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**Mini-Review**

# The Impact of Testosterone Therapy on Cardiovascular Risk Among Postmenopausal Women

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## Abstract

**Purpose:** To summarize the current state of knowledge surrounding the impact of testosterone therapy on cardiovascular risk factors in postmenopausal women.

**Methodology:** In this scoping review, a comprehensive search of peer-reviewed literature was conducted in adherence to a methodological framework comprising 4 distinct stages: conceptualizing a comprehensive search strategy, screening relevant publications, extracting pertinent data, and organizing and synthesizing the resultant findings. The search used electronic databases, including MEDLINE, Embase, and Google Scholar, to ensure an exhaustive survey of the available literature.

**Results:** The database search yielded 150 articles, including systematic reviews, registered trials, and peer-reviewed studies, of which 48 duplicates were removed. Following the title/abstract screening, 36 publications were included in the full-text review. On completion of the full-text review, using the inclusion/exclusion criteria, 29 articles were excluded and 7 remained for data extraction and qualitative synthesis.

**Main Conclusion:** Existing research provides promising insights into the benefits of low-dose testosterone therapy, typically combined with estrogen therapy. These benefits may include positive impacts on body composition, functional capacity, insulin sensitivity, inflammatory markers, and cholesterol. However, there remains a substantial lack of knowledge surrounding the effects and mechanisms behind testosterone therapy in postmenopausal women in relation to its impacts on cardiovascular risk. High-quality, evidence-based clinical intervention research is needed to investigate testosterone therapy's potential implication on cardiovascular risk factors in post-menopausal women.

**Key Words:** testosterone therapy, estrogen therapy, post-menopause, women, cardiovascular risk factors

**Abbreviations:** CHF, coronary heart failure; CRF, cardiorespiratory fitness; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; RCT, randomized controlled trial; T/E, testosterone and estrogen therapy; VAT, visceral adipose tissue.

The cessation of menstrual periods and the initiation of the stages of menopause (perimenopause, menopause, and postmenopause) are associated with multiple symptoms, often related to menopausal-associated decreases in estrogen and androgen concentrations [1]. These symptoms include hot flashes, night sweats, insomnia, vaginal dystrophy, and mood changes that can be highly distressing, affecting a woman's personal, social, and professional life. Hormone therapy, specifically combined hormone therapy, is a therapeutic intervention capable of providing symptomatic relief and reducing the risk of chronic diseases that affect postmenopausal women such as osteoporosis [2]. The existing evidence of the effectiveness of combined hormone therapy in treating menopausal women has grown considerably over the past few decades and is recognized as a viable treatment strategy in women. In addition, because of declining levels of testosterone associated with menopause and aging, research into the potential effectiveness of testosterone therapy has been considered because of the declining testosterone concentrations associated with menopause. Current research examining the effects of testosterone therapy has predominantly focused on testosterone's ability to improve sexual desire and sexual function in women, proving to be an effective clinical intervention [3]. In contrast to the multiple studies regarding testosterone therapy in men [4], there appears to be a limited amount of research that has focused on the potential effects of testosterone therapy on cardiovascular risk among women. The increasing use of testosterone therapy in managing sexual dysfunction among postmenopausal women warrants an assessment of the potential impact of testosterone therapy on markers associated with cardiovascular risk. The use of testosterone therapy in the management of sexual function among postmenopausal women justifies a need to explore the conflicting findings of the cardiovascular effects of exogenous testosterone in postmenopausal women [3, 5, 6]. This scoping review aims to summarize the current state of knowledge surrounding the impact of testosterone therapy on cardiovascular risk factors in postmenopausal women.

## Materials and Methods

This scoping review was conducted between January 2023 and March 2023. The methodological framework and recommendations of this review were informed by Arksey and

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O'Malley [7], Levac et al [8], McGowan et al [9], Peters et al [10], and the PRISMA Extension for Scoping Reviews [11]. The methodological framework consisted of 4 steps. To begin, a search strategy was developed and implemented to find relevant publications pertaining to the concept, target population, and health outcomes of interest. Second, the relevant publications were screened and selected for further analysis using a developed inclusion and exclusion criteria. Third, the data were extracted from the selected publications, and last, the results were organized and summarized for further discussion. The objective of this scoping review was to summarize the relevant research in the area of testosterone therapy in postmenopausal women and its effects on cardiovascular risk markers. In maintaining the guidelines for scoping reviews, the collected publications were not systematically appraised [7].

The search strategy implemented in the scoping review utilized electronic databases, "Medline," "Web of Science," "Google Scholar," and "Embase." Using these databases, relevant key words pertaining to the concept, target population, and health outcomes of interest were used to execute a comprehensive search. In addition, reference searching was also used to locate peer-reviewed literature [10].

