Effects of Hormone Replacement Therapy in Menopause on Bone and Cardiovascular Health

Efeitos do Uso de Terapia Hormonal na Menopausa na Saúde Óssea e Cardiovascular

Efectos de la Terapia de Reemplazo Hormonal en la Menopausia Sobre la Salud Ósea y Cardiovascular

RESUMO

Objetivo: Analisar os efeitos da terapia hormonal na menopausa sobre a saúde óssea e cardiovascular. **Método:** Realizou-se uma revisão sistemática da literatura nas bases PubMed e SciELO, incluindo estudos publicados entre 2003 e 2023. Foram selecionados 12 artigos conforme critérios de inclusão e exclusão previamente definidos. Os dados foram analisados qualitativamente e sintetizados em forma narrativa, com apoio de tabelas e gráficos descritivos. **Resultado:** Observou-se efeito positivo consistente da terapia hormonal na manutenção da densidade mineral óssea e na redução do risco de osteoporose e fraturas. Quanto aos desfechos cardiovasculares, os achados foram heterogêneos, com benefícios mais evidentes quando a terapia foi iniciada precocemente e riscos maiores em situações de uso tardio ou em pacientes com condições clínicas associadas. **Conclusão:** A terapia hormonal contribui para a proteção óssea, enquanto seus efeitos cardiovasculares permanecem incertos, reforçando a necessidade de indicação individualizada e de novos estudos de maior robustez metodológica.

DESCRITORES: Menopausa; Terapia hormonal; Osteoporose; Doenças cardiovasculares; Saúde da mulher.

ABSTRACT

Objective: To analyze the effects of hormone therapy in menopause on bone and cardiovascular health. **Method:** A systematic review of the literature was conducted in the PubMed and SciELO databases, including studies published between 2003 and 2023. Twelve articles were selected according to previously defined inclusion and exclusion criteria. The data were analyzed qualitatively and synthesized in narrative form, supported by descriptive tables and graphs. **Results:** A consistent positive effect of hormone therapy on maintaining bone mineral density and reducing the risk of osteoporosis and fractures was observed. Regarding cardiovascular outcomes, the findings were heterogeneous, with more evident benefits when therapy was started early and greater risks in situations of late use or in patients with associated clinical conditions. **Conclusion:** Hormone therapy contributes to bone protection, while its cardiovascular effects remain uncertain, reinforcing the need for individualized indication and new studies with greater methodological robustness.

DESCRIPTORS: Menopause; Hormone therapy; Osteoporosis; Cardiovascular diseases; Women's health.

RESUMEN

Objetivo: Analizar los efectos de la terapia hormonal en la menopausia sobre la salud ósea y cardiovascular. **Método:** Se realizó una revisión sistemática de la literatura en las bases de datos PubMed y SciELO, incluyendo estudios publicados entre 2003 y 2023. Se seleccionaron doce artículos según criterios de inclusión y exclusión previamente definidos. Los datos se analizaron cualitativamente y se sintetizaron de forma narrativa, con el apoyo de tablas y gráficos descriptivos. **Resultados:** Se observó un efecto positivo consistente de la terapia hormonal en el mantenimiento de la densidad mineral ósea y la reducción del riesgo de osteoporosis y fracturas. En cuanto a los resultados cardiovasculares, los hallazgos fueron heterogéneos, con beneficios más evidentes cuando la terapia se inició temprano y mayores riesgos en situaciones de uso tardío o en pacientes con afecciones clínicas asociadas. **Conclusión:** La terapia hormonal contribuye a la protección ósea, mientras que sus efectos cardiovasculares siguen siendo inciertos, lo que refuerza la necesidad de una indicación individualizada y de nuevos estudios con mayor solidez metodológica.

DESCRIPTORES: Menopausia; Terapia hormonal; Osteoporosis; Enfermedades cardiovasculares; Salud de la mujer.

