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Review Article

The Effects of Pulmonary Rehabilitation on Bone Mineral Density in Patients with known Pulmonary Conditions: A Narrative Review

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Abstract

Pulmonary Rehabilitation (PR) is a standard treatment for patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) with exercise training being a key component of this intervention. COPD patients have a high prevalence of osteopenia and osteoporosis, primarily due to corticosteroid use, which significantly increases their risks of falls and fractures. Given the substantial impact of fractures on COPD patients, preventative measures are essential to mitigate bone mineral density loss and reduce fracture risk and associated adverse consequences.

Research on the effects of exercise on BMD in COPD patients is notably limited. This review aims to examine the effects of PR on BMD, fall and fracture risks, and functional exercise capacity in patients with COPD. A systematic search was conducted using MEDLINE Complete (via EBSCOhost), AgeLine (via EBSCOhost), Google Scholar and HyDi (Hybrid Discovery) for articles published between 2003 and 2021. The PICO (Population, Intervention, Comparator, Outcomes) framework was used to formulate the research question, define inclusion criteria and report the study characteristics: (P) subjects with stable COPD, (I) PR, (C) no PR during the duration of the study and (O) BMD, risks of falls and fractures, and functional exercise capacity.

Critical evaluation, data abstraction and synthesis were conducted by the authors. Evidence suggests that exercise training positively influences BMD outcomes. However, the evidence regarding the effects of PR on BMD in COPD patients, along with its impact on fall and fracture risks, and functional exercise capacity remains insufficient. This highlights the need for further research. Implementing PR may help COPD patients prevent additional BMD loss, reduce fall and fracture risks, and minimise related complications, ultimately improving their health-related quality of life and long term prognosis.

Keywords: Pulmonary Rehabilitation, Exercise, Physical Activity, Chronic Obstructive Pulmonary Disease, Osteoporosis, Bone Mineral Density

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Introduction

Reduced bone mineral density (BMD) is a significant comorbidity in patients with pulmonary conditions, particularly Chronic Obstructive Pulmonary Disease (COPD) (Ma et al., 2022; Taveira-DaSilva et al., 2005;

Zeng et al., 2019). Osteoporosis, as defined by the World Health Organisation (WHO), is present when BMD is "2.5 standard deviations or more below the young adult mean (a T-score of <-2.5 SD)" (WHO, 1994), leading to compromised bone strength and an increased risk of fractures, particularly in the vertebrae and femur (Bouvard et al., 2021; Meyer et al., 2019). Among pulmonary conditions, COPD is most closely associated with osteoporosis, with affected patients experiencing reduced BMD two to five times more frequently that age-matched healthy individuals (Chen, et al., 2019; Ma et al., 2022).

COPD is a multisystem disease characterised by progressive and partially reversible chronic airflow limitation, accompanied by an increased inflammatory response to noxious particles or gases. It is a significant global burden, with rising global prevalence and mortality rates. In 2019, COPD accounted for approximately 455 million cases and 3.9 million deaths worldwide (Vos et al., 2020), making it the third leading cause of death globally, with projections indicating it may become the leading cause within the next decade (The Global Initiative for Chronic Obstructive Pulmonary Disease [GOLD] guidelines 2021 cited in Gupta et al., 2021). While COPD is largely preventable and manageable, its pulmonary and extra-pulmonary manifestations, such as osteoporosis, significantly impact disease severity and quality of life (The GOLD guidelines 2021 cited in Gupta et al., 2021).

Osteoporosis in COPD patients is associated with multiple risk factors, including systemic inflammation, corticosteroid use, smoking, low body mass index, hypogonadism, Vitamin D deficiency, pulmonary dysfunction, and physical inactivity (Lehouck, Boonen et al. 2011, Romme, Geusens et al. 2015, Sarkar, Bhardwaj et al. 2015). Additionally, COPD patients face an elevated risk of falls due to lower limb weakness, impaired postural control, and functional limitations (Lawlor et al., 2003; Roig et al., 2009). Osteopenia, a precursor to osteoporosis, (T Score between – 1 to – 2.5 standard deviations) is a key indicator of fracture risk in these individuals (WHO, 1994).

Fractures in turn can exacerbate COPD symptoms, decrease lung function, and initiate a cycle of impairment that further reduces physical function and daily activity levels. This cycle includes fear of falling, depression, and reduced social interaction, leading to further muscle and bone loss and diminished overall physical capacity (Clynes et al., 2020; Friedman & Mendelson, 2014; Ji & Yu, 2015; Kerr et al., 2017; Liao et al., 2016; Sarkar et al., 2015).

