

Major Considerations on Hormone Replacement Therapy in Both Sexes for the Prevention of Cardiovascular Events

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Abstract

Introduction: Vasomotor symptoms affect about 60.0 to 80.0% of postmenopausal women and may have a 90.0% incidence in peri-menopausal women. The main studies in the last 20 years studies to invest the effects of estrogen therapy on symptoms and women's health in the climacteric. In men, hormone therapy for men improves fatigue, muscle strength and mood. The problem is that some studies suggested an association between the replacement and the higher incidence of cardiovascular diseases.

Objective: to make a systematic review to better understand the main findings and discussions of international consensus on hormonal therapies in both sexes regarding cardiovascular events.

Methods: Study Model: Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", a total of 56 papers were submitted that were submitted to the eligibility analysis and, after that, were selected 21 studies, following the rules of systematic review - PRISMA.

Sources of Information: The review protocol was based on the criteria of literary search with the use of mesh terms in the main databases such as Pubmed, Medline, Bireme, EBSCO, Scielo, etc.

Conclusion: Based on the literary findings, hormone therapy in both sexes proved to be important for the improvement of organic functions and quality of life, as well as showed a bias in reducing cardiovascular events.

Keywords: Clinical trials, Cardiometabolic diseases, Heart failure, Hormonal therapy, Hormone replacement

Introduction

Vasomotor symptoms affect about 60.0 to 80.0% of postmenopausal women and may have a 90.0% incidence in peri-menopausal women (1 to 2 years before menopause) ^[1,2]. With the increase of hypoestrogenism, hypotrophy of the breasts and the urogenital apparatus, alterations in the skin and acceleration of the loss of bone mass may occur^[2]. Hypoestrogenism causes an increase in total cholesterol and triglycerides, LDL lipoproteins and a decrease in HDL. There is also fat accumulation in the visceral region, decreased secretion and sensitivity of the organism to the action of insulin and compensatory hyperinsulinemia. There is also increased renal sodium reabsorption, increased sympathetic nerve activity and changes in the vascular bed, with increased blood pressure^[3].

The main studies in the last 20 years studies to invest the effects of estrogen therapy on symptoms and women's health in the climacteric. As a major vasomotor symptom, hot flushes affect about 75.0% of Caucasian women and, for the North Amer-

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ican Menopause Society (NAMS), hot flushes are the primary indication for hormonal administration^[3,4].

One study found a reduction in vasomotor symptoms regardless of the estrogen dose associated with progestogen, but higher doses of estrogen alone were more effective in reducing symptoms. In the cardiovascular system, a study with 121,700 nurses verified the reduction of coronary artery disease and mortality in women after the use of estrogen therapy^[5].

In men, hormone therapy for men improves fatigue, muscle strength and mood^[16]. The problem is that some studies suggested an association between the replacement and the higher incidence of cardiovascular diseases. In addition, there are experts who argue that the substance may favor the emergence of prostate and breast cancer. Because of these controversies, American researchers conducted a series of tests to check the potential benefits and harms of gel-based testosterone replacement^[17].

However, the formations were not associated with the occurrence of infarctions and strokes^[17,18]. These studies still have limitations. The number of participants is not sufficient to determine the risks of treatment, whether major cardiovascular events or prostate cancer. There are many benefits, but we do not know the risks yet. Our next step is a longer and longer test to determine if replacement can increase the incidence of heart attack and prostate tumors, and reduce the risk of fractures^[17].

The results, published in the journal of the American Medical Association (JAMA)^[30], show that compared to placebo, the substance corrects anemia and increases bone density. On the other hand, there was no improvement or worsening of memory and other cognitive functions. For the heart, although one of the studies found an increase in the number of uncalcified plaques in the arteries, another one, made with a larger number of participants, detected a reduction in cardiovascular risk^[30].

Therefore, the present study aimed to make a systematic review to better understand the main findings and discussions of international consensus on hormonal therapies in both sexes regarding cardiovascular events.

Methods

Study design

Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on “Search strategies”, a total of 96 papers that were submitted to the eligibility analysis were collated and, after that, 30 studies were selected, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyses- <http://www.prisma-statement.org/>).