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INTRODUCTION

Menopause is a physiological process characterized by the definitive cessation of ovarian function and the consequent decline in estrogen and progesterone production, generating significant repercussions on women's health [1]. Among the main impacts are accelerated bone loss, which increases the prevalence of osteopenia and osteoporosis, as well as raising the risk of fragility fractures [1,4–6], and greater susceptibility to cardiovascular dis-

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eases (CVD), which are the leading cause of morbidity and mortality in this population [2,3,9,12].

Hormone therapy (HT) has been considered as a strategy to mitigate the effects of estrogen deficiency. Evidence shows that its use can preserve bone mineral density and reduce the incidence of osteoporotic fractures[1,4–6,11], while, in the cardiovascular sphere, results point to potential benefits when therapy is instituted early, close to the menopause period [3,9,10,12]. On the other hand, studies also indicate significant risks in women with pre-existing comorbidities or when HRT is started late[7,9,12].

That said, clinical and reproductive factors, such as age at menopause onset, age at menarche, body mass index, and family history of fractures, are directly associated with both bone health and cardiovascular risk [1,4,5,6]. Another relevant aspect refers to the suspension of HT, which has been associated with the progressive loss of bone protective effects; however, regular physical activity can mitigate part of this negative impact [10].

Thus, hormone therapy should be prescribed on an individual basis, considering the clinical profile, potential risks, and expected benefits [3,7,9,11,12]. However, there are still gaps in knowledge regarding the ideal duration of treatment, the safest formulations, and the long-term impact on bone and cardiovascular health.

MATERIALS AND METHODS

A systematic review of the literature was conducted to analyze the effects of hormone therapy (HT) use during menopause on bone and cardiovascular health. The search was conducted in the MEDLINE/PubMed and SciELO databases to include scientific articles of greater relevance and scope on the subject.

Descriptors in English and terms related to the theme were used, combined by Boolean operators, including: "Effects," "Hormone replacement therapy," "Menopause," and "Bone and cardiovascular health." Initially, 127 articles were identified. After applying the time filter (publications from 2003 onwards), 107 articles remained. Of these, based on the reading of titles, abstracts, methodological design, objectives, and results, 29 articles were selected for full analysis. After exclusions, a compilation of 12 articles was obtained.

Inclusion criteria:

- Studies addressing the effects of hormone therapy in menopause on bone and/or cardiovascular health.
- Research published in peer-reviewed scientific journals.
- Studies available in **English, Spanish, or Portuguese**.
- Articles that presented clear methodological data and evaluation of outcomes related to the theme.

Exclusion Criteria:

- Studies that did not specifically address the effects of hormone therapy on bone and cardiovascular health.
- Isolated case reports with no relevance to the synthesis of the topic.
- Duplicate studies.
- Articles without access to the full text.

The identified studies were initially reviewed based on their titles and abstracts to determine their relevance to the topic in question. The selected articles were then analyzed in full to confirm their inclusion in the literature review. Relevant data were extracted from the selected articles, including information on the effects of hormone therapy use during menopause on bone and cardiovascular health. The extracted data were analyzed qualitatively and synthesized narratively.

Patterns and trends were identified in the assessment of the effects of hormone therapy use in menopause on bone and cardiovascular health, and the results were presented in an organized and understandable manner. The methodological quality of the included studies was assessed using specific criteria for each type of study. Aspects such as study design, sample representativeness, and analysis methodology were considered.

This literature review is based on the analysis of previously published data and does not involve the collection of information directly from human participants. Therefore, no additional ethical considerations are necessary. The results of this literature review will be presented in a scientific manuscript for publication in a peer-reviewed journal. The findings may also be shared at relevant scientific conferences and disseminated to health professionals interested in the topic.

RESULTS

Twelve studies were included in this review, addressing the effects of hormone therapy in menopause on bone and cardiovascular health. The sample of articles included national and international publications, published since 2003, distributed mainly in Brazil, the United States, and Europe.