Management of osteoporosis and osteopenia in COPD involves pharmacotherapy, smoking cessations, disease monitoring, and Pulmonary Rehabilitation (PR) (Bollmeier & Hartmann, 2020). Pulmonary Rehabilitation (PR), a standard non-pharmacological intervention for COPD (Vestbo et al., 2013), includes exercise training ~ a cost effective, non-invasive strategy that enhances mechanical bone loading, preserves BMD, and improves muscle strength, balance, and coordination (Brooke-Wavell et al., 2022; Cheung & Giangregorio, 2021; Compston et al., 2017; Marini et al., 2020; Mohammad Rahimi et al., 2021; Spruit et al., 2013). These benefits collectively reduce fall risk and fracture likelihood. However, research on the direct effects of PR on BMD, fracture prevention, and fall risk in COPD patients remains limited (Jarvinen et al., 2008).

Due to this gap in research, this narrative review primarily examines the effects of PR on BMD in COPD patients but also considered findings from studies on other pulmonary conditions such as cystic fibrosis (CF) and lymphangioleiomyomatosis (LAM). While these conditions differ in pathophysiology and typically affect younger demographics, their association with reduced BMD and the role of PR in mitigating bone loss provide valuable insights into potential benefits from COPD patients.

Review of the Literature

Aims

The aim of this review is to determine whether PR affects BMD, the risks of falls and fractures and functional exercise capacity in patients diagnosed with COPD. The research question posed is: *Does PR have an effect on BMD, on risks of falls and fractures and on functional exercise capacity in patients with stable COPD?*

Search Methods

A narrative review design was selected to facilitate and a comprehensive and critical analysis of the research evidence. This review employed the population (P), intervention (I), comparator (C) and outcomes (O) (PICO) framework to formulate the research question, define inclusion criteria and report study characteristics. Table 1 outlines the key PICO search terms.

Table 1: PICO search terms			
Population	**Intervention**	**Comparison**	**Outcome**
Subjects with stable COPD	PR intervention	PR intervention compared to no PR intervention during the duration of the study	BMD Risks of falls and fractures Functional exercise capacity

Relevant studies were identified through searches in the following databases: MEDLINE Complete (via EBSCOhost), AgeLine (via EBSCOhost), Google Scholar and HyDi (Hybrid Discovery). The keywords used included Pulmonary Rehabilitation, Exercise, Physical Activity, Chronic Obstructive Pulmonary Disease, Osteoporosis, Bone Mineral Density and Bone Mineral Status.

Search Strategy

The search strategy yielded a total of 597 research articles through the selected databases using the specified keywords, restricting results to peer-reviewed, English Language articles involving human participants. Subsequently, a secondary search was conducted from references cited in reviewed articles, yielding an additional 3 research articles. The search process is illustrated in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) flow diagram (Page et al., 2021) (Figure 1), which outlines the identification, screening, inclusion, and exclusion of studies based on the inclusion and exclusion criteria detailed in Table 2.

