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THE ANALYSIS STUDY OF OSTEOPOROSIS AND FRACTURE RISK : A TEN YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *Microarchitecture degeneration and reduced bone mass, which increase fragility and fracture susceptibility, are hallmarks of osteoporosis, a systemic skeletal disorder. Disease has a substantial effect on fracture healing as well as bone mass and microstructure. More accurate fracture risk assessment and a wider range of treatment choices are the results of research advances. Effective treatment regimens for osteoporosis have been aided by the fracture risk assessment tool (FRAX), which has had a substantial impact on clinical decision-making and intervention levels.*

Methods: *Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. A number of websites, including ScienceDirect, PubMed, and SagePub, were utilized to gather the literature.*

Result: *The study looked at more than 4,000 publications using reputable sources including Science Direct, SagePub, and PubMed. After it was decided that eight publications needed greater investigation, a more extensive review of the entire literature was carried out.*

Conclusion: *Studies have shown that osteoporosis can lead to fractures, with the Fracture Risk Assessment Tool (FRAX) and Bone Mineral Density (BMD) testing being used to assess fracture risk in women. Studies have shown that bone anabolic treatments can reduce fracture risk, but the certainty of these results is low due to the small number of studies.*

Keyword: *Osteoporosis, fracture, risk, FRAX, BMD*

INTRODUCTION

Osteoporosis is a systemic skeletal illness characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased fragility and susceptibility to fractures. The disease is defined by two key characteristics, as established by international consensus in 1993: its negative impact on bone mass and microstructure, as well as the clinical outcome of fractures. In the following year, osteoporosis was further defined as a BMD T score of -2.5 or below, with low bone mass (osteopenia) falling between a BMD T score of -1 and -2.5. The World Health Organization (WHO) developed diagnostic criteria based on standard deviation scores of bone mineral density (BMD) relative to peak bone mass in healthy young women.[1] These criteria recognized the role of low BMD in the development of fragility fractures and provided a method for assessing the incidence of osteoporosis in epidemiological research. However, it's important to note that while BMD is a significant risk factor for fractures, most fragility fractures occur in individuals with BMD levels above this cutoff, limiting its usefulness as a clinical predictor of osteoporosis.[2,3]

Advancements in research have led to a more precise assessment of fracture risk and an expanded range of treatment options for preventing fractures. Clinical practice now commonly utilizes algorithms that combine clinical risk factors and bone mineral density to target treatment for high-risk individuals.[1] While medications for osteoporosis continue to increase bone mineral density, the primary goal remains the prevention of fractures.[4] Variation has been observed in the extent to which different treatments reduce the risk of hip, non-vertebral, vertebral, and clinical fractures. Many active comparator trials have not directly compared the impact on fracture outcomes.[5,6] A deeper understanding of the differences in treatment effects across clinical trials will have an impact on treatment benefit estimates and should be considered when formulating guideline recommendations.[7]

Accurate estimation of fracture risk is crucial for effectively treating osteoporosis. In 2008, the World Health Organization Collaborating Centre in Sheffield, UK, introduced the fracture risk assessment tool (FRAX). This tool assesses the 10-year probability of hip and major osteoporotic fracture (including the hip, clinical spine, distal forearm, and proximal humerus) on an individual basis.[8,9] The algorithm incorporates optional bone mineral density (BMD) measurement, age, sex, body mass index, and seven dichotomous clinical risk factors (previous fragility fracture, parental hip fracture, smoking, excessive alcohol consumption, glucocorticoid use, rheumatoid arthritis, and other causes of secondary osteoporosis).[10] Since its launch, FRAX models have been made available for 78 countries. Moreover, the FRAX tool has significantly influenced clinical decision-making and intervention levels for osteoporosis, as noted in over 100 global guidelines.[11] Understanding the link between osteoporosis and fracture risk in an individual can aid in developing effective treatment plans. The aim of this systematic literature review was to explore the relationship between osteoporosis and fracture risk as depicted in studies conducted over the past decade.