Table 1 presents a summary of the included studies, containing information on authors, year, objectives, main results, and conclusions.

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TABLE 1: SUMMARY OF INCLUDED STUDIES

TITLE	AUTHOR, YEAR	OBJECTIVES	RESULTS	CONCLUSIONS
O impacto da terapia de reposição hormonal na saúde cardiovascular em mulheres após menopausa: uma revisão de literatura	Costa et al. (2023)	To assess the prevalence of osteoporosis and clinical and reproductive factors associated with decreased bone mineral density.	Prevalence of osteoporosis in the lumbar spine: 14.7% and osteopenia: 38%; in the femur, 3.8% and 32.7%, respectively. Associated variables: education level, age at menarche, age at menopause, and BMI.	The prevalence of osteoporosis and osteopenia was high. Factors such as advanced age, low education, late menarche, early menopause, and low BMI were associated with lower bone mass.
Qualidade de vida de mulheres com baixa massa óssea na pós-menopausa	Dallanezi et al. (2011)	To assess the quality of life in women with osteoporosis and osteopenia compared to women with normal bone density.	There were no significant differences between the groups, except in the vitality domain, which was higher in women with osteoporosis.	Quality of life was similar between the groups, with the exception of vitality, which was paradoxically better in the osteoporosis group.
The effect of soy dietary supplement and low dose of hormone therapy on main cardiovascular health biomarkers: a randomized controlled trial	Carmignani et al. (2014)	To evaluate the effects of soy supplementation and low-dose hormone therapy on cardiovascular markers.	After 16 weeks, there was an 11.3% reduction in total cholesterol and an 18.6% reduction in LDL in the HT group; no changes were observed in the soy or placebo groups.	Soy supplementation had no significant effect; HT showed a positive impact on the lipid profile.
Fatores de risco para osteoporose em mulheres na pós-menopausa do sudeste brasileiro	Buttros et al. (2011)	To assess bone mineral density and risk factors for osteoporosis.	Menopause <40 years: 80% osteopenia/osteoporosis; BMI <20 kg/m²: 50% osteoporotic. Use of HT and high BMI were protective factors.	Age, duration of menopause, smoking, and maternal history of fracture were risk factors; HT and high BMI acted as protection.
Risk factors for osteoporotic fractures and low bone density in pre and postmenopausal women	Pinheiro et al. (2010)	To estimate the prevalence and risk factors for osteoporosis and fractures.	Osteoporosis in 33% and fragility fractures in 11.5%. Risk factors: age, menopause, previous fracture, smoking. Protective factors: high BMI, physical activity, current HT.	Identifying clinical factors can help prevent fractures in women at risk.
Osteoporose: prevalência e fatores de risco em mulheres de clínica privada maiores de 49 anos de idade	Faisal-Cury et al. (2007)	To assess the prevalence and risk factors for osteoporosis in private practice.	Prevalence of osteoporosis: 32.7%. Associated factors: advanced age, prolonged menopause, white/yellow ethnicity, late menarche. Higher BMI was protective.	Reproductive and anthropometric variables had a greater impact than lifestyle factors.
Qualidade de vida em usuárias e não usuárias de terapia de reposição hormonal	Zahar et al. (2005)	Compare quality of life between HRT users and non-users.	Users reported fewer climacteric symptoms. Only the vitality domain scored below 50 in both groups.	Both groups reported good quality of life, with no significant overall differences.
Padrão hormonal feminino: menopausa e terapia de reposição	Oliveira et al. (2016)	Review aspects of the female hormonal pattern and the effects of replacement therapy.	The article describes hormonal changes in menopause and the impacts of HRT on symptoms and clinical outcomes.	HRT should be prescribed on an individual basis, considering risks and benefits.
Terapia hormonal na menopausa: quando não usar	Spritzer & Wender (2007)	Review contraindications for HRT in menopause.	Estrogen may have increased risks in women with comorbidities or cardiovascular history.	HRT should not be universally indicated, but rather restricted to selected cases.
Discontinuation of hormone therapy and bone mineral density: does physical activity modify that relationship	Sheedy et al. (2023)	To assess the impact of HRT discontinuation on bone density and the role of physical activity.	Discontinuation of HRT is associated with accelerated loss of bone mineral density. Physical activity partially mitigates this effect.	Physical activity can mitigate the negative effects of discontinuing HT, but it does not replace the bone protection provided by the treatment.
Estrogen hormone therapy and postmenopausal osteoporosis: does it really take two to tango?	Silva & Rodrigues (2023)	Review the role of estrogen in the prevention of postmenopausal osteoporosis.	Evidence suggests a positive effect of estrogen on maintaining bone density, although controversies persist.	Estrogen therapy may be beneficial in certain contexts, but requires individualization.
Menopause and women's cardiovascular health: is it really an obvious relationship?	Ryczkowska et al. (2022)	To evaluate the relationship between menopause and cardiovascular risk.	A higher cardiovascular risk associated with menopause was observed, mediated by hormonal and metabolic changes.	The relationship between menopause and cardiovascular health is multifactorial, requiring a personalized preventive approach.