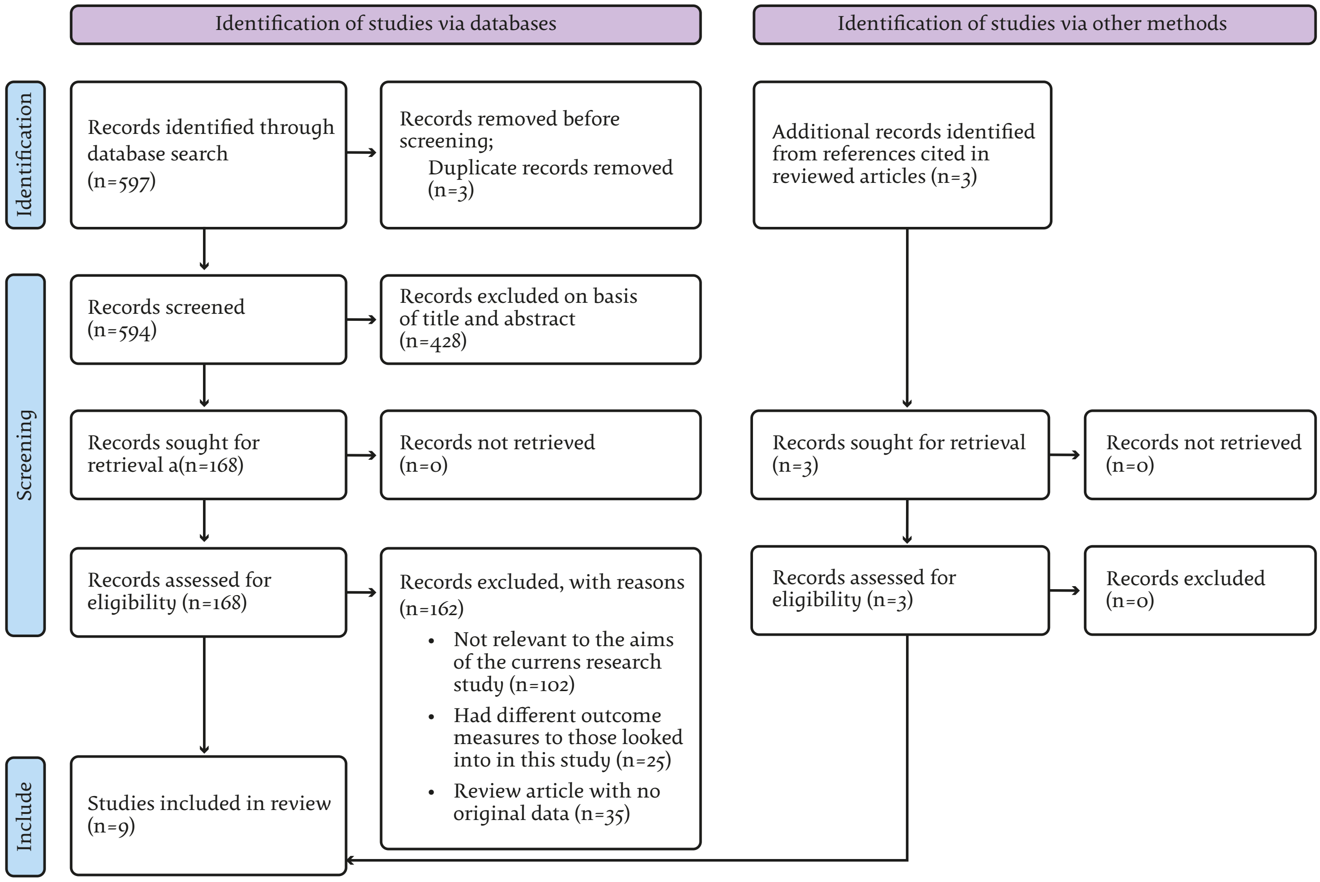

Figure 1: The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" Flow Diagram (Adapted from Page et al., 2021)

Ultimately, 9 articles were selected for review. Because of the limited number of eligible articles, the review expanded its scope to include studies published between 2003 and 2021 and included studies on pulmonary conditions other than COPD.

Table 2: Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Publication date	A study published less than 12 years ago	Study published more than 12 years ago
Patient selection	Subjects have a confirmed COPD or any other lung condition	Study which included subjects with unconfirmed COPD or any other lung condition
Aims	The study aims to investigate whether exercise training/PR has an effect on one or more of the following: BMD, risks of falls and fractures and functional exercise capacity in patients diagnosed with COPD or any other lung condition	The study's aims not related to the current narrative review's aims
Outcome measures	The study assessed one or more of the following outcome measures: BMD, risks of falls and fractures and functional exercise capacity	The study does not assess one or more of the primary outcome measures
Originality of data	Article contains original data	Article lacking original data

Study Selection and Quality Appraisal

Nine articles were included in this narrative review, and their characteristics are summarized in Table 3. These studies examined the effects of exercise training/PR on BMD, the risk of falls and fractures and functional exercise capacity in patients with COPD or other lung conditions.

Table 3: A summary of the studies reviewed through this narrative review				
Author and Year of Publication	**Title**	**Study Design and Outcome Measures**	**Key Findings**	**Strengths and Limitations**
Frangolias et al. (2003)	Role of Exercise and Nutrition Status on Bone Mineral Density in Cystic Fibrosis	A cross-sectional and prospective study was designed in which 67 subjects diagnosed with Cystic Fibrosis (CF) were recruited. Outcome measures: Lung function test, Exercise capacity (VO2max) assessed during a progressive incremental exercise test to maximal effort, BMD of lumbar spine, proximal femur and whole body using the DEXA scanner, documentation of corticosteroid use, anthropometric measures, CF severity assessed using the Shwachman-Kulczycki (S-K) score (Shwachman & Kulczycki, 1958), information gathered on subjects` patterns of physical activity, pulmonary status and nutritional status, thoracic vertebral compressions' evidence obtained through chest and lateral spine radiography, fracture history collected by the Canadian Multicenter Osteoporosis Study Questionnaire (CaMOS) (Adachi et al., 2001).	A moderate correlation was reported between exercise capacity and BMD (r = 0.42, P = 0.001). Those subjects who had a normal BMD were noted to have a higher exercise capacity than those with osteopenia, and those with osteopenia were noted to have a higher exercise capacity than those with osteoporosis (32.4 (3.0) vs 30.5(1.2) 22.6(3.3) respectively, P = 0.03). There were no correlations between rate of fractures and BMD or exercise capacity.	Strengths: Exercise capacity measurement was objective rather than from patient recall. Limitations: Small sample size, a one-time point assessment without follow-ups which could bring anxiety effects, and lack of an intervention with a control group indicating an association not a cause-and-effect relationship between exercise and BMD.