Sources of information

The review protocol was based on the criteria of literary search with the use of mesh terms in the main databases such as Pubmed, Medline, Bireme, EBSCO, Scielo, etc. All references are registered in End Note by the site:

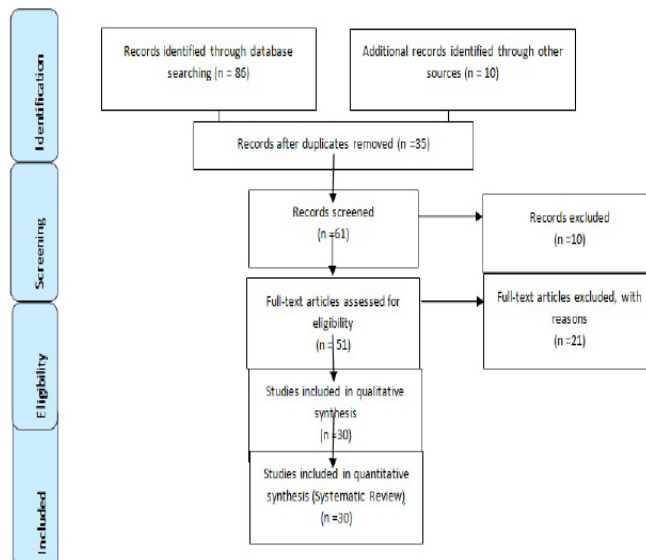
<http://www.myendnoteweb.com/EndNoteWeb.html?cat=myrefs&>.

Search strategy

In general, as an example, the search strategy in MEDLINE / Pubmed, Web Of Science, Science Direct Journals (Elsevier), Scopus (Elsevier), One File (Gale) followed the following steps:

- search for mesh terms: Clinical Trials, cardiometabolic diseases, Heart Failure, hormonal therapy, Hormone replacement, use of the bouleanos “and” between mesh terms and “or” among historical findings.

Flow chart



Literature Review and Discussion

Hormonal therapy in women

Stress, sedentary lifestyle, contraceptive use and irregular diet are some factors that lead to a decrease in testosterone in young women, presenting symptoms such as fatigue, lack of libido, weight gain, difficulty in gaining muscle mass^[1,2]. After menopause testosterone production falls significantly, leading to worsening of these symptoms. Often the woman complains of intense fatigue associated with unexplained discouragement and even depression. Testosterone at optimal levels brings numerous benefits, as shown in Figure 1.

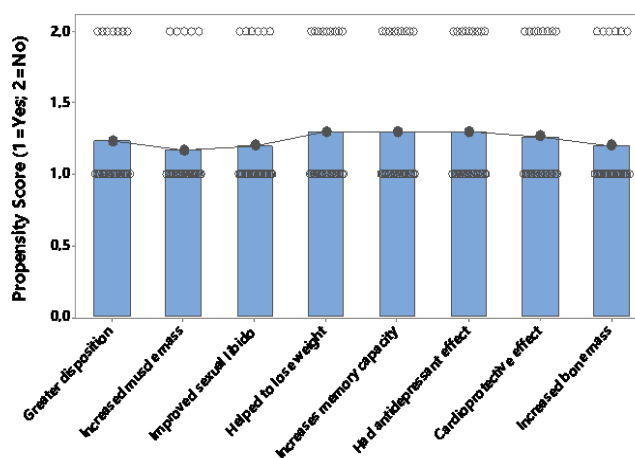


Figure 1: Graph showing the propensity score of the main literary findings of hormonal therapy benefits in women.

The last positioning of the American Endocrinology Society maintains that the diagnosis of androgen insufficiency in women is not well defined^[3,4]. The Princeton Consensus in 2002 suggest-

ed a lack of motivation, fatigue, malaise, depressed mood, sexual dysfunction, decreased pubic and muscle mass, climacteric syndrome, and bone loss unresponsive to estrogen. Laboratorially, total testosterone would be < 150 pg / mL, testosterone free by equilibration dialysis $< 1\%$ (2 pg / mL) or S-DHEA < 100 ng / mL, and testosterone dosages should be collected in the morning and in the medium of the cycle in premenopausal women^[5].

The Consensus itself, however, admitted that kits for androgen dosages are inappropriate for low values^[5]. In women, these levels are often below the sensitivity of the trial, so this was a nonspecific clinical picture of difficult laboratory evidence. Both ovarian and adrenal androgens are reduced in women from the age of 25, especially early in the reproductive years. The fall is continuous with age and more precocious and marked in adrenal androgens^[6].

Among women aged 45 to 54 years with natural menopause, the ovary continues to secrete androgens. As the estrogen drop is about 16 times and that of androgens only two to four times, there is a relative hyperandrogenism at menopause, even with low absolute levels of androgens. In women with bilateral oophorectomy, total and free calculated testosterone levels fall significantly^[2,7].

