin reuptake inhibitors (SSRI) medication has also been shown to influence bone metabolism [23,24,70,71,78] and could be a possible confounder in assessing the influence of MDD on bone turnover markers. Even though in most of our included studies, the participants took anti-depressant medications or SSRIs, most did not provide specific information on the duration of medication use and type of medication. Therefore, the influence of anti-depressant medication on bone could not sufficiently be assessed based on the included studies of this review. A few

included studies did assess the effect of SSRIs on bone markers and BMD explicitly, and their results were conflicting [68,69]. Malik et al., (2013) found no (significant) influence of SSRIs on bone markers; in the study of Calarge et al., (2017), the influence of SSRIs on bone was sex-specific. Wadhwa et al., (2017) reviewed the influence of SSRIs on bone health [79]. Even though the review by Wadhwa et al., (2017) included multiple studies that detected reduced BMD levels in patients treated with SSRIs, the researchers only included one study assessing the effect of SSRI intake on bone turnover markers (P1NP and CTX). That study detected no effect of SSRI consumption on P1NP and serum CTX levels after eight weeks of treatment with anti-depressant medication [79]. The review concludes that more prospective studies need to be performed to assess the influence of SSRIs on bone health. Therefore, even though no conclusive effect of SSRIs on bone metabolism can be drawn, the clinical consumption of SSRIs for depression treatment should be taken into consideration when assessing the influence of depression on bone health.

OPG and RANKL were detected as bone regulation markers [69,70]. When OPG and RANKL are bound together, there is a termination of osteoclast activity, resulting in the inhibition of bone resorption [70]. A possible explanation for the conflicting results found regarding OPG and RANKL could be the varying characteristics of the populations in the bone marker concentrations were assessed in (young–middle-aged vs. postmenopausal women). Unfortunately, the study of Malik et al. (2013) only assessed OPG and RANKL in 18 out of their 50 participants.

In addition to the factors mentioned above, age and gender are also two factors that could be underlying causes of the conflicting results regarding the up or downregulation of bone markers among depressed patients. Regarding gender, three out of the eight included studies for this review only included female participants [67,70,71]. The other five studies included both females and males. Calarge et al., (2017) suggested that the skeletal sites that are affected by depression may be sex-specific. The notion that gender affects the influence of depression on bone health is supported by the study of Fazeli et al. (2013), which found a lower BMD in boys with MDD compared to healthy controls, but this phenomenon was not detected in girls. In the study of Skowrońska-Józwiak et al. (2020), there was a significant upregulation of CTX compared to healthy controls in females, a difference that was not significant when both males and females were included in the sample.

Concerning age, various age groups (young adults, middle-aged, pre- or postmenopausal) were included. During a lifetime, depression can have varying influences on bone health, depending on age.

Lastly, in addition to the consumption of anti-depressant medications, behavioral effects of MDD, such as Vitamin D intake and physical activity (PA), may also moderate the influence of depression on bone markers. Generally, the studies assessed the physical activity levels of participants at baseline to determine PA differences between depressed patients and controls. Even though a correlation between PA and bone markers in depressed patients was not assessed in the included studies, two studies did detect relevant results regarding PA and BMD and/or bone markers. The study of Malik et al., (2013) detected a positive correlation between OC and physical activity in depressed patients, which might be of interest for further investigations in future studies. Furthermore, Atteritano et al., (2013) concluded that the lower BMD scores in MDD patients compared with controls are not related to physical activity levels since these levels in both groups were similar. Therefore, the precise influence of physical activity levels on bone markers in depressed patients remains unknown but should be assessed in future studies with larger sample sizes.

To summarize, OC, BAP, and CTX were the most assessed bone markers among the included studies. Differing results of lowered, normal, or elevated bone marker concentrations between studies might depend on differences in the operationalization of depression, age, gender, allostatic load, depression severity, and (anti-depressant) medication consumption. Bone markers can indicate changed bone metabolism earlier than BMD can, which indicates the possibility of the use of bone markers to detect the risk of osteoporosis at an early stage. It has to be noted that the above-mentioned results have to be interpreted with

caution due to the lower quality of some included studies and methodological issues (e.g., small sample, no control group). Future studies with more longitudinal designs should take age, depression severity, allostatic load, PA, and the influence of anti-depressant medication into account to assess the influence of depression on bone marker concentrations.