Table 3: A summary of the studies reviewed through this narrative review

Author and Year of Publication	Title	Study Design and Outcome Measures	Key Findings	Strengths and Limitations
Dodd et al. (2008)	Bone Mineral Density in Cystic Fibrosis: Benefit of Exercise Capacity	A cross-sectional and prospective type of study was conducted. A total of 25 subjects with CF were randomly chosen. Outcome measures: Objective exercise parameters of gas exchange, exercise performance and respiratory mechanics measured by maximal exercise cycle ergometry, BMD of lumbar spine and total proximal femur assessed with DEXA scans, lung function using a spirometer, anthropometric and biochemical measurements.	The results showed a significant correlation between objective exercise parameters and BMD. The strongest correlation was seen between % Peak-predicted Oxygen uptake and BMD (correlation with total proximal femur Z-score, $r = 0.59$, $P < 0.01$; correlation with lumbar spine Z-score, $r = 0.44$, $P < 0.01$). There was a greater correlation between objective exercise measures and BMD of the total proximal femur than with BMD of the lumbar spine.	Strengths: Random allocation of participants and exercise parameters were measured objectively in real time. Limitations: Small number of subjects, a single-day assessment, absence of an intervention, no consideration of factors contributing to low BMD including corticosteroid use and bone turnover, and exercise diaries were not recorded for subjects thus each subject' fitness level may have differed.

Table 3: A summary of the studies reviewed through this narrative review				
Author and Year of Publication	**Title**	**Study Design and Outcome Measures**	**Key Findings**	**Strengths and Limitations**
Garcia et al. (2011)	Bone Health, Daily Physical Activity, and Exercise Tolerance in Patients with Cystic Fibrosis	A cross-sectional and an observational analytic study was conducted in 50 subjects with CF. Outcome measures: Demographic data collection excluding subjects on corticosteroids, BMD measures of lumbar spine, femoral neck and whole body using DEXA scans, record of daily average physical activity (PA) in minutes over 5 days with a portable monitor quantified as low, moderate and vigorous, exercise capacity assessed by a six-minute walk test (6MWT) (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002) and cycle ergometry (Ross, 2003) vertebral fractures and deformities radiologic evaluation by the Genant and Cobb methods (Genant et al., 2000)	Daily PA performed at low and moderate intensities showed a positive correlation with BMD of the lumbar spine ($r = 0.36$, $P < 0.01$ and $r = 0.59$, $P < 0.001$), femoral neck ($r = 0.51$, $P < 0.001$ and $r = 0.72$ $P < 0.001$), and total hip ($r = 0.54$, $P < 0.001$ and $r = 0.74$, $P < 0.001$). The correlation between daily PA and BMD in the hip was stronger than in the lumbar spine. Daily PA performed at low, moderate and vigorous intensities demonstrated a positive correlation with exercise capacity assessed using the 6MWT ($r = 0.36$, $P < 0.05$) and during the cycle ergometry ($r = 0.4$, $r=0.38$, and $r=0.42$, respectively; $P < 0.05$). BMD did not correlate with vertebral fractures and kyphosis ($P = 0.35$ and $P = 0.4$, respectively).	Strengths: PA was assessed without the use of questionnaires outside the controlled environment of an exercise laboratory, potential confounding factors increasing the risk for low BMD including the use of corticosteroids were excluded from the study. Limitations: A small number of participants, the cross-sectional design of the study being a short-term study precludes objective observation of fracture incidence in subjects with low BMD, absence of an exercise intervention.

