

Effect of estrogen and progesterone therapy on intraocular pressure: a systematic review and meta-analysis study

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Abstract

This systematic review and meta-analysis aimed to assess the effect of Hormone Replacement Therapy (HRT) with estrogen and progesterone on Intraocular Pressure (IOP) in postmenopausal women, with the objective of determining whether HRT can lower IOP and potentially reduce glaucoma risk. Following PRISMA guidelines, a comprehensive search was conducted up to June 2024. Eligible studies included randomized controlled trials and observational studies that reported IOP changes in postmenopausal women undergoing HRT. The pooled mean differences in IOP were calculated using both random-effects and fixed-effect models. The meta-analysis included 9 studies with a total of 1,024 participants. The pooled analysis showed a significant reduction in IOP among women receiving HRT compared to controls, with a mean difference of 3.84 mmHg (95% CI: 2.26 to 5.41, $p < 0.01$) in the random-effects model, and 2.36 mmHg (95% CI: 2.08 to 2.64, $p < 0.01$) in the fixed-effect model. Despite these significant results, there was high heterogeneity across studies ($I^2 = 97\%$), likely due to variations in hormone types, dosages, and treatment durations. HRT is associated with a significant decrease in IOP in postmenopausal women, potentially offering protective benefits against glaucoma, although further research is needed to address the observed variability.

Key Words: estrogen, glaucoma, hormone replacement therapy, intraocular pressure, progesterone, postmenopausal women, systematic review.

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Glaucoma is a leading cause of irreversible blindness worldwide, with Primary Open-Angle Glaucoma (POAG) being the most prevalent form. It is characterized by the progressive degeneration of the optic nerve, often associated with elevated Intraocular Pressure (IOP), which is a major risk factor for the disease.^{1,2} Although lowering IOP is the only proven method to slow the progression of glaucoma, understanding the factors that influence IOP is crucial for developing effective prevention and treatment strategies. Among these factors, hormonal changes, particularly those related to estrogen and progesterone levels, have attracted considerable attention due to their potential impact on eye health, especially in postmenopausal women.^{3,4} Estrogen and progesterone, the primary female sex hormones, are known to exert a wide range of physiological

effects beyond the reproductive system, including on ocular tissues. These hormones have been shown to influence the structure and function of the trabecular meshwork, a critical component in the regulation of aqueous humor outflow and, consequently, IOP.⁵⁻⁷ During menopause, a significant decline in estrogen and progesterone levels occurs, which may contribute to an increased risk of developing conditions associated with elevated IOP, such as glaucoma. This hormonal decline has led to the hypothesis that Hormone Replacement Therapy (HRT), which aims to supplement the reduced levels of estrogen and/or progesterone, might play a role in modulating IOP and potentially reducing glaucoma risk in postmenopausal women.⁸⁻¹¹ Numerous studies have investigated the relationship between hormone replacement therapy and IOP, yielding mixed results. Some research has reported that HRT is as-

sociated with a reduction in IOP, suggesting a protective effect against glaucoma. This is thought to be due to the influence of estrogen on the ocular tissues, where it may enhance aqueous humor outflow or reduce its production, thereby lowering IOP.¹²⁻¹⁴ Conversely, other studies have found no significant association or even reported an increase in IOP with HRT use, indicating that the effect of hormone therapy on IOP might be more complex and influenced by various factors such as the type of hormone used, dosage, duration of therapy, and individual patient characteristics.¹⁵⁻¹⁷

Furthermore, understanding the role of hormone therapy in IOP modulation has broader implications for women's health. With the aging population, a growing number of women are experiencing menopause and the associated hormonal changes, leading to increased interest in HRT for managing menopausal symptoms and preventing related health issues.¹⁸⁻²⁰ However, concerns about the risks and benefits of HRT, particularly in the context of long-term use, remain. If hormone therapy is shown to have a significant impact on IOP, it could inform clinical guidelines for glaucoma management and highlight the importance of individualized therapy based on hormonal status.^{21,22}

In this systematic review and meta-analysis, we aim to examine the effect of estrogen and progesterone therapy on IOP in postmenopausal women by synthesizing the evidence from existing studies. This review will assess the pooled mean differences in IOP between HRT users and non-users and evaluate the consistency of findings across studies. The results will provide insights into the potential role of hormone therapy in the management of glaucoma and contribute to a more comprehensive understanding of hormonal influences on ocular health.