Source: Own elaboration based on the articles included in this review (Costa-Paiva et al., 2003; Dallanezi et al., 2011; Carmignani et al., 2014; Buttros et al., 2011; Pinheiro et al., 2010; Faisal-Cury et al., 2007; Zahar et al., 2005; Oliveira et al., 2016; Spritzer & Wender, 2007; Sheedy et al., 2023; Silva & Rodrigues, 2023; Ryczkowska et al., 2022).

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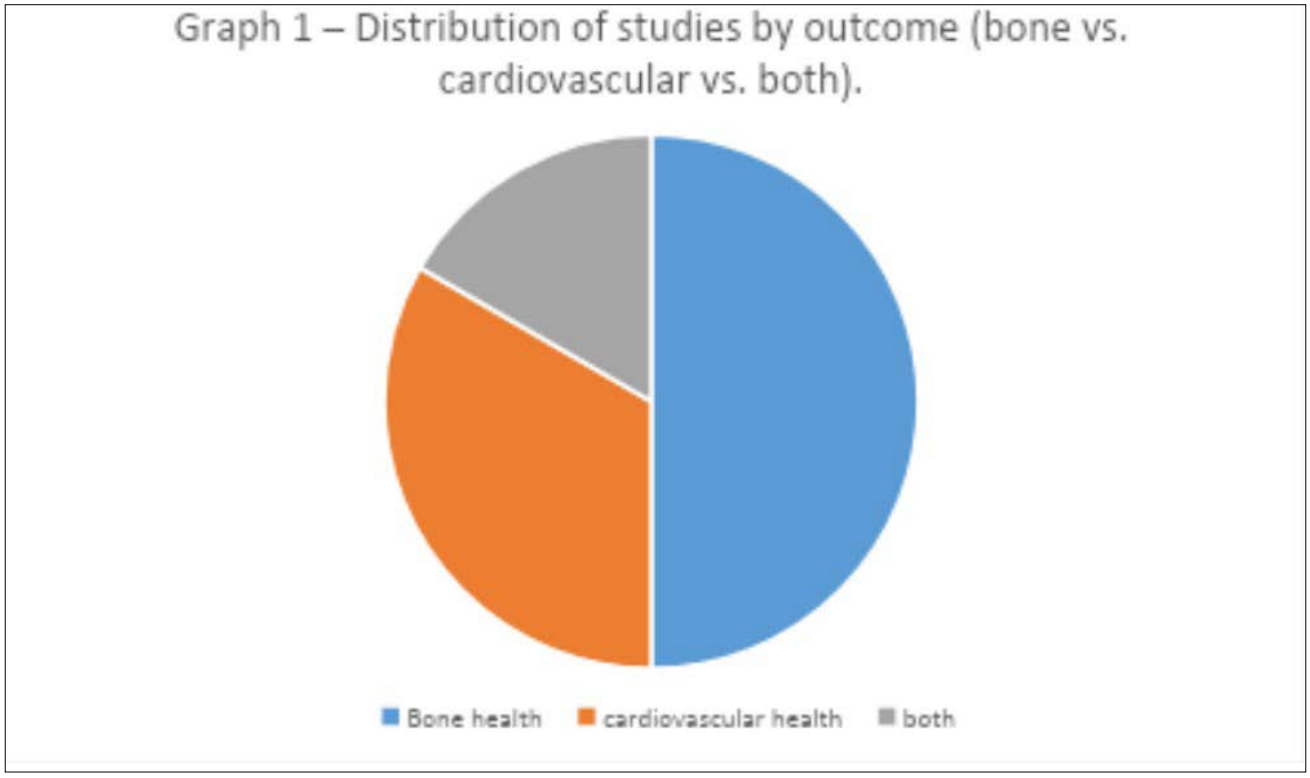
Distribution of studies by outcome