Table 3: A summary of the studies reviewed through this narrative review

Author and Year of Publication	Title	Study Design and Outcome Measures	Key Findings	Strengths and Limitations
Gaowgzeh (2015)	Bone Mineral Status Response to Aerobic Exercises in Asthmatic Patients	A randomised controlled trial. 50 recruited asthmatic patients on long-term high-dosage inhaled corticosteroids were randomly divided into 2 equal groups; one being the active group and the other the control group. The former group received 6 months of progressive aerobic exercise training at a moderate intensity whilst the latter did not receive any structured exercise programme during the duration of the study. Outcome measures: Anthropometric measures at baseline, BMD of lumbar spine and radius assessed with DEXA scanner at baseline and after 6 months for both groups.	At the 6th month, only the exercise group showed significant improvements in lumbar spine BMD (from 120.96 ±9.17 at baseline to 150.32 ±8.37 at month 6, $P < 0.05$) and radius (from 266.62 ±12.37 at baseline to 311.26 ±11.35 at month 6, $P < 0.05$). The control group saw a significant decrease in lumbar spine BMD (from 122.16 ±7.98 at baseline to 120.47 ±7.87 at month 6, $P > 0.05$) and radius (from 268.12 ±10.21 at baseline to 265.96 ±9.73 at month 6, $P > 0.05$). At the 6th month, BMD values at the lumbar spine and radius locations differed significantly between the two groups.	Strengths: Both groups were homogenous regarding their demographic variables at baseline. Randomised allocation of the recruited subjects eliminating potential allocation bias, and the presence of a supervised intervention with a control group ensuring that only the independent variable of exercise caused a change in the dependent variable of BMD. Limitations: A small number of participants.

Table 3: A summary of the studies reviewed through this narrative review				
Author and Year of Publication	**Title**	**Study Design and Outcome Measures**	**Key Findings**	**Strengths and Limitations**
Liu et al. (2015)	Low Bone Mineral Density in COPD Patients with Osteoporosis is Related to Low Daily Physical Activity and High COPD Assessment Test Scores	Cross-sectional study. 30 subjects diagnosed with COPD recruited. Outcome measures: Collection of basic demographic data, lifestyle and disease-related data by a personal interview, BMD of femoral neck, total hip and lumbar spine measured using DEXA scanner, 24hour daily physical activity (PA) measured using an actigraph and oxygen saturation using a pulse oximeter, CAT (Jones et al., 2009) administration, pulmonary function parameters using spirometry, serum samples for laboratory measurements.	No statistically significant differences were observed between pulmonary function parameters of those with and without osteoporosis ($P > 0.05$). Subjects without osteoporosis had statistically significantly greater daily PA ($P = 0.0193$) counts per minute and lower CAT scores (5.0 ±3.8 vs 8.1 ±5.8, $P < 0.05$) than those with osteoporosis. BMD values of lumbar spine, total hip and femoral neck were significantly positively correlated with DPA (r=0.399, r=0.602, r=0.438, respectively, all $P < 0.05$). BMD of total hip and femoral neck were significantly negatively correlated with CAT scores (r=-0.412, $P < 0.05$; r=-0.552, $P < 0.01$, respectively).	Strengths: Revealed a relationship between DPA and BMD in a short period of time. Eliminated the confounding influence of variables including the use of systemic corticosteroids. Limitations: Small sample size, short duration of study not able to investigate long-term effects, no exercise intervention and use of control group to establish a cause – and-effect relationship between exercise and BMD. No consideration of potential underlying comorbidities of COPD including symptoms of GERD, anxiety and depression which may correlate with DPA, BMD and CAT scores.

Table 3: A summary of the studies reviewed through this narrative review

Author and Year of Publication	Title	Study Design and Outcome Measures	Key Findings	Strengths and Limitations
Abd El-Kader et al. (2016)	Aerobic Exercise Training Modulates Bone Mineral Status in Patients with Chronic Obstructive Pulmonary Disease	A randomised controlled trial was designed. 60 patients diagnosed with COPD on high dosage of inhaled corticosteroids were recruited and randomly allocated into 2 equal groups. The active group participated in a 6 – month moderate aerobic exercise programme whilst the control group did not participate in any structured exercise programme for 6 months. Outcome measures (measured for both groups): demographic data, anthropometric measures, clinical history and lung function using spirometry at baseline, BMD measurements of lumbar spine and radius taken with DEXA scanner at baseline and month 6, serum calcium and parathyroid hormone measurements through collection of peripheral blood at baseline and month 6.	Lumbar spine and radius BMD increased significantly in the active group (from 122.16 ±10.54 at baseline to 147.63 ±12.81 at month 6, $P < 0.05$; from 257.13 ±15.72 at baseline to 323.42 ±17.95 at month 6, $P < 0.05$, respectively) whilst decreased non-significantly in the control group after 6 months (from 124.36 ±11.27 at baseline to 122.98 ±11.23 at month 6, $P > 0.05$; from 261.58 ±14.65 at baseline to 257.12 ±14.51 at month 6, $P > 0.05$, respectively). Additionally, at the 6 month, a significant difference was noted between both groups ($P < 0.05$).	Strengths: A randomised block procedure was used to assign subjects into the 2 groups. Baseline characteristics of both groups were similar. Includes supervised intervention with a control group. Both groups were considered homogenous at baseline with regards to their demographic and baseline data. Excluded potential confounding factors including those taking any medication likely to influence BMD. Limitations: Small number of participants.