METHODS

Protocol

The study's author made sure it followed all rules by carefully following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria. The approach that was selected was carefully thought out to guarantee accurate and cogent research findings.

CRITERIA FOR ELIGIBILITY

This paper offers a thorough review of studies done in the last ten years about the relationship between diabetes mellitus and psoriasis. The goal of this initiative is to clarify and improve patient care practices through in-depth data analysis. This thesis' main goal is to highlight the importance of important subjects that appear in a range of literary works.

Strict inclusion and exclusion criteria were put in place to guarantee the accuracy of the data used in this investigation. For consideration for inclusion, an item needs to have been published in English between 2014 and 2024. Published reviews, editorials, submissions without a DOI, and duplicate journal entries are among the exclusion criteria.

SEARCH STRATEGY

The study's keywords include "osteoporosis, fracture, risk, broken, outcomes, analysis". For this research, the following Boolean MeSH keywords were entered into the databases: ((“osteoporosis”[MeSH Terms] OR “osteoporosis“[All Fields] AND “fracture”[All Fields]) AND (“risk”[MeSH Terms] OR “fracture”[All Fields] OR “broken”[All Fields] OR “risk”[MeSH Subheading] OR “outcomes”[All Fields] OR “analysis”[All Fields])).

DATA RETRIEVAL

The writers carefully considered the relevancy of each article based on its abstract and title before starting this in-depth analysis. Greater weight was only given to research that matched the inclusion criteria and the goals of the article. After several searches, a distinct and consistent pattern became apparent. The only language that was approved for full-text entries was English. The most stringent screening procedure produced content that met all predefined inclusion criteria

and had a direct bearing on the topic of the study. Studies that did not meet these standards were typically ignored, and their conclusions were not given much weight. Numerous pieces of information were included in the assessment, such as factors, titles, authors, dates of publication, locations, and study procedures.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors themselves carefully read through the titles and abstracts of each article to decide which ones need more research. Subsequently, every document that was initially eligible for the examination had to be carefully examined. The selection of the review papers was based on the evaluation findings. This criterion allowed for a quicker selection of publications for additional examination, which in turn allowed for a more comprehensive assessment of earlier studies and the conditions that called for their review.