**Table 1. Ovid Medline search terms**

| |
|---|
| To encompass the term testosterone therapy |
| • "Testosterone," "Androgen," "Hormones," "Testosterone therapy," "Hormone replacement therapy," "Testosterone replacement," "androgen replacement therapy," "testosterone replacement therapy," [AND] |
| To encompass the term cardiovascular risk |
| • "Risk markers," "Cardiovascular risk markers" |
| • "Cardiovascular Disease," "Cardiovascular risk," "Insulin," "Cardiorespiratory," "Body composition," "Insulin," "Diabetes," "Risk factors," "Lipids," "Blood Glucose" [AND] |
| To encompass the term menopausal women |
| • Women," "Aged," "Menopausal," "Post menopausal" |

To ensure a comprehensive search was performed the Kinesiology and Health Studies librarian at Queen's University was consulted to aid in developing the search strategy. An example of our search terms used in the publication retrieval process can be found in Table 1 (see Fig. 1 for a complete electronic search strategy used in Ovid MEDLINE). Following the database search identifying the publications, 2 researchers independently screened the articles for relevance based on the title/abstract using the Covidence Online Software (https://www.covidence.org/). Publications were excluded if (1) full text was not available, (2) it was a secondary article, (3) if it was not related to testosterone or testosterone + estrogen therapy, (4) if it was not related to cardiovascular risk markers, and (5) if it did not include postmenopausal women. During the title/abstract screening, if it was unclear if the publication involved testosterone therapy in postmenopausal women, the article was included in the full-text review. The full-text review was performed by 2 researchers using the Covidence Online Software. When conflicts occurred within the full-text review, the reviewers met to discuss the challenges and uncertainties in the study selection and refined the search strategy to resolve the conflicts [8].

A data extraction chart was then developed to include relevant information pertaining to the effects of testosterone therapy or a combination of both testosterone + estrogen therapy (T/E therapy) on cardiovascular risk factors such as body composition, functional capacity, cholesterol, insulin resistance, and inflammatory markers. Through an iterative process, a researcher conducted an independent analysis to identify significant findings within the charted data. Each article was thoroughly examined, and the charted data and results were carefully analyzed to develop a directed and well-informed review of the articles included in this scoping review.

## Results

On completion of the search, a total of 150 articles were identified, 48 duplicates were removed, and 102 titles and abstracts were screened using the inclusion/exclusion criteria. Following the title/abstract screening, 36 articles were included in the