Other groups of women at risk for androgen failure are those with premature ovarian failure, those on anti-androgens, oral contraceptives or oral hormone therapy (which reduce LH and increase SHBG, decreasing free androgens), those with adrenal insufficiency primary or secondary to the use of corticoids or hypopituitarism^[7]. The classical and previously established indications for prescribing testosterone in women are in the sexual sphere as a decrease in libido and sexual pleasure. Effects such as bone mass gain and increased muscle mass are also well established with the use of testosterone^[8].

Major Benefits of Using Testosterone in Women

More recently, several studies have correlated testosterone with breast cell proliferation and breast cancer. There are already considered numbers of evidence that both testosterone and its hydrotestosterone derivative exert an inhibitory effect on the growth of the mammary cell promoted by estradiol^[1-3,9-11]. Although progesterone has no influence on the proliferative effect of estradiol on the mammary cell, testosterone can reduce this effect by 40.0% and abolish α - estrogen receptor (ER - α) expression^[22].

Several studies have concluded that androgen induces a down regulation of breast epithelial proliferation and estrogen receptor expression, suggesting that the estrogen / androgen association in menopausal hormone therapy may reduce the risk of breast cancer^[1-6].

Information gap

No direct relationship between endogenous levels of androgens and libido has been demonstrated. The response occurred only with suprphysiological doses of testosterone, whose long-term safety is uncertain^[2-4]. In women, excess androgens can lead to aesthetic repercussions such as acne, hirsutism and even virilization. Aggression, water retention, increased blood pressure and cardiovascular problems may occur. Laboratorially there is a tendency to polycythemia, decrease of HDL and increase of fibrinogen. Androgens increase visceral fat, free fatty acids and impair insulin action^[5-7].

Hepatic damage may occur with oral formulations. There are several presentations for the use of testosterone in women. In general, injectable testosterone is not recommended because of the pharmacological nature of this route, leading to important variations in circulating levels as well as deposition of the steroid. On the other hand, the intramuscular route has been shown to be efficient in oophorectomized women^[4].

Low-dose methyltestosterone (1.25 - 2.5 mg) has been shown to be effective in relieving menopausal symptoms, bone mass, sexual function, and quality of life variables. Oral testosterone undecanoate is available in Europe and Canada and is preferably lymphatic absorption. Testosterone implants are inserted every 4 to 6 months apart, monitoring circulating levels is critical to patient safety and should never exceed physiological levels (70 - 90 ng / dL)^[10].

Women's testosterone patches are not yet marketed in Brazil, but studies using 150 to 300 μ g have been very satisfactory. The hydroalcoholic testosterone gel used for women (1 g / day) at a dose of 1/5 of the value used in men may be efficient for body composition, muscle strength and sexual function^[11]. DHEA, although used in several studies at the dose of 50 mg / day, has its only efficacy releasing testosterone. Up to the present it is not recommended for THM in women with preserved adrenal function.

Major literary findings of correlation of testosterone use and cardiovascular system

Testosterone is an essential hormone for women, with physiological actions mediated directly or through aromatization to estradiol throughout the body^[1-4]. Despite the crucial role of testosterone and the high circulating concentrations of this hormone in relation to estradiol in women, studies of its action and the effects of testosterone deficiency and replacement in women are scarce. The main indication for the prescription of testosterone for women is the loss of sexual desire, which causes substantial concern of the affected women. That no formulation has been approved for this purpose has not prevented the widespread use of testosterone by women - off label or as combination therapy^[5-7].

Observational studies indicate that testosterone has favorable cardiovascular effects measured by substitution results. However, the associations between endogenous testosterone and the risk of cardiovascular disease and total mortality, particularly in older women, have not yet been established^[8-11]. No adverse cardiovascular effects have been observed in studies of transdermal testosterone therapy in women. Clinical trials suggest that exogenous testosterone increases cognitive performance and improves musculoskeletal health in postmenopausal women. Unmet needs include the availability of women-approved testosterone formulations and studies to elucidate the contribution of testosterone to cardiovascular, cognitive and musculoskeletal health and cancer risk^[12].

Androgen levels differed substantially between women with and without ovarian dysfunction, and elevated androgen levels were associated with cardiometabolic deficiency in all women regardless of clinical condition^[13-15]. Sexual steroid hormones play important roles in the development of cardiovascular diseases, both high and low levels. This cross-sectional study included 680 women with polycystic ovary syndrome, premature ovarian failure, natural postmenopausal women, or regular

menstrual cycles (170 women per group)^[15].