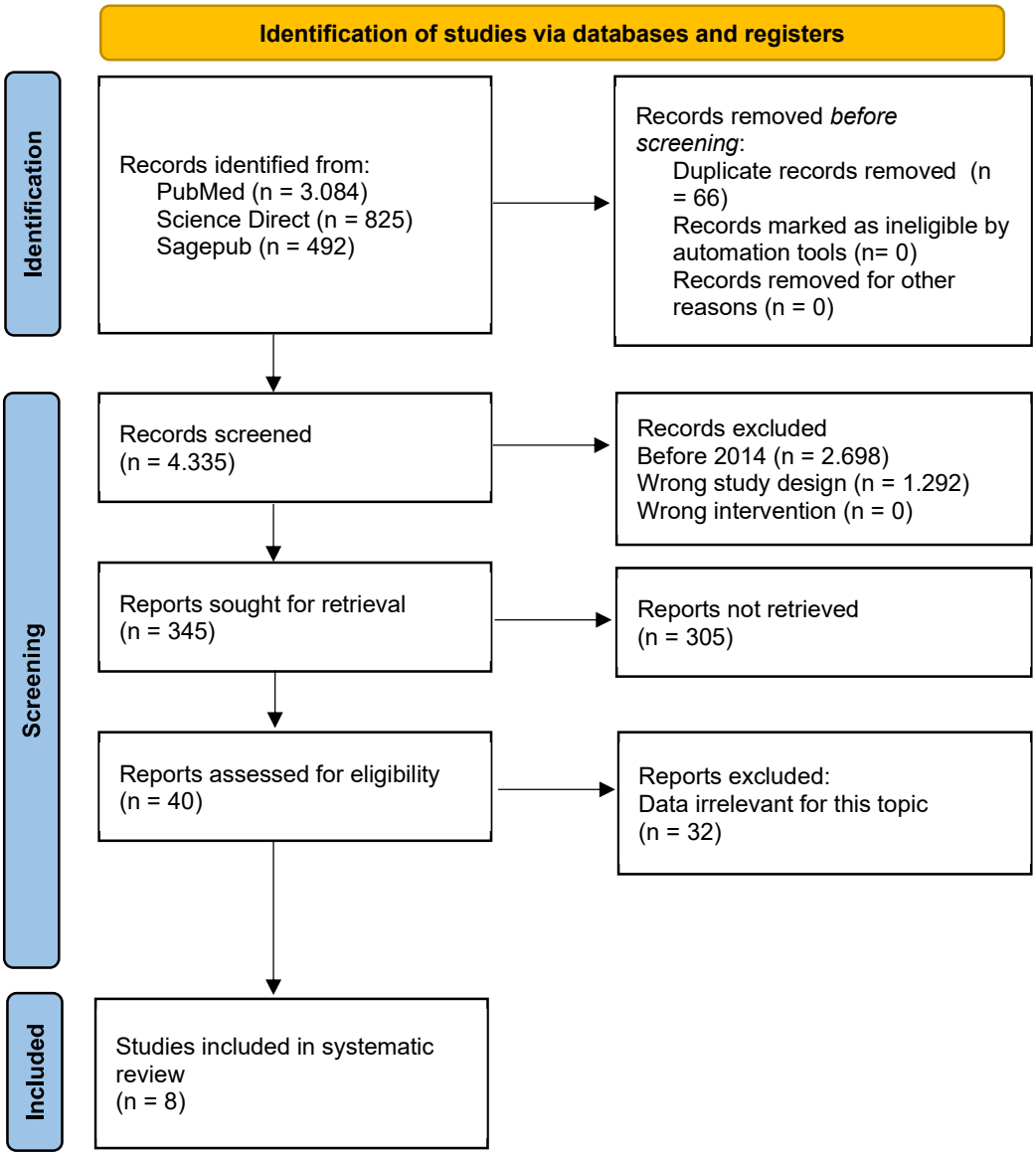

Figure 1. Article search flow chart

RESULT

Early on in the study, our group carefully assembled a sizable library of articles from reputable sources such as Science Direct, PubMed, and SagePub. Following a rigorous three-stage screening procedure, we identified eight papers that were considered extremely relevant to our current systematic study. After that, we focused on particular topics for more research and gave each manuscript a thorough evaluation. For your convenience, we've included a brief description of the assessed content in Table 1 to help expedite our study.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Fink et al.[12] (2019)	USA	Systematic Review	48 studies	Research indicates that women with osteoporosis have fewer clinical fractures when treated with alendronate and raloxifene, whereas women with osteopenia or osteoporosis have fewer clinical fractures when treated with zoledronic acid. Nevertheless, long-term use of bisphosphonates raises the possibility of uncommon side effects such as atypical femur fractures and mandibular osteonecrosis. Reducing radiographic vertebral fractures over the long run as opposed to stopping bisphosphonates did not affect nonvertebral fractures.
Kim et al.[13] (2020)	Korea	Review	-	Osteoporosis, a bone condition associated with osteoporotic vertebral fracture (OVF), is influenced by genetic factors and epigenetics, which can alter DNA structure and gene expression during bone remodeling, leading to increased medical costs and poor quality of life.
Shevroja et al.[14] (2021)	Switzerland	Review	-	Osteoporosis, a disease characterized by low bone mass and alterations in bone microarchitecture, increases the risk of fragility fractures and fractures. Trabecular bone score (TBS), an index of bone microarchitecture, has been shown to predict fractures independently of bone mineral density, highlighting its role in bone health assessment in endocrine disorders.
Imamudeen et al.[15] (2022)	USA	Narrative Review	-	This review explores fracture diagnosis and management in osteoporotic patients, focusing on the risk of fractures due to osteoporosis. It highlights the use of modern scoring systems, pharmacological intervention, and evidence-based clinical management algorithms for treating osteoporotic vertebral body compression fractures