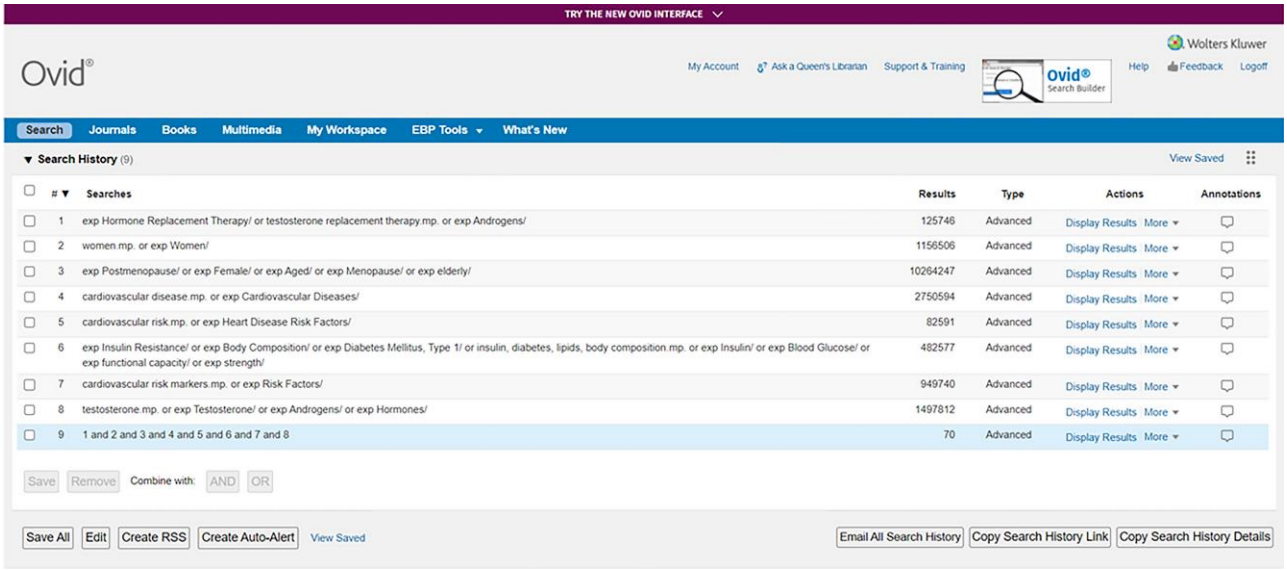


**Figure 1.** Electronic search strategy used in Ovid Medline.

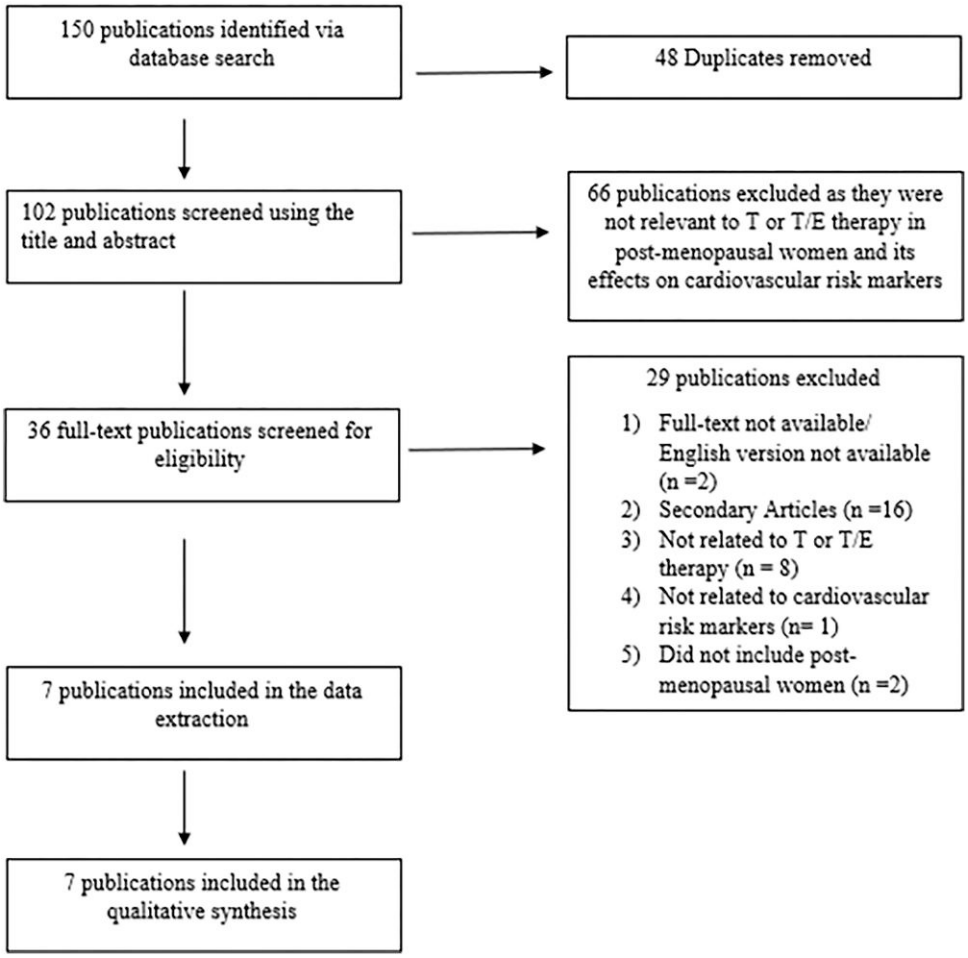


**Figure 2.** Flowchart representing the publication retrieval process, inclusion/exclusion criteria, and the articles included in the scoping review.

full-text review. Following the completion of the full-text review, using the inclusion/exclusion criteria, 29 articles were excluded and 7 were identified as relevant and were included in the data extraction and qualitative synthesis. A visual representation of the publication retrieval process and the inclusion/exclusion criteria are displayed in Fig. 2. The 7 articles included in the scoping review are summarized in Table 2. All studies included menopausal and postmenopausal participants and consisted of either oral, intramuscular, or transdermal testosterone administration. Four studies were double-blind randomized controlled trials, 2 were randomized controlled trials, and 1 was observational. Of the 7 studies included in the data extraction, 4 reported improvements in cardiovascular risk markers, which included improvements in functional capacity [12], ventilatory efficiency [12], muscle strength [12-14], cholesterol [13, 15, 16], inflammatory markers [16, 17], and lean body mass [13, 14, 16, 18]. Conversely, 4 of the 7 studies reported negative effects on high-density lipoprotein (HDL) cholesterol [14, 15, 17], visceral adipose tissue (VAT) [15], increased insulin resistance, and increased risk of cardiovascular disease (CVD) [12, 14].

