

International Journal of Health Science

Acceptance date: 21/01/2025

USE OF HORMONAL THERAPIES AND IMPACT ON THE CARDIOVASCULAR SYSTEM

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Abstract: One of the areas of great scientific interest is research into the effects of hormone therapy on the cardiovascular system, given its potential influence on the health of the heart and blood vessels. In view of this, the aim of this study is to develop a study on what types of diseases can be caused by electronic cigarettes and how they can trigger health problems. The methodology used in the study was a literature review, based on books and scientific articles from various areas on the subject. As a result, the use of hormonal therapies has a significant impact on the cardiovascular system, and is a subject that has been widely studied and debated in the medical literature. The analysis of the benefits and risks associated with these therapies shows that the time of initiation, the dosage, the route of administration and the patient's clinical profile are determining factors for the safety and efficacy of the treatment. In conclusion, the use of hormonal therapies in the cardiovascular context should be approached individually, with a careful analysis of the risks and benefits, with the aim of maximizing therapeutic results and minimizing potential adverse effects. The clinical decision must always take into account the specific characteristics of the patient and the most up-to-date scientific data, guaranteeing safe and effective treatment.

Keywords: hormonal therapies. Cardiovascular system. Hormones. Estrogen

INTRODUCTION

Hormone therapy is widely used in women to relieve symptoms associated with the menopause, such as hot flushes, night sweats and sleep disorders, as well as being used in other clinical conditions, such as hormone replacement for patients with hormone deficiency (Costa *et al.*, 2024).

One of the areas of great scientific interest is the investigation of the effects of hormone therapy on the cardiovascular system,

given its potential influence on the health of the heart and blood vessels, since according to Ferreira *et al.* (2022), the impact of this use on the cardiovascular system has generated debate, since although there is evidence indicating benefits, there are also concerns about the risks, especially in women with a history of cardiovascular disease.

According to Costa *et al.* (2023), the relationship between hormone therapy and cardiovascular health is complex, since various factors, such as the form of administration of hormone therapy (oral, transdermal, etc.), the dosage and the timing of the start of therapy, can affect the cardiovascular response.

Given this, postmenopausal women face an increased cardiovascular risk due to the reduction in estrogen levels, which can negatively affect vascular function and increase predisposition to conditions such as hypertension, atherosclerosis and myocardial infarction (Maciel *et al.*, 2021).

Studies show that estrogen has a protective effect on blood vessel walls, improving endothelial function, reducing inflammation and favoring vessel dilation (Ferreira *et al.*, 2022; Maciel *et al.*, 2021).

This effect can result in a reduced risk of atherosclerosis, a condition characterized by the accumulation of fatty plaques in the arteries, which is one of the main causes of heart disease. However, hormone therapy can also have adverse effects, such as an increased risk of thrombosis, especially in women who start treatment after the menopause (Oliveira *et al.*, 2022).

Although hormone therapy can bring cardiovascular benefits, it is also associated with risks, especially when used inappropriately. Prolonged use of hormone therapy, especially in women with a history of heart disease, can increase the risk of myocardial infarction, stroke and deep vein thrombosis. In addition, the type of therapy (estrogen alone versus com-

bination with progestogen) and the route of administration (oral versus transdermal) significantly influence these risks (Kalil *et al.*, 2024).

In view of this, the work has the following problem: how can the use hormonal therapies impact on the cardiovascular system?

This research is therefore justified by the relevance of the subject, since the use of these therapies in the cardiovascular context is a complex issue that requires a careful and individualized approach. Although there is evidence that hormone therapy can bring benefits in preserving vascular function and reducing cardiovascular risks in post-menopausal women, the risks of complications such as heart attacks and strokes cannot be ignored.

Therefore, this study aims to develop a study on the use of hormonal therapies and their impact on the cardiovascular system.

METHODOLOGY

The work was a literature review, which according to Gil (2017) can be carried out as part of different types of academic studies, such as course completion papers, dissertations, theses, scientific articles and research projects. It is essential to contextualize the research, provide a theoretical basis for arguments and provide a comprehensive overview of the current state of knowledge on the topic in question.