Serum testosterone, androstenedione, and dehydroepiandrosterone sulfate measurements were performed using mass spectrometry on liquid chromatography. Body mass index (BMI), blood pressure, lipid profiles, glucose, insulin and SHBG were evaluated, and the bioactive fraction of circulating testosterone was calculated using the androgen free index (FAI)^[16].

Female PCOS were hyperandrogenic [FAI mean 4.9 (IQR 3.6 - 7.4)], and POI women were hypoandrogenic [FAI = 1.2 (0.8 - 1.7)] compared to women RC [FAI = 1.7 (1.1 - 2.8)], after adjusting for age, ethnicity, smoking and BMI ($P < 0.001$). After adjusting for age, there were no significant differences in androgens between POI and NM ($P = 0.15$) women and between NM and CR ($P = .27$), the latter indicating that chronological aging rather than aging ovary influences the differences between pre- and postmenopausal women. A high FAI was associated with high triglycerides (β log FAI for PCOS: 0.45, $P < 0.001$, POI: 0.25, $P < 0.001$, NM: 0.20, $P = 0.002$), insulin (β log FAI for PCOS: 0.77, POI: 0.44, NM: 0.40, all $P < 0.001$), HOMA-IR (β log FAI for PCOS: 0.82, POI: 0.46, NM: all $P < 0.001$) and mean arterial pressure (log β FAI for PCOS: 0.05, $P = 0.002$, POI: 0.07, $P < 0.001$, NM: 0.04, $P = 0.04$) in all women. With increased glucose (β log FAI for PCOS: 0.05, $P = 0.003$, NM: 0.07, $P < 0.001$) and decreased high density lipoprotein (β log FAI for PCOS: -0.23, $P < 0.001$, NM: -0.09, $P = 0.03$) in PCOS and NM women; And with increased low density lipoprotein (β log FAI for POI: 0.083, $P = 0.041$) in female POI. Adjustment for BMI attenuated the associations observed. The associations between FAI and cardiometabolic characteristics were the strongest in women of PCOS, even after adjustment for BMI^[10].

The incidence of cardiovascular disease increases dramatically with age in men and women^[11]. As a woman's risk of cardiovascular disease increases markedly after the onset of menopause, there has been increasing interest in the effect of estrogen on the heart and its role in the pathophysiology of these diseases. Much less attention has been given to the impact of testosterone on the heart, even though testosterone levels also decrease with age and low levels of testosterone are linked to the development of cardiovascular disease^[11].

The knowledge that the receptors of all major sex steroid hormones, including testosterone, are present in individual cardiomyocytes suggests that these hormones can influence the heart at the cellular level. In fact, it is well established that there are male-female differences in the release and intracellular contraction of Ca (2+) in isolated ventricular myocytes. Increasing evidence suggests that these differences arise from the effects of sex steroid hormones on processes involved in intracellular homeostasis of Ca (2+)^[11].

The myocardial contractile function is modified by testosterone, focusing on the impact of testosterone on processes that regulate the handling of Ca (2+) in ventricular myocyte level. The idea that testosterone regulates Ca (2+) treatment in the heart is important, as Ca (2+) deregulation plays a key role in the pathogenesis of a variety of different cardiovascular diseases. A better understanding of the sexual hormonal regulation of myocardial homeostasis (2+) may reveal new targets for the treatment of cardiovascular disease in all older adults^[11].

Androgens play a key role in cardiovascular function and their effects differ between men and women^[12]. In postmenopausal women, the replacement of testosterone at physiological

levels is associated with general well-being. However, a definitive explanation on how androgens have an impact on cardiovascular health in postmenopausal women and whether they can be used for cardiovascular treatment has not yet been established. With these objectives, a systematic review of existing studies on the relationship between androgens and cardiovascular diseases and the effects of testosterone therapy on cardiovascular outcomes in postmenopausal women was carried out^[12].

The few existing studies on cardiovascular outcomes in postmenopausal women indicate no deleterious effect or effect of increased androgen and increased cardiovascular risk. However, there is evidence of a favorable effect of androgens on cardiovascular markers of substitution in postmenopausal women, such as high density lipoprotein cholesterol, total cholesterol, body fat mass, and triglycerides. Therefore, further studies are needed to elucidate the impact of androgen therapy on cardiovascular health in postmenopausal women. The cardiovascular effect of testosterone or methyltestosterone with or without concomitant estrogens needs to be clarified^[12]. The addition of testosterone to a hormone therapy regimen has beneficial effects on sexual function in postmenopausal women, and subsequent studies have supported the role of testosterone in sexual function and well-being^[6].