Table 3: A summary of the studies reviewed through this narrative review

Author and Year of Publication	Title	Study Design and Outcome Measures	Key Findings	Strengths and Limitations
Tejero et al. (2016)	The Role of Daily Physical Activity and Nutritional Status on Bone Turnover in Cystic Fibrosis: a Cross-Sectional Study	Cross-sectional study. 50 people with stable CF were enrolled in this study throughout which 96% of participants received systemic corticosteroids. Outcome measures: Femoral neck, lumbar spine and total body BMD assessed with DEXA scanner, exercise capacity assessed with maximal cardiopulmonary exercise test using a cycle ergometer, 24hr daily PA monitoring for 5 days using a portable device in minutes quantified as MET levels, anthropometric measures, lung function measures, lean muscle mass and fat mass measured with DEXA scanner, biochemical and bone turnover biomarkers assays.	A positive correlation was found between time spent on all levels of daily PA and BMD of at least two different sites. The strongest correlation was seen between daily 'moderate' PA and BMD at the total hip location ($r = 0.74$, $P < 0.001$). The correlation between the amount of time allocated to daily PA at a 'moderate' level and BMD was shown to be stronger than the correlation between the duration of daily PA at a 'vigorous' intensity and BMD in all regions. The time spent on all different intensities of daily PA was found to have a better correlation with hip BMD than the lumbar spine.	Strengths: Physical activity was objectively measured in real time outside of the exercise laboratory. Limitations: Small number of participants, corticosteroid treatment might have acted as a potential confounding factor, duration of study was short with no exercise intervention unable to demonstrate a cause-and-effect relationship between exercise and BMD.

Table 3: A summary of the studies reviewed through this narrative review				
Author and Year of Publication	**Title**	**Study Design and Outcome Measures**	**Key Findings**	**Strengths and Limitations**
Gupta et al. (2019)	Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: a Randomized Controlled Trial	A randomised controlled trial in which 52 CF subjects were randomly allocated to exercise and control groups. The exercise group performed a prescribed home exercise programme (HEP) and the control group continued with their usual daily PA level for a period of 1 year. The HEP for the active group included resistance training and a plyometric regime. A 3-monthly (+/ – 2 weeks) follow-up was carried out for both groups for a period of 1 year. Outcome measures (for both groups): Following assessed at baseline and at 1 year: BMD of whole body and lumbar spine using DEXA scanner, anthropometric measures, exercise capacity through maximal exercise testing on a treadmill (Thompson et al., 2010) lung function using spirometry, bone related biochemical parameters, dietary intake assessed with validated 24-hr food recall and semi-quantitative foo frequency questionnaire for sources rich in calcium, quality of life assessed using validated Cystic fibrosis questionnaire-revised (CFQ-R) (Hay, 1995) and habitual activity estimation scale (HAES) used to assess daily physical activity (Kir et al., 2015). Following assessed in every 3 monthly follow-up: Spirometric measurements and compliance assessment for both groups, exercise intensity assessment for the active group. Telephonic guidance and assessment of exercise compliance were carried out every 2 weeks for the intervention group.	All subjects in the active group performed the HEP with an overall compliance of 63%. The change in lumbar spine BMD over 1 year was 0.001g/cm2 (95% Cl – 0.02 to 0.02) higher in active group as compared to control group, although this change was statistically insignificant. The change in whole-body BMD over 1 year of study was 0.006 g/cm2 (95% Cl – 0.04 to 0.03) lower in the active group compared to controls, although this change was also statistically insignificant. No significant difference was noted between the groups' changes in lung function parameters after 1 year. A higher significant positive change in the exercise capacity was noted for the exercise group over the 12-month period.	Strengths: Randomised allocation of participants into groups decreasing potential allocation bias, study being an interventional trial including a control group with similar baseline characteristics for both groups, BMD was performed and analysed by the same blinded technician minimising potential inter-observer variation. Both groups treated identically except for the intervention being tested preventing any potential performance bias, no drop-outs from both groups eliminating attrition bias. Limitations: Small sample size, the intervention was not supervised potentially influencing compliance rates with the exercise programme, follow-ups were not frequent and inclusion of subjects with severe lung disease may have impacted their performance of high impact exercises, possible confounding factors such as corticosteroids use, lack of adherence of vitamin D and calcium supplementation which for both groups might have influenced the relationship between exercise and BMD.