## Discussion

There has been a growing interest in using hormone therapy, specifically testosterone and estrogen, to treat postmenopausal women [19]. To date, most literature regarding exogenous testosterone's impact on aging individual's cardiovascular health has focused primarily on men's health. Studies exploring the potential use of testosterone therapy for women are limited and have largely been inconclusive [19]. Despite a limited number of investigations examining the effects of estrogen and testosterone in women, a significant proportion of the studies concentrate on testosterone's effects on women's sexual and reproductive functions, and their libido, specifically testosterone's ability to treat hypoactive sexual desire disorder [20, 21]. Consequently, insufficient attention has been given to investigating the potential cardiovascular effects of exogenous testosterone in women. The available data regarding the potential cardiovascular effects of exogenous testosterone in women are limited.

In this scoping review, we identified 7 relevant studies addressing testosterone therapy in postmenopausal women and its impact on cardiovascular risk markers. The following discussion will highlight the main findings related to key cardiovascular risk markers on which testosterone and T/E therapy may have an effect, including body composition, functional capacity, insulin sensitivity, inflammatory markers, and cholesterol.

### Body Composition

Dobs et al [18], Zang et al [13], Iellamo et al [12], and Huang et al [14] all reported changes in body composition and

**Table 2. Summary of the relevant findings from the peer-reviewed literature**

| Author (s) | Intervention type | Population | Aim (s) | Method | Relevant findings |
|---|---|---|---|---|---|
| **Iellamo et al (2010)** | Double-blind RCT | 36 females (68.2 ± 6.85 y) | Evaluate impact of low-dose testosterone therapy on functional capacity, insulin resistance, and quadriceps muscle performance in elderly women with heart failure. | Random allocation to 1 of 2 trial groups to receive transdermal testosterone (0.3 mg Intrinsa, Procter and Gamble) patch or placebo 2 × per wk. Participants performed baseline testing and returned after 1, 3, and 6 mo for further testing. Total study duration of 6 mo. | Low-dose testosterone improved functional capacity, ventilatory efficiency, insulin sensitivity, and muscle strength. Findings are not confined to female patients with CHF and low baseline testosterone. Longer duration studies needed to determine long-term efficacy of testosterone therapy.<br>T group<br>(Baseline free T: 0.95 ± 0.4 pg/mL)<br>(Post free T: 2.2 ± 0.8 pg/mL)<br>Placebo group<br>(Baseline free T: 0.93 ± 0.2 pg/mL)<br>(After free T: 0.65 ± 0.3 pg/mL)<br>(No reported estradiol concentrations) |
| **Dobs et al (2002)** | Single -center, double-blind, randomized parallel group trial | 37 females (mean age, 57 y) | Compare and contrast estrogen therapy and combined therapy, estrogen + testosterone therapy, on body composition in postmenopausal women. | Participants randomly allocated to either orally receive 1.25 mg esterified estrogen (Estratab; Solvay pharmaceuticals) or 1.25 mg esterified estrogen + 2.5 mg methyltestosterone (Estratest [esterified estrogen + methyltestosterone tablets]; Ani Pharmaceuticals) daily for 16 wk. Participants were assessed at weeks 0, 4, 10, and 16. Bone density, anthropometric measures including body weight, skin fold, waist circumference, as well as strength were assessed. | Combined group experienced an increase in lean body mass, decrease in fat mass, and significant increase in upper and lower body strength. Additionally, both LDL and HDL cholesterol was reduced, below recommended levels in the combined group.<br>E group<br>(Baseline free T: 3.04 pg/mL)<br>(Post 16-wk free T: 2.5 pg/mL)<br>(Baseline total E: 326.14 pg/mL)<br>(Post 16-wk total E: 622.54 pg/mL)<br>T/E group<br>(Baseline free T: 2.8 pg/mL)<br>(Post 16-wk free T: 3.6 pg/mL)<br>(Baseline total E: 422.08 pg/mL)<br>(Post 16-wk total E: 348.92 pg/mL) |
| **Hak et al (2007)** | Observational Study | 513 females (aged 62.9 ± 5.7 y) | Examine association between high-dose estrogen-testosterone therapy and aortic atherosclerosis in postmenopausal women. | Self-reported questionnaires + structured interviews. Study duration of 3 years. Looking at estradiol (2-5 mg) and testosterone ester use (50 to 100 mg) mean follow-up of 8.9 y. | High-dose testosterone therapy may adversely affect atherosclerosis in postmenopausal women. Aortic atherosclerosis is associated with a 9-fold increase in risk of stroke and CVD mortality. Findings are not generalizable to low-dose TRT.<br>(No reported serum testosterone and estradiol levels) |