The thematic analysis of the articles showed that most studies focused on the effects of hormone therapy (HT) on bone health, assessing the prevalence of osteoporosis, bone mineral density (BMD), and associated risk or protective factors [1,4–6,10,11]. These represented about 50% of the total sample, demonstrating a historical concern with understanding the impact of estrogen deficiency on maintaining bone tissue integrity.

On the other hand, approximately 33% of the publications analyzed cardiovascular outcomes, including both intervention and review studies, which evaluated parameters such as lipid profile, risk of coronary events, and the association of HT with cardiovascular mortality [3,7,9,12]. Of particular note is the relevance of the timing of therapy initiation and the patient's previous clinical condition in determining benefits or risks.

Finally, a smaller proportion of studies sought to integrate bone and cardiovascular outcomes together, providing a more comprehensive perspective on the effects of hormone replacement [2,8]. In these cases, the authors emphasized that menopause should not be considered only as a marker of bone decline, but also as a period of vulnerability for cardiovascular events, requiring individualized therapeutic approaches. The distribution of publications according to the central outcome is shown in Graph 1.



Source: Prepared by the authors based on the articles included in this review [1–12].

Main bone outcomes reported

Analysis of studies focused on bone health revealed high prevalences of osteopenia and osteoporosis in postmenopausal women, with osteoporosis in 14.7% and osteopenia in 38% of participants in the lumbar spine, and prevalences of 3.8% and 32.7%, respectively, in the femur [1]. Similar results were observed, with a reported prevalence of osteoporosis of 32.7% in women over 49 years of age. Furthermore, early menopause (<40 years) was associated with a higher risk of osteopenia/osteoporosis (80%) [4,6].

Another relevant observation was the influence of clinical and reproductive factors on bone density. Advanced age, low educational attainment, late menarche, early menopause, and low body mass index were strongly associated with reduced bone mass [1,4,6]. In contrast, the use of HT [4,5,10,11], high BMI [4,6], and regular physical activity[5] were identified as protective factors.

Regarding fragility fractures, Pinheiro et al. (2010) [5] reported a prevalence of 11.5%, highlighting advanced age, current smoking, and previous fracture as significant predictors. The study by Sheedy et al. (2023) [10] demonstrated that discontinuation of hormone therapy is associated with