Materials and Methods

The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.²³

Systematic search

A comprehensive search was performed across Web of Science, Scopus, and PubMed, covering all available records up to June 2024. We used relevant Medical Subject Headings (MeSH) and relevant keywords, specifically targeting («hormone replacement therapy» OR «HRT» OR «progesterone» OR «estrogen») AND («open-angle glaucoma» OR «OAG» OR «intraocular pressure» OR «IOP»).

Inclusion and eligibility

The eligibility criteria were defined based on the PICO framework: Population (P): postmenopausal women; Intervention (I): hormone therapy; Comparison (C): change of intraocular pressure; Outcome (O): IOP reduction or increase. The exclusion criteria were defined as: animal studies, case reports, studies on other types of glaucoma, studies not involving HRT, unclear or undefined HRT protocols, absence of clear clinical outcomes, lack of IOP change data, lack of sufficient data, and histologic and in

vitro studies.

Data extraction and outcome measures

Data extraction was performed independently by two authors using a standardized form, with disagreements resolved by a third author. Extracted information included study details (authors, publication year, design), sample characteristics (number of participants, age, menopausal status), hormone therapy specifics (type, dosage, duration), and follow-up duration for intraocular pressure (IOP) measurements. The primary outcome was the change in IOP following hormone therapy, with additional data collected on reported IOP outcomes (mean and standard deviation before and after treatment) and comparison groups (e.g., estrogen versus combination therapy).

Statistical analysis and data synthesis

The pooled Mean Differences (MD) in IOP changes between hormone therapy and control groups were calculated using a random-effects model. Hedges' *g* was used to estimate the effect sizes. The *I*² statistic was applied to evaluate heterogeneity among studies. A Mantel-Haenszel method with a random-effects model was employed to pool effect sizes and calculate standard deviations. Subgroup analyses (e.g., estrogen vs. progesterone, different dosages) were conducted to assess potential sources of heterogeneity. Statistical significance was evaluated using a *z*-test for the overall model and subgroup comparisons. Publication bias was assessed with funnel plots. All statistical analyses, including the creation of forest and funnel plots, were performed using the meta package in R (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio Inc., Boston, MA).

Results

Our initial search yielded 1486 articles from PubMed, Scopus, and Web of Science, from which we eliminated 271 duplicates. After reviewing the titles and abstracts of the remaining 1215 records, we retrieved 53 full-text articles for further evaluation. Ultimately, 9 studies met our eligibility criteria and were included in the systematic review,²⁴⁻³² and all of these studies were included in the meta-analysis (Figure 1). Detailed characteristics of the included studies are summarized in Table 1.

Under the random-effects model, the pooled standardized mean difference (SMD) is 3.84, with a 95% confidence interval (CI) of [2.26, 5.41], indicating a statistically significant decrease in IOP among those who received hormone replacement therapy (HRT) compared to the control group (*p* < 0.01). Under the common-effect model, the pooled SMD is 2.36, with a 95% CI of [2.08, 2.64], also showing a statistically significant effect (*p* < 0.01). The heterogeneity is very high, with an *I*² value of 97%, suggesting substantial variability across the included studies that cannot be attributed to chance alone. The (τ^2) value is 4.2067, further indicating significant differences in effect sizes between studies. This level of heterogeneity suggests that the studies may differ in terms of study design, population character-

istics, HRT protocols, or other factors influencing the IOP outcome. Therefore, the random-effects model is more appropriate for interpreting these results, as it accounts for between-study variability (Figure 2).

The pooled analysis of intraocular pressure (IOP) changes among HRT recipients after follow-up shows a mean difference of 1.42 (95% CI: 0.76 to 2.08, $p < 0.01$) using a random-effects model, indicating a significant decrease in IOP following HRT. The common-effect model presents a pooled mean difference of 0.11 (95% CI: 0.09 to 0.12), also statistically significant. However, there is extreme heterogeneity ($I^2 = 100\%$, $\tau^2 = 1.1290$, $p < 0.01$), reflecting substantial variability between studies, likely due to differences in follow-up duration, HRT regimens, or baseline characteristics, thus supporting the use of the random-effects model for interpretation (Figure 3).

Figure 4 displays the distribution of studies based on standard error and mean difference. The observed asymmetry, with a greater number of studies on one side of the mean and a few outliers, suggests potential publication bias or small-study effects. This implies that smaller studies showing significant results may be more likely to be published. Figure 5 shows the funnel plot of pooled standardised mean difference for studies on HRT and controls. Similar to Figure 4,

asymmetry is observed, with studies unevenly distributed around the pooled estimate. The presence of outliers far from the center further indicates potential publication bias or heterogeneity, suggesting that results might be influenced by factors like study size, methodological differences, or selective reporting.