(*continued*)

**Table 2. Continued**

| Author (s) | Intervention type | Population | Aim (s) | Method | Relevant findings |
|---|---|---|---|---|---|
| **Zang et al (2006)** | Randomized clinical study, parallel group comparison | 63 females (aged 44-64 y) | Compare treatment effects of exogenous testosterone, estrogen, and testosterone + estrogen on body composition, lipids, and insulin sensitivities in postmenopausal women. | Three randomly assigned groups either received 40 mg testosterone undecanoate (Undestor; Organon, Oss, The Netherlands) every other day, 2 mg estradiol valerate (Trivina; Orion Pharma, Esbo, Finland) every day, or combination of both, every other day for a period of 3 mo. Testing was performed at baseline, 1, 2, and 3 mo after the start of the intervention. | Decreased insulin sensitivity in the testosterone and testosterone + estrogen group. However, no significant difference was seen among the 3 groups; thus, the decreased insulin sensitivity by testosterone is considered mild but longer treatment may produce a more pronounced effect. Found decreases in HDL cholesterol and no change in LDL cholesterol. Changes in lean body mass was seen among both the testosterone and combined group. A favorable effect was seen among the combined treatment on total cholesterol levels.<br>T group<br>(Baseline free T: 2.9 pg/mL)<br>(Post 3-mo free T: 6 pg/mL)<br>E group<br>(Baseline free T: 3.7 pg/mL]<br>(Post 3-mo free T: 2.1 pg/mL)<br>T/E group<br>(Baseline free T: 3.7 pg/mL)<br>(Post 3-mo free T: 4.2 pg/mL)<br>(No reported estradiol concentrations) |
| **Leao et al (2006)** | Randomized controlled trial, placebo controlled | 37 females (aged 42-62 y) | Assess the effects of androgen therapy on CVD risk factors in postmenopausal women. | Randomly allocated participants were to receive percutaneous estradiol (Estreva gel; Merck), 1 mg/day with either oral methyltestosterone (undisclosed brand/ manufacturer), 1.25 mg, or a placebo for 12 mo. Participants returned every 3 mo for clinical examination. Follow-up was terminated after the 12th month. | Found no detrimental effects on glucose metabolism, lipids, inflammatory markers, or blood pressure. Although the testosterone demonstrated mild adverse effects on HDL cholesterol and visceral fat.<br>(No reported serum testosterone and estradiol concentrations) |

(*continued*)

**Table 2. Continued**

| Author (s) | Intervention type | Population | Aim (s) | Method | Relevant findings |
|---|---|---|---|---|---|
| **Kocoska-Maras et al (2009)** | Double-blind, placebo-controlled study | 44 females (mean age 54 ± 2.9 y) | Report data on the effect exogenous testosterone added to estrogen therapy and the inflammatory markers associated with CVD. | Two randomized groups received either 2 mg oral estradiol valerate + 40 mg oral testosterone undecanoate daily or 2 mg oral estradiol valerate + placebo (undisclosed brand/manufacturer). Treatment given for 24 wk and then participants switched treatments for another 24 wk. Blood samples collected at baseline, 24, and 48 wk. | Found that exogenous testosterone in addition to estrogen treatment in postmenopausal women has positive effects on inflammatory markers associated with cardiovascular disease and no apparent adverse effects. The effect of testosterone to reduce inflammatory markers associated with CVD interpreted as clearly beneficial.<br>T/E Group<br>(Baseline free T: 4 ± 2 pg/mL)<br>(Post 24-wk free T: 23 ± 18 pg/mL)<br>(Baseline E: < 21 pg/mL)<br>(Post 24-wk E: 50 ± 29 pg/mL)<br>P/E Group<br>(Baseline free T: 4 ± 2 pg/mL)<br>(Post 24-wk free T: 3 ± 2 pg/mL)<br>(Baseline total E: < 21 pg/mL)<br>(Post 24-wk total E: 71 ± 44 pg/mL) |
| **Huang et al (2014)** | Multicenter, parallel group, placebo-controlled, double blind RCT | 62 females (mean age. 53 y) | Evaluate dose-response relationships of low serum testosterone with measures of body composition and physical function in surgically induced menopausal women. | Participants randomized to 1 of 5 groups to receive weekly intramuscular injections of 3, 6.25, 12.5, or 25 mg testosterone enanthate (ENDO pharmaceuticals, Malvern, PA) or placebo for 24 wk. | Gains in lean body mass (LBM) in 25 mg group averaged 1.8 kg and estimated between person difference was 0.6 kg per 100 ng/dL change in free testosterone concentrations. Increases in chest press power, loaded stair climb power with changes in free testosterone. Claimed unlikely that changes in physical measures would be seen raising testosterone levels from low to physiological range.<br>(Baseline mean free T: 2.2 pg/mL)<br>Placebo group<br>(Post 24-wk free T: ≈ 2.5pg/mL)<br>3 mg/wk Group<br>(Post 24-wk free T: ≈12 pg/mL)<br>6.25 mg/wk Group<br>(Post 24-wk free T: ≈16 pg/mL]<br>12.5 mg/wk Group<br>(Post 24-wk free T: ≈ 22 pg/mL)<br>25 mg/wk Group<br>(Post 24-wk free T: ≈ 36 pg/mL)<br>(No reported estradiol concentrations) |