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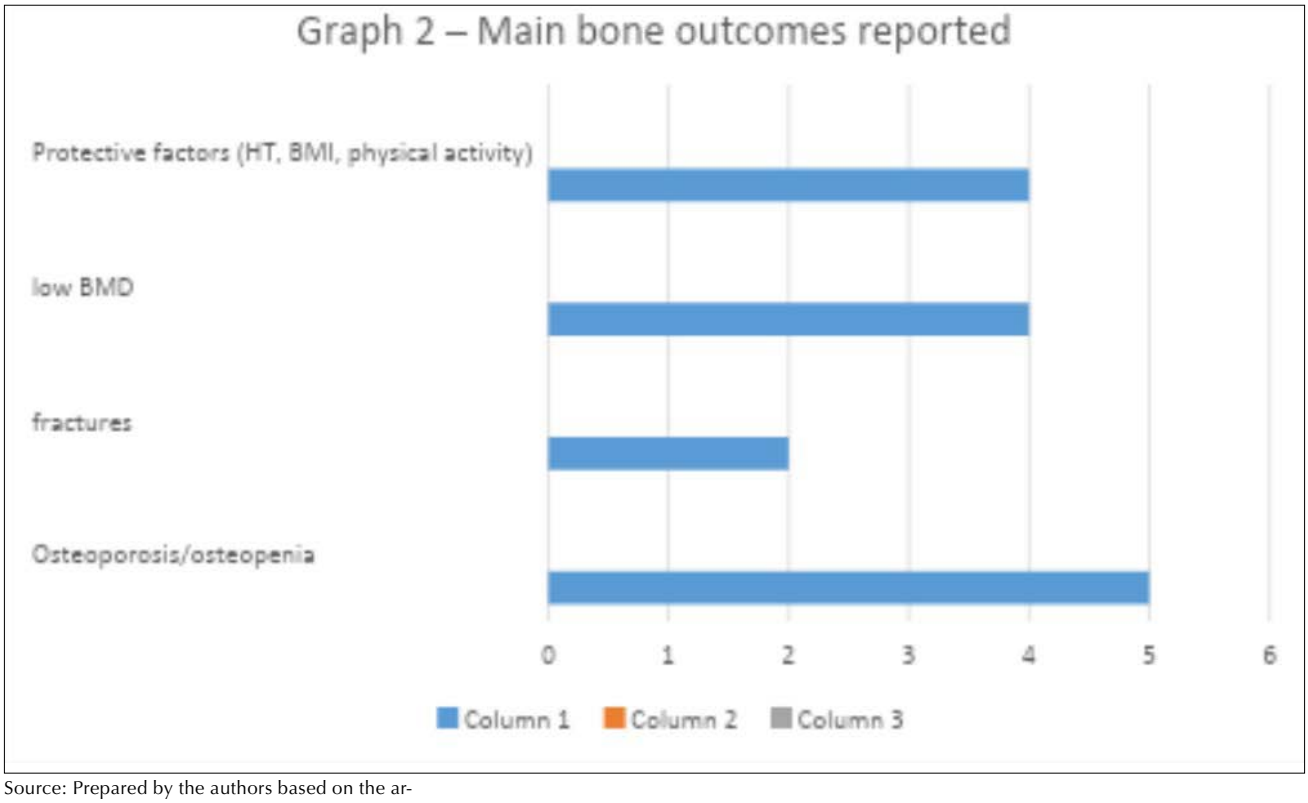
accelerated loss of BMD, although physical exercise partially mitigates this negative effect. These findings are consolidated in Graph 2.



Source: Prepared by the authors based on the articles included in this review [1,4–6,10,11].

Main cardiovascular outcomes reported

Studies investigating the cardiovascular dimension presented more heterogeneous and, in some cases, controversial results. In a randomized clinical trial, reductions of 11.3% in total cholesterol and 18.6% in LDL cholesterol were observed in women undergoing low-dose HT, with no significant effects on triglycerides, HDL, or blood glucose [3]. Similar results of favorable impact on cardiovascular biomarkers were observed in more recent reviews [9,12].

On the other hand, another study pointed out that, although HRT improves climacteric symptoms and quality of life, there is no consensus on its protective role in major cardiovascular events [7]. It was reinforced that HRT should not be recommended as primary or secondary prevention of cardiovascular disease, especially in high-risk women or those with previous coronary artery disease [9,12].