The second aim of this scoping review was to assess the influence of exercise programs on bone health through bone markers and BMD in depressed patients. Eight studies were included that assessed the influence of exercise on bone health in combination with depressive symptoms. Firstly, as an important finding, it has to be stated that there are, to the authors' knowledge, no current clinical trials in which the influence of exercise on bone health is assessed in patients with a confirmed depression diagnosis. In all studies included for this sub-question, depressive symptoms were assessed, but none of the found studies listed the diagnosis of depression as an inclusion criterion, meaning that also participants who were classified as non-depressed could/would have been included. Nevertheless, it is of value to provide a comprehensive overview of the knowledge available regarding exercise and bone health in depressed patients to identify gaps of knowledge that future studies should address. Therefore, the results of the eight included studies will be split and discussed in the following order: studies that assessed the correlation of depressive symptoms and bone health in exercising participants (n = 1), studies that assessed depressive symptoms and bone health before and after an exercise intervention (n = 5), and lastly, studies that assessed depressive symptoms before and after an exercise and rehabilitation intervention in osteoporotic patients (n = 2).

Firstly, Milliken et al., (2006) is the only included study that investigated depression with a causal influence on bone mineral density instead of a consequence of pathologies (such as OP) [74]. In this study, BMD changes after a 1-year supervised exercise program and the correlation of depressive symptoms with BMD at baseline were investigated in a sample of 266 postmenopausal women. The authors noted that, even though previous studies had suggested otherwise [80], bone alterations were found in a population with lower depression scores (BDI: 4.5; range 0–27) as well. Furthermore, in a subsample (n = 140) of exercising women (sedentary prior to the intervention), Milliken et al. (2006) found that the influence of exercise on BMD was lower than the effect of depressive symptoms on the same parameter, indicating that depression can have a negative influence on bone, regardless of exercise behavior [74]. The authors concluded that the negative consequences of depression had influenced BMD, with exercise unable to counteract this phenomenon adequately. However, the authors note that the association between depression, BMD, and behavioral factors should be assessed more extensively in future trials.

Further, even though none of the studies verified depression diagnosis as an inclusion criterion, it is of interest to assess whether exercise can influence bone health in participants who have simultaneously improved depressive symptoms scores. This could indicate whether it is realistic to improve bone health through exercise in a population with a form of depression. Six of the included studies for SQ2 assessed depressive symptoms before and after an exercise intervention. It has to be noted that Matthews et al., (2020) and Kukuljan et al., (2009) are two articles based on the same intervention [9,72] and will therefore be discussed as one intervention/study in the upcoming paragraph. Overall, five out of the six included studies found significant improvements in depressive symptoms after the exercise intervention [5,6,12,73,75], and three out of these five studies also assessed bone health [5,73,75]. Two out of these three studies found an improvement in BMD [5,73] and one an increase in bone formation markers [75]. Remarkably, even though Dieli-Conwright et al., (2018) could not detect an influence on BMD, an improvement in OC and BAP levels was detected [75]. The results of Dieli-Conwright et al., (2018) support the assumption that the effects of exercise can be detected earlier in bone markers compared to BMD, and therefore bone markers should be included as additional markers of bone health instead of solely BMD to provide a complete picture of bone health.

On the other hand, Sen, Esmaeilzadeh, and Eskiyurt (2020) found that the concentrations of bone turnover markers OC and CTX were not improved at the 6-month follow-up

in the whole-body vibration group, even though they did detect an improvement in BMD scores. There was even a decrease in OC concentrations at six months. The finding is that improved BMD scores were detected, but no increased concentrations of bone formation markers are notable. One of the possible reasons provided by the authors is that a longer time period than six months might be necessary to detect the influence of exercise on bone markers. However, the accuracy of this explanation must be confirmed since this is contrary to the above-mentioned belief that changes in bone health are firstly detectable through a change in bone marker concentrations before BMD scores improve, and in this particular study, BMD scores were already improved. Further, the study explains that this finding could also be due to an uncoupled bone formation/resorption process and could be an indicator of a slowing down of the increased bone turnover process due to hormonal changes, e.g., during the post-menopausal phase [73].

In summary, five included studies found improvements in depressive symptoms, and three of these studies also assessed bone health and found positive influences on either BMD or/and bone markers. However, in all of these studies, there was no focus on depression which was perceived as a consequence of osteoporosis or other pathologies [5,73,75]. Nevertheless, these results indicate the possibility of improving bone health through the treatment of depression using exercise, but the causal relationship between the improvement of bone health and depression was not assessed in these studies.