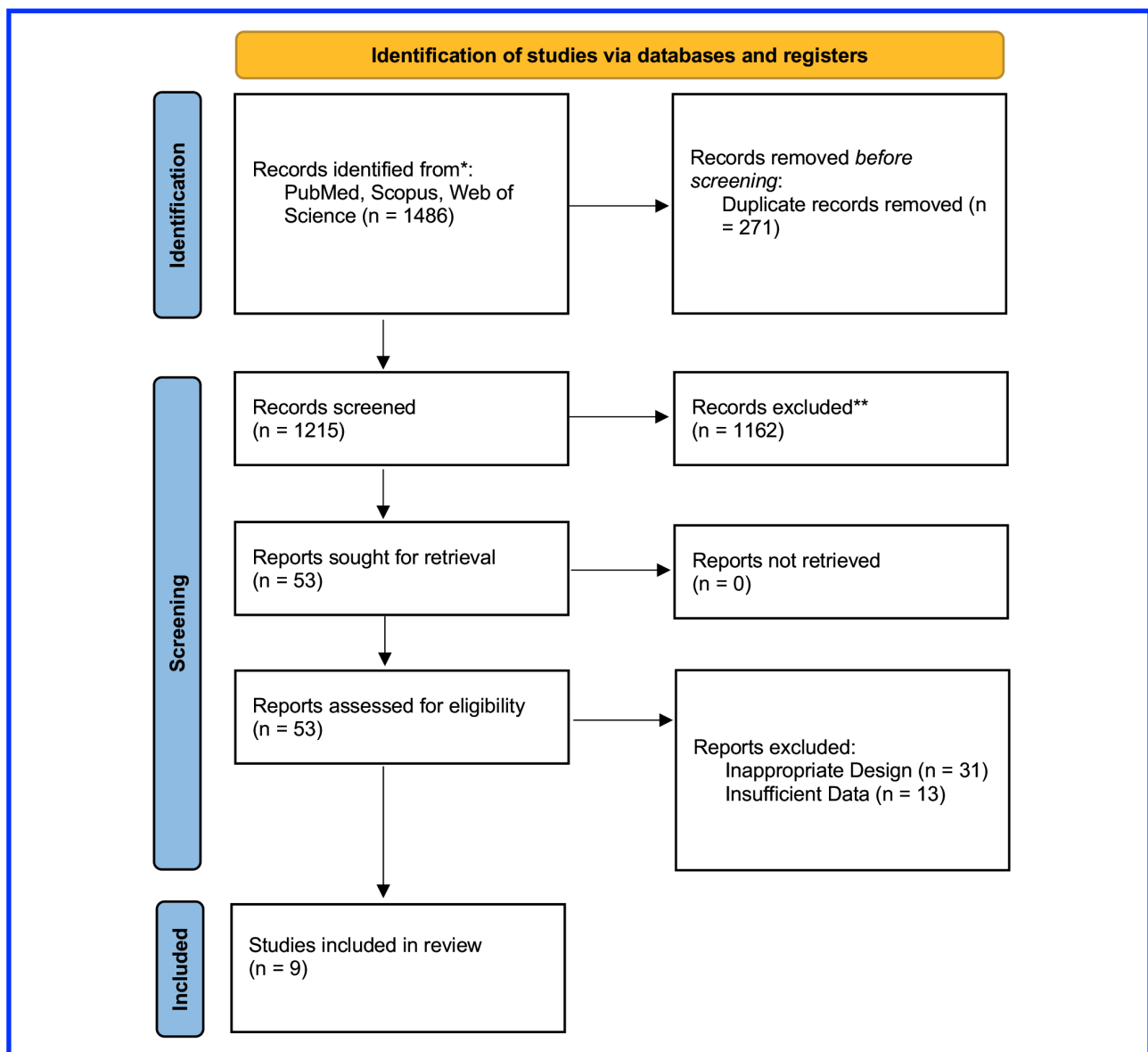


Figure 1. The PRISMA flow diagram of the included studies.