To ensure the relevance and quality of the information collected, the following inclusion criteria were established: Original articles, systematic reviews and meta-analyses; studies that specifically address the use of hormonal therapies (such as hormone replacement therapies, contraceptives and other hormonal treatments) and research that analyzes impacts on the cardiovascular system, including effects on blood pressure, endothelial function, incidence of cardiovascular diseases and other relevant markers, as well as publications in English, Portuguese or Spanish.

Exclusion criteria were: studies focusing exclusively on animals or laboratory models; articles whose main theme is not related to cardiovascular impact and abstracts of conferences and dissertations not published in scientific journals.

The search was carried out in the following databases: *PubMed*; *Scielo* (*Scientific Electronic Library Online*) and *Lilacs* (Latin American and Caribbean Health Sciences Literature). The descriptors used in the search were selected based on the Health Sciences Descriptors (*DeCS*) and *Medical Subject Headings* (*MeSH*), combined with Boolean operators.

The Boolean operators AND and OR were used to optimize the searches. The AND operator was used to combine terms and refine the results, ensuring that the studies addressed multiple aspects simultaneously. For example: “*Hormone Therapy*” AND “*Cardiovascular System*”; “*Hormone Replacement Therapy*” AND “*Heart Disease*”; “*Contraceptives*” AND “*Cardiovascular Risk*” and “*Estrogen*” OR “*Progesterone*” AND “*Blood Pressure*”

The articles were selected in three stages: reading the titles, i.e. excluding irrelevant or duplicate studies; reading the abstracts referring to the Preliminary Analysis to check suitability for the inclusion criteria and full reading, i.e. detailed evaluation of the texts for inclusion in the review.

Therefore, the discussion was structured based on the defined objectives, relating the findings of the literature to current practices and proposing avenues for future research, totaling 12 articles.

RESULTS AND DISCUSSIONS

Throughout the articles analyzed, the influence of hormonal therapies and their impact on the cardiovascular system was observed, as in the study by Feldt-Rasmussen *et al.* (2024), which addressed the risks related to thyroid hormone replacement at different ages. The research highlights that both insufficient and excessive thyroid hormone replacement can increase cardiovascular risks in patients with hypothyroidism, and in young adults, inadequate levels of replacement are associated with a greater likelihood of cardiac dysfunction and adverse cardiovascular events.

In older adults, however, over-replacement can result in complications such as atrial fibrillation and heart failure. The study highlighted the importance of carefully monitoring TSH levels and adjusting the dose of levothyroxine as necessary, with the aim of reducing cardiovascular risks. This attention is especially crucial in elderly patients, who are more vulnerable to adverse effects due to the variability in their response to treatment (Feldt-Rasmussen *et al.*, 2024).

While the randomized clinical trial by Gencer *et al.* (2020) investigated the effects of levothyroxine on cardiac function in elderly people with mild subclinical hypothyroidism. The study included 638 participants, with an average age of 74, divided into two groups: one treated with levothyroxine and the other with placebo.

The main objective of the study was to assess whether the use of levothyroxine could improve cardiac function, as measured by left ventricular ejection fraction, a key indicator of cardiac performance. The results showed that treatment with levothyroxine did not provide significant improvements in cardiac function compared to the placebo group, and no differences were observed in other parameters such as left ventricular size or the occurrence of adverse cardiovascular events (Gencer *et al.*, 2020).

The study also suggests that in elderly people with mild subclinical hypothyroidism, thyroid hormone replacement may not be necessary to improve cardiac function, as the expected cardiovascular benefits were not observed (Gencer *et al.*, 2020).

In turn, the study by Montagner *et al.* (2024) evaluated the cardio-vascular impacts of levothyroxine use in an elderly population in the United Kingdom, by means of a cohort study combined with the emulation of a clinical trial. The aim was to determine whether levothyroxine, widely used in the treatment of hypothyroidism, influences cardiovascular events in older patients.

The study used a cohort approach to analyze health data from elderly people taking levothyroxine and used clinical trial emulation to reproduce the conditions of a randomized trial, providing more reliable estimates of cardiovascular effects. The analysis included variables related to cardiovascular events and cardiac function parameters, allowing for a more detailed assessment of the potential impacts of treatment.

The researchers found that the use of levothyroxine was not significantly associated with an increased or reduced risk of serious cardiovascular events in the population analyzed, but they did identify variations in the results depending on individual characteristics and comorbidities (Montagner *et al.*, 2024). Thus, these findings indicate that, for the majority of elderly people, the use of levothyroxine is unlikely to have a significant adverse impact on cardiovascular health.