Table 3: A summary of the studies reviewed through this narrative review				
Author and Year of Publication	**Title**	**Study Design and Outcome Measures**	**Key Findings**	**Strengths and Limitations**
Lowder (2021)	Improved Exercise Tolerance and Lung Function in Women with LAM Following Three Months of Exercise Training	A One-Group Pretest-Posttest quasi-experimental type of design was adopted. 8 subjects with lymphangioleiomyomatosis (LAM) were enrolled in the study and participated in a 12-week supervised exercise intervention consisting of treadmill training, aerobic exercise circuits and strength training. Outcome measures: Following assessed at baseline and at week 12: Whole body BMD assessments with DEXA scanner, exercise tolerance with treadmill ergometry, pulmonary function parameters using spirometry.	After 12 weeks of exercise training, subjects experienced a group mean percent improvements in the whole body BMD (from 1.16 g/cm^2 at baseline to 1.178 ±0.12 g/cm^2 at month 3, $P = 0.28$), in exercise tolerance (VO_2 peak improved by 13.3%, $P = 0.06$), and in pulmonary function measures; FEV_1 ($P = 0.19$), FVC ($P = 0.085$), FEV_1/FVC% ($P = 0.38$), FEV_1 predicted ($P = 0.11$) and peak flow ($P = 0.19$). However, all group mean results were found to be statistically insignificant ($P = 0.05$).	Strengths: Supervised exercise intervention. Limitations: Small number of subjects, duration of intervention was short, being a quasi-experimental study where randomisation is not used and there is lack of control group for comparison increasing vulnerability to internal validity threats.

Critical Appraisal of Articles

A critical appraisal was conducted to assess the reliability of the included studies by evaluating their methodological quality and potential biases. Each study was examined for risk of bias to ensure transparency in evidence synthesis.

The Cochrane Risk of Bias (RoB2) tool (Flemyng et al., 2023) was used to evaluate three randomised controlled trials (RCT) (Abd El-Kader et al., 2016; Gaowgzeh, 2015; Gupta et al., 2019) **(Table 4).** Risk of bias was assessed across five domains: selection, performance, attrition, detection and reporting.

Table 4: Cochrane Risk of Bias (RoB2) Tool (Flemyng, Moore et al., 2023**)**

Author and Year of Publication	Random sequence generation	Allocation concealment	Blinding participants and personnel	Adherence to intervention	Missing outcome data	Blinding of outcome assessment	Selective reporting	Overall risk of bias
Gaowgzeh (2015)	+ *	? †	− ‡	?	+	?	+	−
Abd El-Kader et al. (2016)	+	?	−	?	+	?	+	−
Gupta et al. (2019)	+	?	−	−	+	?	+	−

Key

*Low risk of bias †Unclear risk of bias ‡High risk of bias

All the three studies, had a random allocation sequence and both groups were considered homogenous at baseline strengthening internal validity but the concealment of allocation was not detailed; therefore, this aspect of selection bias was evaluated as having an unclear risk of bias. Performance bias was judged as high risk in all 3 RCT studies because participants and personnel were not blinded to the intervention. A RCT by Gupta et al., (Gupta et al., 2019) indicated a 63% overall adherence to the unsupervised exercise programme, leading to the assessment of a high risk of performance bias due to its potential impact on the study's results. Adherence to the exercise programme was not reported in two RCT studies by Abd El-Kader et al., (2016) and Gaowgzeh (2015), leading to an assessment of unclear risk of bias. The risk for attrition bias was determined to be low since there were no missing outcome data in any of the RCTs. Insufficient information was provided in all 3 RCTs with regards to whether outcome assessors were aware of the intervention received. No selective outcome reporting bias was detected, there is clear evidence that all eligible reported results for the outcome measurements align with the intended outcome measurements and analysis. A high overall risk of bias was judged for all 3 RCTs (Abd El-Kader et al., 2016; Gaowgzeh, 2015; Gupta et al., 2019).

Possible biases in the single quasi-experimental study (Lowder 2021) included were recognised via a critical evaluation of this study outlined below utilising the JBI critical appraisal tool (Barker et al., 2024). In this study it was evident that the 'cause' was manipulated prior to the occurrence of the 'effect' which minimised the potential for bias. The lack of a control group jeopardised the validity of the causal inferences. Outcome measurements were gathered prior to and following the implementation of the intervention to investigate the temporal changes in effect within the group. There was no loss to follow-up suggesting no attrition bias. The reliability of the outcome measures and the statistical analysis method were not sufficiently described, resulting in an unclear risk of bias that impacts the reliability and validity of results.

