REVIEW ARTICLE

Impact of Gender-Affirming Hormone Therapy on Cardiovascular Health

Impacto de la terapia hormonal de reafirmación de género en la salud cardiovascular

M. CAMILA BARTOLOMÉ ROCA[1], WALTER MASSON[1, MTSAC], MARIANO FALCONI[1, MTSAC], JUAN M. IROULART[1], ROCÍO BLANCO[1], RODOLFO PIZARRO[1, MTSAC]

ABSTRACT

Despite advances in the management of cardiovascular risk factors, the approach to the transgender population receiving hormone therapy is not completely defined. Transgender patients are those who present with "gender incongruence," that is, a discrepancy between the individual's expressed gender and the designated gender, which generally corresponds to the biological sex. In these cases, hormonal treatment differs from the "traditional" approach in that it is a "crossover" hormonal treatment. Multiple studies have evaluated the relationship between gender affirming hormone therapy (GAHT), the development of cardiovascular risk factors and the occurrence of cardiovascular events, both for the transfeminine and transmasculine population. These findings are particularly relevant, as cardiovascular disease is the second leading cause of mortality in the transgender population. However, studies that have attempted to stratify this group according to their cardiovascular risk have faced notable difficulties and limitations. The aim of this review is to investigate the impact of GATH on cardiovascular health, to assess the need to reconsider risk stratification and therapeutic targets for these patients, and to discuss the applicability of general recommendations to this specific population.

Keywords: Transgender people - Hormone replacement therapy - Cardiovascular disease

RESUMEN

A pesar de los avances en el manejo de factores de riesgo cardiovascular, el abordaje de la población transgénero que recibe terapia hormonal no está completamente definido. Los pacientes transgénero son aquellos que presentan "incongruencia de género", es decir, una discrepancia entre el género expresado por el individuo y el género designado, el cual generalmente se corresponde con el sexo biológico. En estos casos el tratamiento hormonal difiere del enfoque "tradicional" al tratarse de una hormonización "cruzada". Múltiples estudios han evaluado la relación entre la terapia hormonal para la reafirmación de género (THRG), el desarrollo de factores de riesgo cardiovascular y la ocurrencia de eventos cardiovasculares, tanto para la población transfemenina como transmasculina. Estos hallazgos son particularmente relevantes, ya que la enfermedad cardiovascular es la segunda causa de mortalidad en la población transgénero. Sin embargo, los estudios que han intentado estratificar a este grupo según su riesgo cardiovascular han enfrentado notables dificultades y limitaciones. El objetivo de esta revisión es investigar el impacto de la THRG en la salud cardiovascular, evaluar la necesidad de reconsiderar la estratificación del riesgo y las metas terapéuticas para estos pacientes, y discutir la aplicabilidad de las recomendaciones generales a esta población específica.

Palabras claves: Personas transgénero - Terapia de reemplazo hormonal - Enfermedad cardiovascular.

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. (1) Despite significant advances in the management of cardiovascular risk factors (CVRF) and the publication of numerous clinical practice guidelines, the approach to certain subpopulations in relation to cardiovascular prevention is still not completely well defined. (2) Within this group are patients receiving hormonal treatments, including those receiving gender affirming hormone therapy (GAHT), for whom specific recommendations on cardiovascular prevention, which are very clear for the general population, are not adequately defined. Given that numerous studies have reported the impact of these therapies on CVRF and an association between hormone treatments and the occurrence of cardiovascular events, the aim of this review is to investigate the impact of GAHT on cardiovascular health, to analyze

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Correspondence: Camila Bartolomé. E-mail: camila.bartolome@hospitalitaliano.org.ar. Tte. Gral. Juan Domingo Perón 4190. Ciudad Autónoma de Buenos Aires. Argentina (Postal Code: C1199ABB).

[1] Department of Cardiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

whether risk stratification and therapeutic goals for these patients need to be reconsidered, and to discuss whether recommendations for the general population are applicable to this specific population.

Gender incongruence and "crossover hormonization"

Transgender patients are those who present "gender incongruence", that is, a discrepancy between the gender expressed by the individual and the biological sex. (3) The incorporation of this term by the World Health Organization is intended to facilitate the diagnostic approach to issues related with gender identity, understood as the individual's perception of gender, and to guarantee access to health services for this population. Similarly, the term "gender dysphoria" refers to the distress experienced as a result of the aforementioned incongruence. (4) A transgender man is an individual whose biological sex is female, but whose gender identity is male, professing a gender transition from female to male. A transgender woman has a male biological sex, but with a female gender identity, posing a transition from male to female.

As part of the depathologization of gender identities, the Gender Identity Law (Law No. 26,743) stipulates that all persons have the right to the free development of their person in accordance with their gender identity, and in this context, GAHT is presented as a therapeutic strategy whose objective is to eliminate the physical characteristics associated with the biological sex and to develop those of the perceived gender. (5,6) Hormone therapy protocols for these patients are based on the administration of estrogens and testosterone, and are detailed in Table 1. (5)

Hormonization, risk factors and cardiovascular health: what evidence do we start from?