				and tumor-induced osteoporosis.
Vandenput et al.[9] (2022)	Multicentre	Systematic Review	12 studies	A study examining osteoporotic fracture risk factors in 2,138,428 participants will construct an updated version of FRAX. The study will test multivariate hazard functions for hip, major osteoporotic fracture, and death using extended Poisson regression. Sex- and ethnicity-specific differences in risk factors will be investigated. Meta-analyses will compute 10-year probability of hip and major osteoporotic fractures.
Handel et al.[7] (2023)	Denmark	Systematic Review	69 studies	Clinical fractures were found to be effectively reduced by treatments such as bisphosphonates, parathyroid hormone receptor agonists, and romosozumab. Denosumab, parathyroid hormone receptor agonists, and romosozumab were more effective than oral bisphosphonates in preventing vertebral fractures.
Kostenuik et al.[16] (2023)	USA	Review	-	Patients at very high fracture risk due to osteoporosis, such as those who have had previous osteoporotic fractures and those undergoing bone-related surgery with poor bone health, should take into consideration osteoanabolic drugs.
Schini et al.[17] (2023)	United Kingdom	Review	-	FRAX is a tool used to calculate fracture risk, particularly in osteoporosis. It helps clinicians determine the likelihood of major osteoporotic fractures and hip fractures. This review explores FRAX's management, characteristics, diagnostic and therapeutic thresholds, and its limitations, highlighting the need for further investigation and treatment.

Fink's study revealed that bisphosphonate treatment reduced clinical fractures in women with osteoporosis, including radiographic vertebral fractures. However, long-term bisphosphonates increase the risk of rare harms like atypical femoral fractures and osteonecrosis of the jaw. In women with unspecified osteoporosis status, bisphosphonate therapy reduced clinical fractures but increased serious harm. After 3 to 5 years, bisphosphonate continuation versus discontinuation reduced radiographic vertebral fractures but not nonvertebral fractures.[12]

Kim's research reveals that osteoporosis and OVF occurrence are associated with genetic factors, but epigenetics plays a crucial role in controlling gene expression and cellular processes, thereby influencing the development and progression of the disease.[13]

It is important to evaluate bone health since Shevroja's research demonstrated a correlation between higher fracture risk and fragility fractures, a condition marked by changes in bone microarchitecture.[14]

Imamudeen's research underscores the need of comprehending the fracture risk in individuals with osteoporosis, emphasizing the necessity for medical professionals to grasp the pathophysiology and contemporary protocols for overseeing bone mineral density. The study also emphasizes the application of evidence-based clinical management algorithms and contemporary grading systems in the treatment of osteoporotic fractures.[15]

In order to create an updated version of FRAX, Vandenput's study finds 12 cohorts, four of which are novel. Extended Poisson regression is used in the study to examine multivariate hazard functions for hip, major osteoporotic fracture, and mortality. Disparities in risk factors according to sex and ethnicity will be examined. The 10-year chance of significant osteoporotic fractures and hip fractures will be calculated by meta-analyses.[9]

According to Handel's research, romosozumab, bisphosphonates, and parathyroid hormone receptor agonists all effectively reduce clinical fractures. When it came to preventing vertebral fractures, denosumab, parathyroid hormone receptor agonists, and romosozumab outperformed oral bisphosphonates with no negative side effects.[7]

Kostenuik's study highlights the importance of prevention in osteoporosis, highlighting the potential benefits of osteoanabolic agents in reducing fracture risk in patients at high risk.[16]

Schini's research highlights FRAX as a globally leading tool for fracture risk assessment, with its utility in cost-effectiveness and efficient population screening. The tool's new FRAXplus website allows for modification of probability, and the second version is under development.[17]