A systematic review and meta-analysis by Holley *et al.* (2024) investigated the effects of levothyroxine treatment in elderly people with subclinical hypothyroidism, focusing on outcomes related to cardiovascular and health. The review included studies that assessed cardiac events, blood pressure, bone mineral density and fracture risk.

The results indicated that treatment with levothyroxine had no significant impact on the cardiovascular health of these patients, nor were there any significant reductions in the risk of serious cardiovascular events or improvements in blood pressure. With regard to bone health, the analysis also did not identify conclusive evidence that levothyroxine substantially affects bone mineral density or the risk of fractures in elderly people with subclinical hypothyroidism (Holley *et al.*, 2024).

The study conducted by Wang *et al.* (2022) consisted of a systematic review and meta-analysis that assessed the effects of levothyroxine supplementation on cardiac morphology and function in patients with subclinical hypothyroidism. The aim was to identify whether treatment with levothyroxine could improve parameters related to cardiac performance in these individuals, analyzing data on changes in cardiac measurements such as ventricular wall thickness, the size of cardiac cavities and left ventricular ejection fraction.

The research also considered the variability of results between the included studies and the overall impact of levothyroxine therapy. The findings indicated that levothyroxine supplementation had positive effects on cardiac function, with significant improvements in left ventricular ejection fraction and ventricular wall thickness. However, the results related to changes cardiac morphology, such as the size of cardiac cavities, were less consistent (Wang *et al.*, 2022).

The authors also noted the evidence that treatment with levothyroxine can improve diastolic function and increase the overall efficiency of the heart, although the results varied between the studies analyzed. Thus, the study concluded that levothyroxine can bring benefits to cardiac function in patients with subclinical hypothyroidism, especially in relation to ejection fraction and diastolic function (Wang *et al.*, 2022).

Zijlstra *et al.* (2021) performed a combined data analysis of two randomized clinical trials examining the impact of levothyroxine treatment on cardiovascular outcomes in elderly people with subclinical hypothyroidism, which according to the authors included major cardiovascular events such as myocardial infarction, stroke and death as primary outcomes.

The evaluation also took into account aspects such as the dose of levothyroxine, the length of treatment and TSH levels. The findings indicated that treatment with levothyroxine did not lead to a significant reduction in the occurrence of cardiovascular events compared to placebo, showing that there is no evidence that levothyroxine reduces the risk of heart attack, stroke or death from cardiovascular causes (Wang *et al.*, 2022).

The evaluation also pointed out that the effectiveness of levothyroxine in preventing cardiovascular events was limited, and the impacts of the treatment were not uniform among all the participants. The study concluded that, for elderly people with subclinical hypothyroidism, treatment with levothyroxine may not bring advantages in reducing cardiovascular events, which highlights the importance of a more comprehensive approach when analyzing the use of this substance in the prevention of cardiovascular diseases in patients with subclinical hypothyroidism (Wang *et al.*, 2022).

According to Costa *et al.* (2023), observational research conducted in the 1990s indicated the advantages of hormone replacement therapy in reducing

However, more recent clinical studies have shown controversial results, highlighting dangers such as an increase in the incidence of breast cancer.

The explanation for these discrepancies is based on the “timing hypothesis”, which proposes that the benefits of hormone replacement therapy depend on when it is started,

and that it is most effective when implemented soon after the menopause. Some studies and clinical trials support the idea that estrogen may not have a significant impact on the progression of established atherosclerotic plaques, but may reduce the progression of sub-clinical atherosclerosis in healthy endothelia, which suggests that HRT is more effective in preserving the health of the vascular endothelium than in treating atherosclerosis that has already developed (Costa *et al.*, 2023).

It is worth emphasizing that the age at which hormone therapy is started plays a crucial role in reducing cardiovascular risk, highlighting the importance of starting therapy at the appropriate time. However, the use of these therapies is not recommended for the primary or secondary prevention of cardiovascular disease, especially in women at high risk or with already diagnosed coronary artery disease (Costa *et al.*, 2023).