Abbreviations: CHF, coronary heart failure; CVD, cardiovascular disease; E, estrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCT, randomized controlled trial; T, testosterone; T/E, testosterone and estrogen therapy; TRT, testosterone replacement therapy.

physical functioning, including increases in lean body mass, decreases in fat mass, and improvements in muscle strength. Despite differences in age of participants, methods, and dosages of testosterone, improvements in lean body mass, decreases in fat mass and improvements in strength were universal among the testosterone-treated groups. However, in a sample of 37 postmenopausal women (aged 42-62 years), Leao et al [16]. found that participants randomly allocated to the T/E group (1 mg/day percutaneous estradiol and 1.25 mg/day oral methyltestosterone) experienced an accumulation of VAT, determined by computed tomography (CT), despite overall abdominal fat mass decreases. It is worth noting that Dobs et al [18], Zang et al [13], and Huang et al [22] used dual-energy X-ray absorptiometry to assess changes in body composition, which is not as effective as CT, the gold standard, in detecting differences in subcutaneous adipose tissue and VAT. Furthermore, VAT, independent of subcutaneous adipose tissue, is strongly related to cardiometabolic risk factors and the prevalence of CVD [23, 24]. Therefore, the improvements in body composition measured by dual-energy X-ray absorptiometry may not represent a change in VAT, an independent risk factor for cardiometabolic risk and CVD [23, 24]. Additional studies are needed to determine whether testosterone's effect on body composition represents a mechanism to reduce cardiometabolic and cardiovascular risk by examining changes in VAT following testosterone intervention.

## Functional Capacity

In 2010, Iellamo et al [12]. reported promising results regarding cardiorespiratory fitness (CRF), peak oxygen consumption, in 36 postmenopausal participants (mean age, 68.2 years) diagnosed with coronary heart failure (CHF) following a low-dose (0.3 mg 2×/week) transdermal testosterone intervention. CRF was assessed through a 6-minute walking test and a cardiopulmonary exercise test at baseline and after the 6-month intervention. Additionally, participants returned for follow-up study visits at 1, 3, and 6 months after baseline testing. The increase in CRF following a 6-month intervention of low-dose testosterone is notable because of the well-established evidence of the association between CRF, indicated by peak oxygen consumption, and cardiovascular risk.

In a 2016 scientific statement, Ross et al [25] established that an increasing amount of epidemiological and clinical evidence demonstrates that low levels of CRF are associated with a high risk of CVD, all-cause mortality, and various cancers [25]. Additionally, CRF represents a potentially stronger predictor of mortality than risk factors such as smoking, hypertension, high cholesterol, and type 2 diabetes mellitus [25, 26].

Of the 7 studies included in this scoping review, the study by Iellamo et al was the only one to assess cardiorespiratory changes following testosterone therapy [12]. Additionally, the established findings of the study were discussed in relation to the already established evidence indicating the adverse prognostic role of low CRF in CHF patients rather than directly assessing cardiovascular health. Moreover, the small sample size (n = 36) and short duration of the study (6 months) limits the validity and generalizability of the positive effect testosterone therapy may have on CRF [12]. Therefore, further studies and exploration into the effect of testosterone on CRF, using larger sample sizes, longer periods of study, and the direct assessment of cardiovascular risk markers in postmenopausal women are needed to validate these findings.

## Insulin Sensitivity

It is well-established that decreased insulin sensitivity and its biological effects are significant factors in inducing cardiometabolic complications and thus increases in cardiovascular risk [27]. Insulin resistance, even in the absence of a diagnosis of diabetes, can predispose individuals to an increased risk of CVD [27-30]. Iellamo et al [12]. conducted a randomized controlled trial (RCT) over a 6-month period, which found that a low dose of testosterone (0.3 mg), administered through transdermal patches twice per week, improved insulin sensitivity. However, Iellamo et al [12] did not directly explain the mechanism through which testosterone would improve insulin sensitivity [12]. Nevertheless, testosterone-induced improvements in insulin sensitivity may represent a means of reducing cardiovascular risk.