Lastly, two studies assessed the effect of exercise on depressive symptoms in osteoporotic patients without assessing bone health [6,12]. Solak et al., (2008) performed a trial in a population with OP and compared water- and land-based exercises and found an improvement in depression scores in both exercise groups compared to before the intervention (three months), with a most favorable improvement in the water-based group. However, even though there were no significant differences in baseline depression scores according to the authors, in the provided graph, a difference in depression distribution scores (BDI) between the two groups is detectable with more participants with BDI scores within the 36.7% normal, 56.7% mild–moderate, and 6.6% moderate–severe in the water-based group, compared to 13.2% normal, 66.7% mild–moderate, and 20.0% moderate–severe in the land-based group [12]. Further, the water exercises were performed in a group, whereas the land exercise group performed the exercises at home, which could have influenced the depression scores after the intervention. Zhang (2017) investigated the influence of rehabilitation exercises (based on the Health-Belief Model) combined with physical activity on anxiety, depression, and osteoporosis knowledge in patients with osteoporotic fractures [6]. One group participated in standard rehabilitation care, whereas the other group received additional exercises based on the Health-Belief Model. After three months of rehabilitation, either with or without the Health-Belief Model, the patients had lower depression scores compared to before the intervention. These two studies show that depression scores can be improved by exercise in osteoporotic patients, which in turn could have a positive influence on bone health.

No serious adverse events were reported in any of the included studies. However, the possibility of a negative influence of physical exercise on bone health exists. Mainly, too much strenuous physical activity combined with inadequate recovery can lead to training overload [81]. This encompasses a low energy availability, which can, in turn, lead to a decreased bone mineral density [81]. Additionally, safety during an exercise intervention is a component that needs to be evaluated before conducting the intervention, especially in frail older adults. The safety of an exercise intervention needs to be monitored during the intervention [82].

The included studies have shown that exercise can positively affect depressive symptoms, BMD, and bone markers. However, none of the included studies defined depression as an inclusion criterion for their population. Furthermore, the quality of four out of the eight included studies was considered poor to fair. Therefore, the here presented results should be interpreted with caution, and no definitive conclusions regarding the influence of exercise on bone health in depressed patients could be drawn. Currently, no additional

information regarding the interaction between alterations of bone markers during an acute depressive episode and exercise is available.

Strengths and Limitations

This review summarizes and exposes the current evidence and gap(s) of knowledge regarding the influence of exercise on bone health related to depressive symptoms. For the purpose of a scoping review, the search string allowed for the inclusion of a wide range of articles in order to capture relevant literature.

However, the review has some limitations. Firstly, the evidence and conclusions provided in this review must be interpreted with caution since there was a very limited amount of evidence available regarding exercise and osteoporosis in depressed patients. Secondly, the included bone markers for sub-question 1 were not assessed in all studies. CTX (n = 6) and OC (n = 5) were the most assessed bone markers, but the other bone markers were only detected in some of the remaining studies. Therefore, the results regarding the influence of depression on bone markers should be interpreted with caution.

Furthermore, solely the databases PubMed and Web of Science have been searched systematically for relevant articles. Additional databases could have provided additional articles. Lastly, a precise exercise prescription, including dose, frequency, and duration, could not be provided based on the included studies since none of the studies included a population solely consisting of participants with a depression diagnosis. To be able to make this determination, additional RCTs investigating the influence of exercise, with different intensities, durations, and types of exercises, on bone markers, BMD, and depression in a population with diagnosed depression are needed.

5. Conclusions

The purpose of this scoping review was to summarize the current knowledge regarding the influence of exercise on bone health in patients with depressive symptoms and was divided into two parts. The bone markers OC, P1NP, and CTX have been assessed in multiple studies as markers of bone health influenced by depression. However, even though none of the exercise intervention studies included depression diagnosis as an inclusion criterion, the current study does show improvement of bone health in people with depressive symptoms, and therefore the potential of exercise as a treatment form to improve bone health in depressed patients. Lastly, the assumption that exercise could also harm bone health in patients with a high allostatic load could not be tested. Hence, there is a prominent lack of clinical trials assessing the influence of exercise on bone health in depressed people and people with varying allostatic loads.

Implications for Future Research

Based on the findings of this review, the authors recommend performing randomized controlled trials to investigate the influence of exercise on bone health (BMD and bone markers, e.g., OC, BAP, and CTX) in patients with MDD during an acute depressive episode. Regarding type and duration of exercise, a multi-component exercise type should be applied, performed two to four times a week, and with an intensity depending on the age and physical capabilities of the depressed population.

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Abbreviations

Osteoporosis	OP
Bone Mineral Density	BMD
Major Depressive Disorder	MDD
Sub-question	SQ
Beck's Depression Index	BDI
Osteocalcin	OC
Procollagen 1 intact N-terminal propeptide	P1NP
bone alkaline phosphatase	BAP
collagen crosslinks	CTX
Pyridinoline	PYD
Deoxypyridinoline	DPD
Osteoprotegorin	OPG
Receptor activator of nuclear factor kappa-B ligand	RANKL
Selective Serotonin Reuptake Inhibitor	SSRI
Physical activity	PA

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