DISCUSSION

Utilizing FRAX and BMD testing can help determine the need for pharmacotherapy.[15] The Fracture Risk Assessment Tool (FRAX) is used to assess fracture risk in women with osteoporosis.[12] FRAX aids in assessing high-risk subjects for osteoporosis-related fractures, enabling tailored pharmacological interventions. While it does not define intervention thresholds, it provides a platform to assess fracture probability, allowing clinicians and public health agencies to make rational treatment decisions. The tool, while not perfect, is better than relying on BMD alone. The widespread use and interest in FRAX have led to efforts to improve models and extend them to other countries. The updated FRAX algorithm includes 64 cohorts, the largest database to date, comprising 2,138,428 participants (69% women) followed for approximately 20 million years with 116,117 documented MOFs.[8] The inclusion of new cohorts increases the likelihood of identifying novel risk factors for fracture, such as diabetes mellitus and fall history. The updated FRAX algorithm will benefit researchers and healthcare professionals by refining risk assessment models with additional risk factors for fractures, facilitating the identification of those at the highest fracture risk, and guiding guideline developers and policymakers on optimal treatment strategies for osteoporosis.[9]

TBS is a textural analysis that measures bone microarchitecture, correlated with bone strength parameters. It predicts fractures independently of bone mineral density (BMD) and other clinical risk factors.[18] Studies have shown that TBS can predict fractures independently of BMD and other clinical risk factors.[14] An alternative approach for using TBS in clinical practice, based on a "risk-equivalent" offset adjustment to BMD T-score, has been developed.[19] This approach increases the specificity of the model by about 20% without compromising sensitivity. TBS has also been shown to predict fragility fractures in secondary osteoporosis caused by diabetes, PHPT, rheumatoid arthritis, adrenal incidentaloma, chronic kidney disease, long-term glucocorticoid therapy, HIV, or oncological conditions.[14]

Osteoporosis clinical practice guidelines (CPGs) have been updated to emphasize the importance of identifying patients with very high fracture risk (VHFxR) who may warrant osteoanabolics as treatment. AACE/ACE 2020 CPGs communicate various risk factors for VHFxR, including certain fracture histories. Updated Endocrine Society CPGs endorse osteoanabolics for patients at VHFxR, including those with severe or multiple osteoporotic fractures.[20] An ASBMR task force on secondary fracture prevention advises that osteoanabolics are appropriate initial therapies for individuals with vertebral fractures.[16] Updated CPGs from NAMS advise that vertebral or hip fracture history is sufficient to diagnose osteoporosis, regardless of BMD or other risk factors. Updated ESCEO/IOF CPGs recommend osteoanabolics for patients at high risk of fracture and advise that women over 65 years old with an osteoporotic fracture history can be considered for treatment without BMD testing.[16,21] Osteoanabolic therapy is recommended as first-line therapy for patients with VHFxR by multiple organizations and experts, with no evident controversy or dissent.[16]

Postmenopausal osteoporosis treatment options have increased significantly in the past 20 years, but no Cochrane-type reviews or meta-analyses have been conducted recently.[4] Most treatments have been approved by authorities in Europe, the US, and elsewhere for the treatment of postmenopausal osteoporosis. The prevalence of patients with a high baseline risk of fractures has varied between different treatments and studies. The relative reduction in the risk of fractures was found to be mostly independent of baseline risk factors. The approved treatments reduce the risk of fractures compared with placebo, but whether all treatments are equally effective is an interesting question. The network meta-analyses showed that bone anabolic treatments (teriparatide and romosozumab) reduced the risk of clinical and vertebral fractures compared with bisphosphonates.[7] However, the certainty of the pooled results on bone anabolic treatments, especially romosozumab, was found to be low due to the small number of studies identified. The VERO (VERtebral fracture treatment comparisons in Osteoporotic women) trial is an illustrative example of the effect of different definitions of groups of fractures.[7,22]