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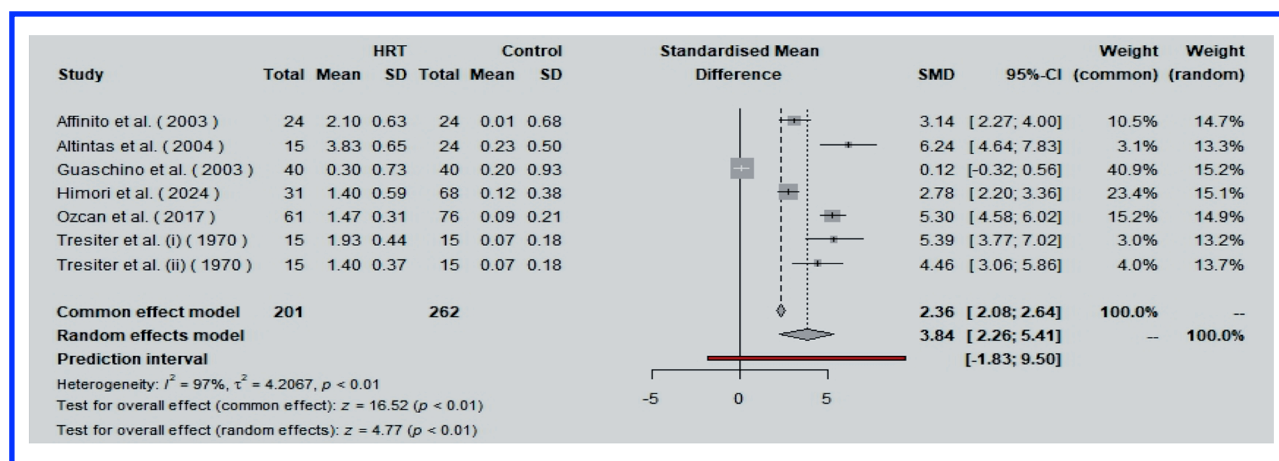


Figure 2. Forest plot of the pooled mean difference of IOP among those who received HRT and controls.

Table 1. Characteristics of the included studies.

Author	Year	Country	Design	Age	N	Dosage	Duration	Follow-up
Tresiter et al. (i) (31)	1970	Israel	RCT	37-55	45	estrogen preparation mestranol 0.1 mg/day	6 m	3 m
Tresiter et al. (ii) (31)	1970	Israel	RCT	37-55	45	1.0 mg of the progestin per day	6 m	3 m
Sator et al. (24)	1997	Austria	PCS	55.7	25	2 mg estradiol valerate 10 mg medroxyprogesterone acetate	3 m	3 m
Affinito et al. (25)	2003	Italy	RCT	53.7	48	estradiol 50 µg/day medroxyprogesterone acetate 10 mg/day	12 d per cycle	3-6 m
Guaschino et al. (26)	2003	Italy	PCS	60	80	conjugated estrogens 0.625 mg/day dydrogesterone 5 mg/day	1 y	1 y
Altintas et al. (27)	2004	Turkey	PCS	47.1	44	0.625 mg estrogen/day + 2.5 mg medroxiprogesterone acetate	2 m	2 m
Uncu et al. (28)	2006	Turkey	PCS	51.8	60	estrogen 0.625 mg medroxyprogesterone acetate 2.5 mg	1 y	6-12 m
Coksuer et al. (29)	2011	Turkey	PCS	51.8	34	DRSP 2 mg and E2 1 mg	6 m	6 m
Ozcan et al. (30)	2017	Turkey	PCS	50	137	1 mg estradio 12 mg drospirenon	6 m	6 m
Himori et al. (32)	2024	Japan	CCS	63-66	99	-	-	-