Another recurring point was the relevance of the timing of therapy initiation: the literature suggests that replacement therapy soon after menopause may offer greater protection, while late initiation may carry additional risks, including increased cardiovascular mortality [9,12].

DISCUSSION

It should be noted that hormone therapy (HT) during menopause has a significant impact on both bone and cardiovascular health, albeit in a heterogeneous manner. In the bone field, the literature confirms that postmenopausal hypoestrogenism is a determining factor in the acceleration of bone mineral density (BMD) loss, increasing the prevalence of osteopenia and osteoporosis [1,4–6,10,11]. The use of HT, when properly instituted, has demonstrated a consistent protective effect, preventing bone loss and reducing the risk of fractures. These findings corroborate international guidelines that position estrogen replacement as an effective strategy in the primary prevention of osteoporosis in symptomatic women during the menopausal transition.

However, the analysis also reinforces that clinical and reproductive factors, such as early age at menopause, low body mass index, and family history of fractures, play a critical role in determining individual risk[1,4,6]. Thus, the indication for HRT should not be universal but evaluated on a case-by-case basis, considering

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reproductive and anthropometric variables that modulate its effectiveness. The study by Sheedy et al. (2023) [10], by highlighting the accelerated loss of BMD after discontinuation of therapy, adds a practical dimension to clinical management: the decision to discontinue treatment should be accompanied by complementary strategies, such as encouraging regular physical activity, to mitigate such repercussions.

In the cardiovascular sphere, the findings revealed greater complexity. Clinical trials have demonstrated metabolic benefits, such as improved lipid profile and possible cardioprotection when HRT is started early [3,9,12]. On the other hand, there is evidence of an increased risk of adverse events in women with previous comorbidities or when replacement is instituted late [7,9]. These observations reinforce the so-called "window of opportunity hypothesis," according to which the beneficial effects of estrogen are more intense when treatment is started close to menopause, a period when the endothelium still preserves a favorable response to the hormone [9,12]. However, the literature remains inconclusive about its role in the primary and secondary prevention of cardiovascular disease, recommending caution in high-risk patients.

Another relevant point concerns the differences between observational studies and randomized clinical trials. While cross-sectional and retrospective investigations suggest a more pronounced protective effect, controlled studies present more balanced and sometimes contradictory results. This discrepancy may be related to the heterogeneity of the samples, the different hormonal formulations used, and the follow-up time, highlighting the need for methodological standardization in future research [3,9,11,12].

The clinical implications of these findings reinforce the importance of individualized assessment before prescribing HRT. Not only climacteric symptoms should be considered, but also bone profile, cardiovascular risk, and patient preferences.

> "Hormone replacement should not be seen as a universal intervention, but as part of a therapeutic arsenal that includes behavioral measures (physical activity, adequate nutrition, smoking cessation) and pharmacological alternatives."

Among the limitations of this review, the predominance of national studies with small samples stands out [1,2,4,6], which may limit the generalization of the findings. In addition, the absence of long-term multicenter clinical trials restricts the robustness of conclusions regarding the cardiovascular safety of the therapy. Finally, methodological heterogeneity among studies makes direct comparisons and the development of standardized recommendations difficult.

CONCLUSION

Evidence shows that hormone therapy during menopause has a positive and consistent impact on bone health, contributing to the preservation of mineral density and reducing the risk of osteoporosis and fractures. In the cardiovascular sphere, the results were heterogeneous, indicating potential benefits when therapy is started early, but also risks in situations of late use or in women with previous comorbidities.

The need for individualized clinical decisions is reinforced, considering the risk profile and therapeutic goals of each patient. However, important gaps remain regarding long-term cardiovascular safety, standardization of hormonal formulations, and optimal duration of treatment. Future research should focus on robust, longer-term clinical trials capable of clarifying these points and providing a solid basis for safer and more effective clinical recommendations.

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