Thirty-one postmenopausal women undergoing transdermal estradiol (E2) replacement therapy, 36 with bilateral oophorectomy (group O) and 45 controls (group C) were studied through venous occlusion plethysmography, bioimpedance, DEXA, biochemical, hormonal and inflammatory. The total testosterone (TT) level in group O was 11.0 (4.0 - 17.75) vs 23.0 (10.0 - 42.5) ng / dl in group C ($P = 0.001$). Blood flow in the forearm in ml / min / 100 ml tissue was lower in group O compared to group C at baseline (1.57 (1.05 - 2.47) versus 2.19 (1.59 - 2.66) $P = 0.036$), after reactive hyperemia response (endothelium-dependent flow-mediated dilation, 3.44 (2.38 - 4.35) versus 4.3 (3.09 - 5.52), $P = 0.031$) and after nitroglycerin (independent endothelial dilatation, 1.39 (0.99 - 1.7) vs 1.76 (1.15-2.0), $P = 0.025$), with a positive correlation between TT and all parameters except for the reactive hyperemia response ($r = 0.233 - 0.312$, $P = 0.036 - 0.004$). The absence of ovarian testosterone production in recent post-menopausal oophorectomized women has been associated with deleterious effects on endothelial function^[8].

The study demonstrated that estradiol and testosterone have a synergistic effect on early-stage atherosclerosis, and definite appropriate E2 / T ratio replacement therapy can significantly suppress the development of atherosclerosis by reducing lipid lesions, reducing the formation of foam cells, reducing endothelial injury, modulating the function of the coagulation system and inhibiting inflammation^[9].

Hormonal Therapy in Men

Of nine US institutions, one of these studies focused on coronary health. 170 men were included, of whom 50.7% had severe calcifications at the beginning of the study^[17]. After 12 months and compared to the placebo group, those who received testosterone had an increase in the volume of the noncalcified plaques, which was visualized by computed tomography and angiography. One of the mechanisms by which testosterone can reduce cardiovascular risks is that, from a cellular point of view, the substance acts on several metabolic fronts, decreasing fat absorption and

increasing insulin sensitivity, for example. These factors protect the body from stroke and stroke, according to Figure 2^[17,18].

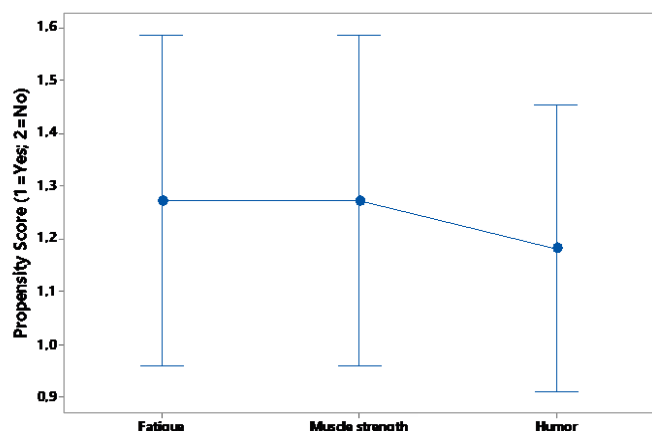


Figure 2: Graph showing the propensity score of the main literary findings of hormonal therapy benefits in men.

Currently, only testosterone therapy is prescribed when the patient, in addition to low levels of the substance, presents symptoms that affect the quality of life. However, he does not rule out that, in the future, with the result of more large studies, hormone replacement may enter into the list of procedures indicated for the reduction of coronary risk in men with insufficient testosterone levels, although there are no associated problems^[19].

Testosterone replacement therapy does not appear to increase the risk of cardiovascular disease or thromboembolic events in middle-aged men but increases the risk of obstructive sleep apnea, suggest the results of a large cohort study^[17-19]. In fact, the risk for a cardiovascular event was lower in men who used testosterone supplementation than in those who did not, said lead researcher Dr. Julian Hanske of Ruhr University Bochum in Herne, Germany, who collaborated in the study during a fellowship at Brigham & Women's Hospital in Boston.