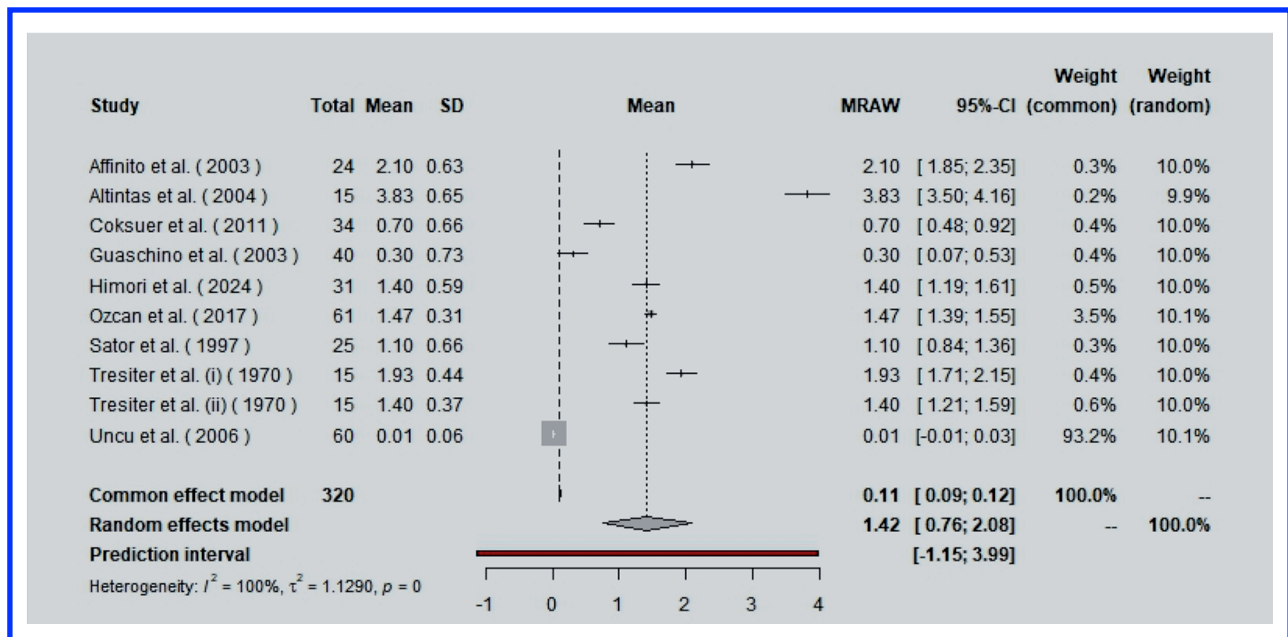


Figure 3. The pooled mean difference among those who received HRT.

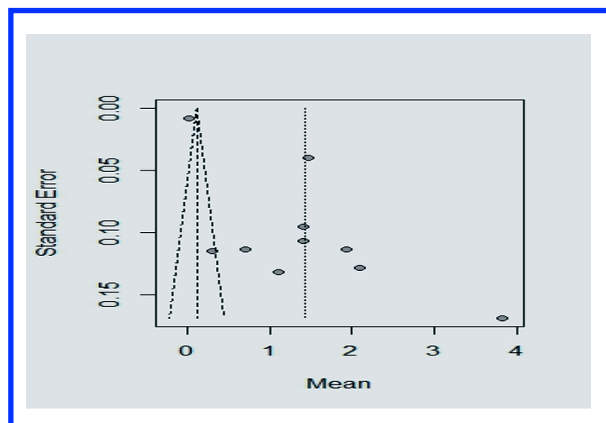


Figure 4. Funnel plot of pooled mean difference among those who received HRT.

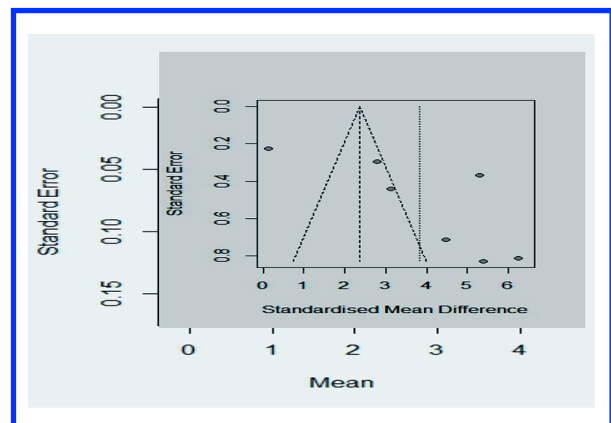


Figure 5. Funnel plot of pooled standardised mean difference among those who received HRT and controls.

Discussion

The aim of this study was to evaluate the effect of estrogen and progesterone therapy on Intraocular Pressure (IOP) in postmenopausal women through a systematic review and meta-analysis. Our findings demonstrated that Hormone Replacement Therapy (HRT) was associated with a significant decrease in IOP when compared to controls, as indicated by the pooled standardized mean differences. The random-effects model showed a substantial mean reduction in IOP, reflecting a consistent pattern across various studies, despite considerable heterogeneity. These results suggest that HRT may not only offer benefits for menopausal symptoms but also contribute to lowering IOP, potentially reduc-

ing the risk of developing or progressing glaucoma in susceptible individuals.