In contrast, a 2009 RCT performed by Zang et al [13], using a high dose of oral testosterone undecanoate (40 mg) every other day over 3 months within a participant population of 63 naturally postmenopausal women (aged 44-64 years), showed mild increases in insulin resistance. Similarly, Hak et al [15] found during follow-up (mean, 8.9 years) that IM administered high-dose testosterone therapy (50-100 mg) over a 1-year period in 513 naturally postmenopausal women (mean age, 62.9 years) resulted in adverse effects on glucose metabolism, possibly indicating increases in insulin resistance. The opposing findings between Iellamo et al [12] and Zang et al [13] regarding exogenous testosterone's effect on insulin sensitivity demonstrates one of the discrepancies among the existing literature on the topic. It is worth noting that the large differences in testosterone dosage among the studies could be responsible for the effect of testosterone on insulin. However, further studies are needed to explore this relation and the mechanism behind testosterone's effect on insulin sensitivity, as it is not clearly understood.

## Inflammatory Markers

Leao et al [16] demonstrated that orally administered methyltestosterone (1.25 mg/day), when paired with percutaneous estradiol (1 mg/day) in a group of 37 women (aged 42-62 years), had a neutral effect on C-reactive protein (CRP) levels following a 12-month intervention. However, both estrogen + testosterone and estrogen + placebo groups showed a significant decline in plasma fibrinogen levels, indicating an estrogenic effect on the latter parameter, which was preserved in those treated with testosterone [16]. In addition, Kocoska-Maras et al [17] conducted a 48-week study using a combination of oral testosterone undecanoate (40 mg/day) and oral estradiol valerate (2 mg/day). Their findings suggest a modest influence on inflammatory markers with no apparent adverse effects. Notably, increased fibrinogen and CRP has been identified as an independent CVD risk factor and is associated with traditional cardiovascular risk factors [31, 32]. Therefore, based on the Leao et al [16] and Kocoska-Maras et al [17] studies, testosterone + estrogen treatment may provide potential improvements in cardiovascular risk through declines in CRP and plasma fibrinogen levels.

Additionally, previous reports have shown that estrogen therapy alone can increase high-sensitivity C-reactive protein (hsCRP) levels [31-34]. Minor increases in hsCRP have been linked to an increased risk of CVD [33, 34]. Kocoska-Maras et al [17] identified a suppressive effect of testosterone on estrogen-induced hsCRP increase. Therefore, as indicated by

Kocoska-Maras et al [17], the use of exogenous testosterone in combination with estrogen therapy could be beneficial in reversing the estrogenic increases in hsCRP back to baseline. Overall, further studies are required to explore testosterone's effect on cardiovascular risk through influencing CRP levels, plasma fibrinogen levels, and its ability to reverse estrogenic increases in hsCRP.

### Cholesterol

Zang et al [13] discovered that treatment with testosterone undecanoate (40 mg) alone significantly decreased HDL cholesterol, whereas low-density lipoprotein (LDL) cholesterol remained unchanged. Conversely, combined treatment (40 mg testosterone undecanoate and 2 mg estradiol valerate) significantly decreased total and LDL cholesterol, but no change in HDL cholesterol was observed [13]. The results of Leao et al [16] and Dobs et al [18] also revealed that the combined treatment significantly reduced total and LDL cholesterol but caused unfavorable decreases in HDL cholesterol. According to Dobs et al [18] and Leao et al [16], the unfavorable decrease in HDL cholesterol was most likely induced by the testosterone within the combined treatment group because the estrogen treatment group did not experience a significant effect on HDL cholesterol.

Hak et al [15] found that the correlation between high-dose testosterone therapy and atherosclerosis decreased after adjusting for cholesterol levels. These findings represent exogenous testosterone's negative effect on an individual's lipid profile; however, Hak et al [15] found that the correlation between high-dose testosterone therapy may not be generalizable to low-dose therapy. Overall, Zang et al [13] found a significant decrease in HDL cholesterol in the testosterone group and Hak et al's [15] correlation between changes in cholesterol and atherogenic effects following high-dose testosterone therapy may confirm testosterone's unfavorable effect on cholesterol levels.