More than 95.0% of circulating testosterone in men is secreted by the testes in Leydig cells, stimulated by luteinizing gonadotrophin (LH), from a series of enzymatic reactions in the cholesterol molecule. In plasma, about 2.0% of testosterone circulates freely, 44% circulate linked to sex-steroid binding globulin (SHBG), and 54.0% bind to albumin and other proteins. Free and bound albumin fractions are readily available to tissues, the junction of these two being called bioavailable testosterone^[20]. Low levels of endogenous testosterone have been linked to the presence of various components of the metabolic syndrome, including dyslipidemia, visceral obesity, systemic arterial hypertension (SAH), and prothrombotic states^[21]. In a large prospective, population-based study of 1,009 men followed up for 12 years, total testosterone had an inverse correlation with body mass index (BMI), fasting glycemia, triglycerides, and systolic and diastolic blood pressure after correction for age. In another longitudinal study with a 13-year follow-up, elevated levels of testosterone were positively correlated with HDL-C and associated with a reduction in LDL-C and triglyceride^[20,21].

In the Telecom study, which compared healthy adult men with normal and low plasma total testosterone, the group with lower hormone levels had higher BMI, waist-hip ratio, systolic blood pressure, fasting glucose and insulin, and two

hours post glucose overload, triglycerides, total cholesterol and LDL-C and apolipoprotein B, and lower levels of HDL-C and apolipoprotein A. However, after correction for BMI and waist-hip ratio, only fasting insulin, post-glucose and triglyceride insulin presented significant difference between groups. In this study SHBG levels were markedly reduced in patients with low total testosterone levels. The authors hypothesized causality to explain the relationship between reduced androgen levels and insulin resistance^[22].

In a meta-analysis, men with higher levels of testosterone were found to have a 42% lower risk of type 2 diabetes mellitus. Results remained significant even after adjustment for race, age, BMI and waist-hip ratio. As the underlying mechanism for this protection, the authors suggest that higher levels of testosterone increase lean mass and reduce tumor necrosis factor- α values, thereby improving insulin resistance^[23].

Individuals morbidly obese and with insulin resistance often have low levels of total testosterone, which increase with weight loss^[24]. The underlying mechanisms responsible for reducing testosterone levels in obese men are not fully understood. The reduction of free testosterone in severe obesity is not accompanied by a reciprocal increase in LH, suggesting a form of hypogonadotropic hypogonadism. A postulated hypothesis would be the functional alteration in the hypothalamic-pituitary-testicular axis, characterized by the decrease of the LH pulses^[24].

Another suggested mechanism would be an increase in the peripheral conversion of androgens to estrogens by the enzyme aromatase, which is present in high concentrations in adipose tissue. In addition, obesity is one of several conditions that may result in low levels of SHBG, and insulin is an important inhibitor of the hepatic production of this globulin^[22]. Thus, individuals with insulin resistance tend to have lower values of total testosterone. Adipocytes express androgen receptors. Androgens activate the β -adrenergic receptors and the sensitive hormone lipase, in addition to inhibiting the activity of lipoprotein lipase, the main enzyme regulating the uptake of triglycerides in adipose tissue. As a result, testosterone stimulates lipolysis and reduces fat stores in adipose tissue, the inverse effect being the increase in body fat mass observed in hypogonadal patients^[22]. With a much larger number of participants - 44,000 men over the age of 40 - another paper published in JAMA^[30] found a lower risk of cardiovascular problems among those who had testosterone replaced. In the universe of volunteers - followed, on average, for three years and four months -, 8,808 had low levels of the substance and had to return it, either by means of gel, tablet or intramuscular injection. Compared to the others, they suffered fewer episodes of infarction and stroke in the period evaluated. At the end of the study, the rate of cardiovascular events among the replacement group was 16.9 per 1,000 people per year, compared to 23.9.

Exogenous testosterone and risk factors for cardiovascular disease

The testosterone formulations available for clinical use are intramuscular, transdermal, buccal, oral and for subcutaneous implantation, the first being the most widely used^[17]. Non-esterified injectable free testosterone has a half-life of the hormone free of only ten minutes, while testosterone esters have a longer

half-life. The disadvantages of esters are that they initially provide supraphysiological levels of testosterone, which decline slowly and, before the next application, reduced levels can already be found. Steroids are easily absorbed through the skin. Transdermal preparations are available in the form of scrotal and non-scrotal adhesives and, more recently, as a gel^[18].

Transdermal modalities, in comparison with all other available preparations, provide more physiological serum testosterone levels. When administered orally in free form, testosterone is well absorbed by the intestine, but is metabolized and inactivated by the liver before reaching target organs (first-pass effect). Only at high doses, the capacity of hepatic metabolism is exceeded^[19-22].

Several attempts have been made to modify the molecule of collateral, such as elevation of serum liver enzymes, peliosis, cholestasis and liver tumors. Testosterone undecanoate is absorbed by the intestinal lymphatics and reaches the circulation via the thoracic duct, escaping from the hepatic first pass effect^[21]. However, serum levels of testosterone vary widely with this therapy, limiting its use. A buccal mucoadhesive model of testosterone has been developed for the treatment of male hypogonadism, marketed by Striant's name in the United States^[21].