These cross-sectional studies (Dodd et al., 2008; Frangolias et al., 2003; Garcia et al., 2011; Liu et al., 2015; Tejero et al., 2016) were evaluated using the AXIS tool (Table 5). These studies examined relationships between physical activity, exercise capacity and BMD.

Table 5: The AXIS tool (Downes et al., 2016):

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Frangolias et al. (2003)	Y	Y	?	Y	Y	?	?	?	Y	Y	?	?	?	?	?	Y	Y	Y	?	Y
Dodd et al. (2008)	Y	Y	?	Y	Y	?	?	?	Y	Y	?	?	?	?	?	Y	?	Y	?	Y
Garcia et al. (2011)	Y	Y	?	Y	Y	?	?	?	Y	Y	?	?	?	?	?	Y	Y	Y	?	Y
Liu et al. (2015)	Y	Y	?	Y	Y	?	?	?	Y	Y	?	?	?	?	?	Y	Y	Y	?	Y
Tejero et al. (2016)	Y	Y	?	Y	Y	?	?	?	Y	Y	?	?	?	?	?	Y	?	Y	?	Y

Key to the AXIS tool (Downes et al., 2016):

No.	Question	Yes (Y)	No (N)	Don't know/ Comment (?)
1	Were the aims/objectives of the study clear?			
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorize non-responders?			

Key to the AXIS tool (Downes et al., 2016):	
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?
9	Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialed, piloted or published previously?
10	Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p values, Cis)
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?
12	Were the basic data adequately described?
13	Does the response rate raise concerns about non-response bias?
14	If appropriate, was information about non-responders described?
15	Were the results internally consistent?
16	Were the results for the analyses described in the methods, presented?
17	Were the authors' discussions and conclusions justified by the results?
18	Were the limitations of the study discussed?
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
20	Was ethical approval or consent of participants attained?

A cross-sectional design was found to be appropriate to fulfill the studies' aims/objectives however this design cannot establish causality due to their short duration and lack of intervention or control group. While the researchers explained the process of sample size calculation, the limited number of participants in each study could have resulted in findings that were underpowered and potentially inaccurate leading to potential bias. Randomisation methods were not outlined, possibly resulting in a non-representative sample being selected, consequently influencing the studies' results and leading to an unclear risk of selection bias.

All outcome variables were assessed in alignment with the study's aims and objectives using standardised procedures, like those utilised for the cardiopulmonary exercise test (Ross, 2003), as well as outcome measures that are previously published and validated, such as the Six-Minute Walk Test (6MWT) (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002) and COPD Assessment Test (CAT) (Jones et al., 2009). However, it was not clear whether the outcome measures were evaluated by the same or different observers across all subjects, which introduces an unclear risk of inter-observer reliability bias. The researchers provided a clear description of the statistical analysis that enabled repeatability in three studies.

Nevertheless, Dodd et al (Dodd et al., 2008) and Tejero et al (Tejero et al., 2016), overlooked the confounding factors associated with low BMD in both the analysis and the interpretation of results, even though this was outlined in the limitations of their studies.

Discussion

This review highlights the positive effects of exercise training on bone mineral density (BMD) in patients with COPD and other pulmonary conditions. Improvements in BMD are attributed to mechanical loading during exercise which stimulates the Wnt3a/β-catenin signaling pathway, enhancing osteoblast differentiation and bone formation. Additionally, exercise-induced acidosis leads to an increase in serum calcium levels which reduces secretion of parathyroid hormone by the parathyroid gland, and contributing to BMD improvement (Chen et al., 2021; Grimston et al., 1993).

Reduced physical activity in COPD patients is associated with a sedentary lifestyle, disease severity and exertional dyspnoea, perpetuating a cycle of inactivity, muscle weakness and BMD loss (De Kam et al., 2009; Katajisto et al., 2012; Robinson et al., 2018; Vrieze et al., 2007). Exercise training improves oxygen transport, muscle strength, and cardiorespiratory fitness, positively impacting exercise capacity and pulmonary function (Farrell & Turgeon, 2023; Liu et al., 2015).

However, this review found insufficient evidence on the effects of exercise on fall and fracture risks due to the limited duration of observational studies. Improved BMD and functional capacity can reduce these risks, but further research is needed to explore this relationship.

Conclusions and Areas of Future Research

Exercise training shows potential for improving BMD in patients with COPD, though evidence remains limited and subject to bias. Future research should focus on long term randomised controlled trials assessing the effects of PR on BMD, fall and fracture risks and functional exercise capacity. Such studies will help develop targeted interventions to prevent adverse outcomes and enhance the quality of life for COPD patients.

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