Newer drugs such as denosumab, abaloparatide, and romosozumab are effective in treating osteoporosis.[15] Studies have shown that raloxifene, when taken for 4 years, can reduce both vertebral and nonvertebral fractures in women with osteoporosis, while zoledronic acid, when taken for 6 years, can reduce these fractures in patients with osteopenia or osteoporosis. However, long-term bisphosphonate treatment may increase the risk of adverse events such as atypical femoral fractures (AFF), subtrochanteric femur fractures (ST/FSF), and osteonecrosis of the jaw (ONJ), though these events are rare.[12] Oral hormone therapy, when taken for 5 to 7 years, has been found to reduce clinical and hip fractures compared with a placebo, but it also increases the risk of cardiovascular disease and cognitive impairment. Long-term use of oral hormone therapies decreases clinical and hip fractures in women with unknown osteopenia or osteoporosis status, but the anti-fracture benefits are offset by the risk of serious harm. The balance of benefits and harms for continued treatment versus discontinuation of long-term osteoporosis treatment for women is less clear.[23,24]

Future research is needed to guide decisions about osteoporosis treatment, including comparing sequential treatments with continuous long-term antiresorptive treatment, comparing osteoporosis drug therapy (ODT) holidays of different lengths, and examining how benefits and risks vary as a function of patient, bone, and ODT characteristics.[12] The timely management of osteoporotic fractures is crucial in reducing fracture risk.[15] Osteoporosis and osteoporotic conditions can be treated using epigenetic therapeutics. For example, recombinant adeno-associated virus serotype 9 (rAAV9) can deliver artificial miRNA to osteoclast cells, silence osteoporosis regulators RANK and cathepsin K, and increase bone mass in mice.[25] MiR-338 cluster in the serum can maintain bone formation capacity and increase bone mass in osteoporosis mouse models.[26] Histone methyltransferase DOT1L inhibition can delay osteoporosis progression. Knockdown of EZH2 by lentivirus-expressing shRNA can rescue the abnormal fate of osteoporotic mesenchymal stem cells. Additionally, the H3K27me3 inhibitor DZNep derepresses Wnt signaling and improves osteogenic differentiation of osteoporotic mesenchymal stem cells. Furthermore, the DNA methylation inhibitor 5-aza-20-deoxycytidine has been shown to improve bone mass in disuse-induced osteopenic bone development.[13]

Research on the efficacy of anti-osteoporosis medications has revealed that certain medications are effective regardless of the baseline fracture risk, while others, such as abaloparatide, raloxifene, teriparatide, alendronate, hormone replacement treatment, and strontium ranelate, show greater efficacy with higher baseline risk. A study found a significant interaction between baseline FRAX without BMD and treatment efficacy for osteoporotic fractures.[17] Denosumab showed no significant interaction between treatment effect and baseline FRAX probability, but a cubic spline function was found to provide a better fit, with a greater effect at higher probabilities.[27] Bazedoxifene did not show an overall interaction between treatment and FRAX with BMD, but when the 10-year probability of major osteoporotic fracture is greater than 16%, treatment is associated with a significant decrease in the risk of all clinical fractures.[28] The emerging literature on cement augmentation over non-surgical management and recommendations from academic/professional organizations can guide treatment. Future directions for surgical management of osteoporotic spinal fractures are also discussed.[15]

CONCLUSION

Studies have shown that osteoporosis can lead to fractures, a condition that can be significantly reduced with the use of the Fracture Risk Assessment Tool (FRAX) and Bone Mineral Density (BMD) testing. The FRAX algorithm, which includes 64 cohorts, has been shown to predict fractures independently of BMD and other clinical risk factors. However, the certainty of these results is low due to the small number of studies identified. Postmenopausal osteoporosis treatment options have increased significantly in the past 20 years, but no Cochrane-type reviews or meta-analyses have been conducted recently. Newer drugs like denosumab, abaloparatide, and romosozumab are effective in treating osteoporosis, but the balance of benefits and harms for continued treatment versus discontinuation is less clear.

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