It appears to be a well-tolerated form of presentation, with a low incidence of side effects. Subcutaneous testosterone implants provide patients with normal plasma levels of the hormone for three to six months^[23]. However, its use is not widespread in clinical practice. The effects of exogenous testosterone on CVD risk factors may depend on route of administration, duration of treatment and age. The results of the studies are not uniform and the disagreement between them is verified, especially in relation to the influence of testosterone replacement on serum levels of HDL-C/testosterone and to make it more orally effective^[23].

17- α -alkylated derivatives, although effective, have effects^[21]. IM testosterone administration was related to the reduction of HDL-C values. In older patients with longer duration of treatment, this effect on HDL-C decrease was less prominent. In studies conducted by Snyder et al. and Howell et al., no differences in lipid profile were observed in hypogonadal patients treated with transdermal testosterone. Dobs et al. found that, in hypogonadal men, both transdermal and IM testosterone replacement resulted in a reduction in HDL-C and an increase in total cholesterol / HDL-C ratio^[24].

The testosterone IM, but not the transdermal, decreased total cholesterol values when compared to the hypogonadal state^[25-27]. There was no difference in lipid profile between the two presentations. The studies already cited in the present study on the effects of testosterone replacement on CVD risk factors have characteristics that deserve consideration. The studies conducted by Snyder et al. and by Dobs et al. are prospective cutaways with a small number of participants, even though it was conducted by Howell et al., despite being randomized, also presents a reduced number of subjects, besides being blind only to patients^[25-28].

Finally, the meta-analysis published by Whitsel et al. presents 272 participants, coming from 19 studies, some of them being observational. Unlike the studies cited and in collaboration with members of The Endocrine Society for Testosterone Task Force on Men with Androgen Deficiency, Haddad et al., In a meta-analysis of 30 randomized, placebo-controlled studies in-

volving 1,642 men, 808 of whom were treated with testosterone in the commercially available (IM, transdermal, oral and buccal) formulations, showed negligible effects of testosterone use on lipid fractions, blood pressure and glycemic control^[29].

It is also necessary that researchers evaluate the relationship between exogenous testosterone and CVD risk factors. Having verified the importance of thrombus formation in the pathogenesis of acute coronary events, several hemostatic factors have been identified as being at risk for CVD. The risk of CAD is positively influenced by platelet aggregation and levels of thrombogenic factors, such as PAI-1, factor VII and fibrinogen. In a study conducted by Philips et al., Circulating testosterone values correlated negatively with fibrinogen and factor VII in patients with CAD^[30].

The administration of testosterone to 32 healthy men, participants in a male contraception study, caused a sustained decrease in fibrinogen by 15% to 20%. On the other hand, exogenous testosterone replacement has been shown to increase platelet aggregation. Thus, testosterone replacement shows both pro-fibrinolytic and pro-aggregatory results, its influence on thrombus formation being the result of the balance of these two effects^[30].

Testosterone and vascular reactivity

Hormone receptors (HRs) are widely distributed throughout the cardiovascular system, such as the aorta, peripheral vasculature, atrial and ventricular cells, endothelial cells, platelets, and megakaryocytes^[17]. Testosterone can exert its cardiovascular effects directly and indirectly after conversion to estradiol (E2). Endothelial, smooth muscle, macrophages and platelets express aromatase and 17- β -hydroxysteroid dehydrogenase, allowing E2 to be produced locally, from circulating precursors such as testosterone and DHEA. Testosterone may also exert effects on the cardiovascular system by genomic models, through RH and non-genomic, for their binding to steroid receptors on the plasma membrane - which can lead to blocking of the L-channels of calcium and opening of the potassium channels activated by calcium^[17]. The variation in the number of CAG repeats in exon 1 of the androgen receptor gene is inversely related to the transcriptional response to testosterone^[18].

In a study of 110 healthy men, a positive association was observed between the number of these replicates and vasodilation by independent and endothelium-dependent mechanisms. Thus, greater sensitivity to testosterone, mediated by genomic action model, would impair arterial vasodilation. It is believed that, through non-genomic mechanisms, testosterone can act as a coronary vasodilator. In a study conducted by Rosano et al, administration of 2.5 mg EV testosterone in men with CAD prolonged the time to onset of 1 mm ST segment depression in the exercise test and total exercise time when compared to placebo^[19].