A previous meta-analysis study showed no significant overall reduction in IOP following HT, with a mean difference of 1.54 mmHg ($p=0.10$). This indicates that HT did not have a statistically significant effect on lowering IOP across the included studies. The study also highlighted considerable heterogeneity, suggesting that factors such as participant age, type of hormone therapy (estrogen-only versus combined therapy), and study quality may have contributed to the variability in results.³³ Comparing these findings to the results of our study, which showed a significant decrease in IOP among HRT users, suggests that the effects of hormone

therapy on IOP may be more nuanced and dependent on specific conditions. Our results align with some previous studies that found estrogen therapy could lower IOP, potentially due to its influence on enhancing aqueous humor outflow through its effects on the trabecular meshwork. However, the meta-analysis by Hao *et al.* (2020) did not confirm a significant reduction in IOP, possibly due to differences in study populations or variations in the duration and type of hormone therapy used. The discrepancies between the two meta-analyses underscore the complexity of hormone therapy's effects on ocular physiology. While our study demonstrated a statistically significant IOP reduction, other systematic reviews have shown mixed or non-significant results, highlighting the need for further research to delineate the factors that might enhance or mitigate the effectiveness of HT in lowering IOP. This may involve more tailored approaches to hormone therapy, considering variables such as the patient's age, menopausal status, and specific hormone regimen used.^{21,33,34}

In contrast, some individual studies have not found a significant association between HRT and IOP reduction. For instance, Sator *et al.* (1997) conducted a clinical study involving postmenopausal women using various forms of HRT and found no significant changes in IOP after a follow-up period. The study suggested that factors such as the type of estrogen used, dosage, and treatment duration could influence outcomes. Similarly, Altintas *et al.* (2004) reported no significant difference in IOP among women receiving HRT compared to a control group. The authors speculated that individual variations in hormone receptor sensitivity or pre-existing ocular conditions might account for the lack of effect observed in their cohort.^{27,35,36}

Conversely, some studies have corroborated the findings of the present meta-analysis, indicating a reduction in IOP with HRT use. Affinito *et al.* (2003) found that postmenopausal women undergoing estrogen therapy exhibited significantly lower IOP compared to those not receiving hormone therapy. This study suggested that estrogen replacement could potentially be beneficial in preventing glaucoma in women at risk due to its IOP-lowering effects. Similarly, Uncu *et al.* (2006) showed a decrease in IOP among HRT users, particularly those on long-term therapy. Ozcan *et al.* (2017) further supported these findings, demonstrating that continuous combined HRT was associated with a significant IOP reduction compared to baseline measurements, suggesting that the duration and regimen of HRT might play a critical role in achieving beneficial ocular outcomes.^{25,28,30}

Overall, while the literature presents mixed findings, there is a substantial body of evidence suggesting that HRT, especially with estrogen, can contribute to IOP reduction in postmenopausal women.^{37,38} The current study's findings align with those studies showing a decrease in IOP, reinforcing the hypothesis that hormone therapy may exert protective effects on ocular health. The variability across studies highlights the need for further research to identify specific patient populations or HRT protocols that yield the most consistent IOP-lowering benefits.^{15,39,40}

This study has several strengths, including a comprehensive search strategy following PRISMA guidelines, the use of

Randomized Controlled Trials (RCTs) to ensure robust evidence, and thorough analyses to account for variability. These factors enhance the reliability and generalizability of the findings. However, significant limitations include high heterogeneity across studies, potential publication bias, and the focus on postmenopausal women, which limits the applicability of the results to other populations. Additionally, variations in hormone therapy protocols, measurement methods, and clinical outcome definitions may impact the consistency and interpretation of the findings.

Conclusions

In conclusion, this systematic review and meta-analysis found that Hormone Replacement Therapy (HRT) in postmenopausal women is associated with a significant reduction in Intraocular Pressure (IOP), suggesting a potential protective role against glaucoma. The results align with some previous studies that reported IOP-lowering effects of estrogen, possibly due to its influence on ocular structures like the trabecular meshwork. However, the significant heterogeneity observed across studies highlights variability in HRT protocols, participant characteristics, and study methodologies, which may influence the consistency of findings. While these results support the consideration of HRT as part of ocular health management for postmenopausal women, further high-quality studies are needed to confirm these benefits and explore the optimal therapy regimens. Overall, individualized approaches based on patient characteristics and hormonal status may enhance the clinical utility of HRT in managing IOP and glaucoma risk.

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval

This is a review article and no need to ethical code. The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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