Future research is needed to explore specific aspects of HRT, such as optimal dosages, forms of administration and duration of treatment, as there are still gaps in knowledge. The decision to prescribe HRT should be personalized, taking into account individual benefits and risks, with an emphasis on carefully assessing each patient's cardiovascular risk (Costa *et al.*, 2023).

Still on the subject, Galvão (2024) found that stanozolol and testosterone pionate are the most common anabolic androgenic steroids (AASs), with average use ranging from 6 months to 5.73 years, and in relation to the effects, there are differences in the results on the effect on pressure. However, it is important to note that the data indicating an increase in BP is transient and does not result in significant clinical hypertension. It should be noted that this study showed that the use of EAAs affects left ventricular mass, resulting in hypertrophy (Galvão, 2024).

The research examined revealed that the use of Anabolic Androgenic Steroids is linked to impacts on the cardiovascular system, particularly Left Ventricular Hypertrophy, highlighting the damage that these substances do to the cardiovascular system.

can cause to health is crucial to support the creation of public policies focused on the prevention of illnesses and the promotion of the health of users of AES (Galvão, 2024).

It should be noted that estrogen is known to regulate vascular function by interacting with receptors on endothelial cells and vascular smooth muscle, resulting in the release of nitric oxide and prostacyclins, both of which are vasodilating agents (Carbonel *et al.*, 2020).

Clinical and experimental research indicates that estrogen controls vascular tone, promoting vasodilation, preventing vascular remodeling, impeding the development of vascular smooth muscle cells, interrupting the vascular response to injury, blocking the renin-angiotensin-aldosterone system, inhibiting endothelin, protecting the kidneys, reducing initial sympathetic tone and increasing the bioavailability of nitric oxide.

On the other hand, a lack of oestrogen can lead to hypertension in menopause, due to a collapse of the circulatory system, insufficiency of vasodilating ovarian hormones that occurs simultaneously with the appearance of atherogenic factors, metabolic syndrome and salt hypersensitivity (Sabbatini; Kararigas, 2020; Maciel *et al.*, 2021).

According to various analyses, estrogen plays a protective role in the development of hypertension and target organ damage, exerting various modulating effects. The reduction in estrogen causes changes in the regulation of the sympathetic nervous system, renin-angiotensin-aldosterone system, body mass, oxidative stress, endothelial function and salt sensitivity. These factors are linked to a crucial inflammatory condition and are influenced by genetic factors, causing cardiac, vascular and renal damage in humans.

pertension (Sabbatini; Kararigas, 2020).

Oral estrogen, used in oral contraceptives and menopausal hormone replacement therapy, presents risks mainly due to first-pass metabolism by the liver, which increases the production of coagulation factors and inflammatory markers. It can also result in hypertriglyceridemia, increased risk of venous thromboembolism and gallstone formation, unlike transdermal and vaginal topicals (Mehta *et al.*, 2021).

Therefore, further research is needed to clarify aspects that are still poorly understood, such as the long-term effects of hormone therapy, the types and the ideal dosages. In this way, hormone therapy can be considered a viable option for some women, but its use must be carefully planned to maximize the benefits and minimize the risks.

FINAL CONSIDERATIONS

The use of hormonal therapies has a significant impact on the cardiovascular system and is a subject that has been widely studied and debated in the medical literature. Analysis of the benefits and risks associated with these therapies shows that the time of initiation, dosage, route of administration and the patient's clinical profile are determining factors for the safety and efficacy of the treatment.

Evidence suggests that hormone therapy can play a protective role in cardiovascular health, especially when started at strategic times, such as just after the menopause, as suggested by the "time hypothesis". However, the benefits appear to be limited in patients with pre-existing cardiovascular conditions, such as advanced atherosclerosis, reinforcing the need to carefully assess each case before starting treatment.

Although hormone replacement therapy is not indicated for the primary or secondary prevention of cardiovascular disease, its potential benefits in maintaining endothelial function and reducing subclinical risk factors warrant further investigation. Therefore, future studies are needed to clarify issues related to the ideal duration of treatment, safe dosages and the most effective forms of administration.

Therefore, it can be concluded that the use of hormonal therapies in the cardiovascular context should be approached individually, with a careful analysis of the risks and benefits, with the aim of maximizing therapeutic results and minimizing potential adverse effects. Clinical decisions should always take into account the patient's specific characteristics and the most up-to-date scientific data, guaranteeing safe and effective treatment.

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