In a randomized, double-blind, placebo-controlled study of 46 men with stable chronic angina, supplementation with 5 mg / day of transdermal testosterone over a 12-week period improved the ischemia threshold when compared to placebo. Contrary to what has been previously reported on improvement in CAD, administration of 200 mg of testosterone IM cypionate to healthy men in a randomized, double-blind, placebo-controlled study increased platelet aggregation by modulating the expression of thromboxane receptors^[26].

In another study, testosterone was implicated in impairing coronary vasodilation in response to adenosine in isolated rat heart models^[28]. Such effect was acutely mediated and attributed to the release of thromboxane, which is a vasoconstricting agent and platelet aggregation, which has been implicated in the pathogenesis of CVD. In summary, the vascular effects of testosterone in this way would probably be due to the balance between vasodilation and vasoconstriction. Testosterone and atherosclerosis Atherosclerosis is a word of Greek origin, which refers to the thickening of the inner layer of the artery and the accumulation of lipids in it. Data on the relationship between testosterone and atherosclerosis are scarce, with contradictory results from available studies. In addition, in some of these the hormonal collection schedule was not mentioned or this was quite broad. Given that testosterone is a hormone with a recognized circadian rhythm, the results of some studies should be interpreted with caution in view of this limitation^[29].

In a population-based study, they found an inverse and independent relationship between total and bioavailable testosterone levels, with severe aortic atherosclerosis and its progression, verified by lumbar spine radiography. Tivesten et al. found no statistical correlation between total and free testosterone and progression of carotid atherosclerosis in 313 healthy 58-year-old men living in Gothenburg, Sweden^[30].

Subsequently, in another study conducted by Tivestene et al., The relationship between total and free testosterone and peripheral lower limb arterial disease was evaluated in 2,784 elderly men. The authors verified that total and free testosterone correlated positively with the ankle-arm index, indicating a negative association between this androgen and atherosclerotic disease of the lower extremities. This index is a ratio of the ankle and arm blood pressure, with the patient in the supine position; a low value indicates the presence of lower extremity arterial disease^[30].

The relationship between testosterone and coronary atherosclerosis has also been studied by several authors. Philips et al. described a negative correlation between total and free testosterone and CAD in 55 men with no previous history of AMI. English et al., in a case-control study (60 cases and 30 controls), found a negative association between bioavailable, free testosterone and free androgen free index (ALI) with CAD. After correction for age and BMI, negative correlation with free testosterone and IAL (NE = 4) persisted. However, Harman et al, in a prospective longitudinal study with 890 men, mean age 53.8 ± 16 years and followed for a period of more than 31 years, did not verify correlation between baseline total and free testosterone levels and subsequent development of CAD^[30].

Testosterone and cardiovascular predominance

The association between testosterone and cardiovascular mortality has also aroused the interest of several researchers, and numerous studies have been published on the subject. As seen from the subjects discussed above, controversies exist in the literature, and additional studies are needed to evaluate this association^[17-19].

In a prospective, 12-year follow-up study of 1,009 men aged 40 - 79 years, residents of the Rancho Bernardo community in California, no statistical correlation was found between baseline total testosterone levels and subsequent development of morbidity and / or mortality due to CVD^[20-22]. Later, in this same

community, in an average follow-up period of 11.8 years, it was verified in 794 elderly men that those with lower levels of total and bioavailable testosterone had higher CVD mortality. In the latter study, mean age at baseline was 71.2 years and mortality rate, 68%, which could partly explain the difference between the results. In a prospective case-control study of healthy patients aged 40 to 79 years and mean follow-up period of seven years, higher concentrations of endogenous testosterone were inversely related to general and cardiovascular mortality^[22].

In a prospective, population-based study with 1,686 men between 40 and 70 years of age followed by an average period of 15.3 years, they did not find a statistical relationship between total testosterone values and mortality due to CAD. However, a positive and a negative association between free testosterone ($p = 0.02$) and dihydrotestosterone ($p = 0.04$) and mortality from CAD were observed, respectively. Two serum samples were collected from each participant, with an interval of 30 minutes, four hours after they had agreed (NE = 3). In a prospective, population-based study conducted by Smith et al., With 2,512 men between 45 and 59 years of age followed by an average period of 16.5 years, no statistical correlation was found between total testosterone and mortality by all causes and by CAD^[24].

Conclusion

Based on the literary findings, hormone therapy in both sexes was shown to be important for the improvement of the organic functions and quality of life, as well as showed a bias in reducing the cardiovascular events.

Conflict of Interest: The authors declare no conflict of interest.

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