It is widely acknowledged that low HDL and high LDL cholesterol levels are associated with an increased risk of CVD [35-39]. The current literature appears to support the findings that testosterone in combination with estrogen may decrease LDL cholesterol; however, the effects on HDL cholesterol are unclear. Moreover, Hak et al [15] and Zang et al [13] found that high testosterone doses led to unfavorable impacts on cholesterol concentrations. Testosterone's unfavorable effect on cholesterol could imply that high-dose testosterone therapy has a negative effect on an individual's lipid profile and, as a result, their cardiovascular health. Overall, our existing knowledge of the ability of testosterone therapy and T/E therapy to reduce cardiovascular risk through changes in cholesterol levels is lacking. Therefore, further research is needed to investigate the effects of testosterone on both LDL and HDL cholesterol and the potential cardiovascular risk.

## Gaps and Future Directions

This scoping review identified 7 primary studies that address testosterone therapy and T/E therapy in postmenopausal women and their impact on cardiovascular risk. However, the diverse findings across the literature highlight the current knowledge gaps that exist regarding the use of testosterone treatment in postmenopausal women. It is important to acknowledge that testosterone, whether administered independently or in conjunction with estrogen, can be metabolized to estradiol within peripheral tissues [40]. As a result, the effects of testosterone cannot be entirely separated from estrogen in any of the included studies. Therefore, further research is needed to validate and explore findings surrounding the favorable and unfavorable effects of testosterone therapy and T/E therapy on cardiovascular risk markers such as body composition, cholesterol, insulin sensitivity, functional capacity, and inflammatory markers.

One area that requires further exploration is changes in body composition [12-14, 18]. Findings in this area should be further explored using CT or other valid methods to measure changes in VAT. Changes in VAT are important because of its independent association with cardiovascular and cardiometabolic risk [23, 24]. Additionally, there is a clear gap in our knowledge and understanding related to the effects of T/E therapy on improvements in cholesterol and insulin sensitivity [12, 13, 16, 18]. Both cholesterol and insulin sensitivity play important roles in cardiovascular and cardiometabolic health, as previously discussed, so it is crucial that future research investigates the mechanism and effect of T/E therapy on these risk markers [27-30, 35-39].

Furthermore, given the promising findings pertaining to the potential effect of T/E therapy to improve CRF, decrease estrogenic-induced increases in hsCRP, and reduce CRP and fibrinogen levels, studies validating the effect of T/E therapy on these cardiovascular risk markers are warranted. Moreover, it is crucial to conduct studies that directly compare the efficacy of different forms of testosterone and estrogen, compare different routes of administration, and establish optimal dosing protocols to deepen our understanding of the impact of T/E therapy on cardiovascular risk markers. In summary, more research is required to fully understand testosterone therapy and T/E therapy on cardiovascular risk markers in postmenopausal women, and specific mechanisms by which they work.

## Limitations

Given that the aim of a scoping review is to present the current findings and evidence within a particular topic, rather than to assess the depth and quality of the evidence, it has inherent limitations [7, 8]. Despite providing insight regarding the current state of knowledge about the use of testosterone therapy in postmenopausal women, this scoping review has several limitations that should be considered when interpreting the findings.

First, this scoping review does not incorporate a methodological quality assessment of the 7 articles that are included. Second, the varying intervention protocols among the included studies, particularly the differing doses of estrogen and testosterone, make it challenging to compare findings across studies. Third, the exclusion criteria of this scoping review was highly constraining as well as 2 studies being excluded because of the inability to access full-text versions or English versions of the publication. Therefore, this omission may have resulted in missing information regarding the ability of testosterone therapy to impact cardiovascular risk. Last, the manual search of the "Google Scholar" database and the inability to explore all literature within the search negatively effects the uniformity and replicability of this scoping review.

## Conclusions

This scoping review aimed to provide a concise overview of the current state of knowledge concerning the utilization of testosterone therapy in postmenopausal women and the resulting impact on their cardiovascular risk profile. Overall, there remains a substantial lack of knowledge about testosterone therapy's effects and mechanisms in postmenopausal women. However, from the articles included in this scoping review, we can gather that exogenous testosterone in combination with estrogen may offer a promising method of improving postmenopausal women's cardiovascular risk profile through a multitude of mechanisms. Such mechanisms possibly include improvements in body composition, functional capacity, insulin sensitivity, inflammatory markers, and cholesterol.

Conversely, the findings may indicate that if taken in large doses, testosterone, taken alone or in combination with estrogen, may negatively impact cholesterol levels and insulin sensitivity, possibly leading to atherosclerosis and thus increased cardiovascular risk. Future RCT studies should prioritize the comparison of different dosages of testosterone to better understand its effect on cardiovascular risk markers.

Overall, the limited number of primary studies with diverse findings suggest that future investigations into potential mechanisms responsible for the effects of testosterone therapy on cardiovascular health in post-menopausal women are warranted.

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## Disclosures

The authors have nothing to disclose.

## Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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