Multiple associations have been established between hormone replacement therapies, the development of CVRF and the occurrence of cardiovascular events. The effects of hormone replacement therapy have been documented mainly in men with hypogonadism and in postmenopausal women.

Estrogens, metabolism and cardiovascular events.

Regarding the impact of estrogens on the metabolic profile, numerous studies have shown a clear association between estrogen treatment and an improvement in the lipid profile. This treatment is associated with a decrease in low-density lipoprotein cholesterol (LDL-C) levels and an increase in high-density lipoprotein cholesterol (HDL-C) concentrations, although an increase in triglyceride levels is also observed. In turn, oral formulations have been found to cause more significant changes in these concentrations compared with transdermal formulations, and these effects are influenced by the dose administered. (7-10) In addition, a 25% reduction in lipoprotein(a) [(Lp(a)] levels was reported in women treated with oral estrogens, and that the association between this lipoprotein levels and the development of coronary heart disease would be modified by hormone treatment. (10,11) Moreover, estrogens have been associated with a reduction in insulin resistance and an increase in C-reactive protein levels secondary to the use of oral formulations (not with transdermal formulations). (10)

However, despite its beneficial impact on multiple components of the metabolic profile, the large randomized clinical trials HERS and WHI in postmenopausal women demonstrated that estrogen treatment carries an increased risk of major cardiovascular events, such as myocardial infarction, stroke, and venous or pulmonary thromboembolism, to such an extent that the WHI study had to be prematurely stopped. (7-9) This could be explained, in part, by a reductive effect on protein S activity, which is involved in the degradation of coagulation factors, as well as by the potentially dual role of estrogens in the atherogenic process. Estrogens may have a beneficial effect on the healthy

Table 1. Hormone schedules for gender-affirming therapy. Adapted from the National Ministry of Health. (5)

Estradiol: administration routes and dosage

Route of administration	Presentation	Schedule	Dose
Oral	17β-estradiol valerate	1 or 2 daily intakes	2 to 6 mg
Transdermal	17β-estradiol 0.06% gel.	1 or 2 daily applications	0.75 to 3 mg (1.25 to 5 mg of gel)
	Estradiol patch	Replacement every 3 or 4 days	50 to 100 mg

Testosterone: administration routes and dosage

Route of administration	Presentation	Scheme	Dose
Intramuscular	Injectable enanthate	Application every 15 to 21 days	250 mg
	Injectable cypionate	Application every 15 to 21 days	250 mg
	Undecanoate injection	Quarterly application (every 10 to 12 weeks)	1000 mg
Transdermal	1% testosterone gel	Daily application	25 to 100 mg (2.5 to 10 g of gel)

endothelium, but a negative impact on atherosclerotic disease with established plaques. (10,12-14)

Testosterone, metabolism and cardiovascular events

Studies in men with hypogonadism have shown conflicting results regarding the impact of testosterone on the metabolic profile. Testosterone has been found to inhibit lipogenesis and promote lipolysis, which could have a beneficial effect on obesity and insulin resistance associated with this condition. However, in men with hypogonadism treated with exogenous testosterone, abrupt discontinuation of treatment may lead to increased fasting glucose levels. (15) On the other hand, although the use of anabolic androgens has been associated with an increased risk of hypertension, treatment with doses that equal physiological testosterone concentrations could have a beneficial effect on blood pressure. (15-17) Nevertheless, the effects of testosterone on atherosclerotic disease are still unclear. While some studies have found that treatment with physiological doses of testosterone is associated with a reduction in carotid intima-media thickness, other studies suggest opposite results. (15)

Notably, the effects of androgens may differ significantly between the male and female cardiovascular systems. In women with hyperandrogenic polycystic ovary syndrome (PCOS), an association has been reported between this disorder and the development of left ventricular hypertrophy, impaired ventricular ejection fraction, and alterations in mitral filling. A tendency towards arterial hypertension has also been observed, which could be related to an impaired release of nitric oxide due to oxidative stress and activation of pathways leading to endothelial dysfunction. (18,19)

Regarding the association with cardiovascular events, the TOM clinical trial observed that, in a group of men of approximately 75 years of age with testosterone levels in the hypogonadism range and a high prevalence of cardiovascular comorbidities, the use of exogenous testosterone was associated with a higher incidence of adverse cardiovascular events. (20) Other observational studies obtained similar results, with a higher cumulative incidence of all-cause death, hospitalization for major myocardial infarction or ischemic stroke in hormone-treated patients. (21-23) However, the recent TRAVERSE randomized clinical trial demonstrated, in a non-inferiority analysis, that hormone replacement therapy with testosterone in men with pre-existing or high risk of presenting cardiovascular disease has no significant difference compared with placebo in the occurrence of major cardiovascular events. (24)

Association of "crossover" hormonization with risk factors and cardiovascular events in transgender patients

In transgender patients receiving GAHT, changes have been observed in CVRF as well as in the rate of cardiovascular events. This aspect is of particular interest, since in these cases the hormonal treatment differs from the "traditional" approach as it is a "crossover" hormonization.

Estrogen crossover therapy and cardiovascular health in the transfeminine population.

Several studies have assessed the impact of crossover hormonization on CVRF in transgender women. Regarding its influence on blood pressure, the results of these studies have been contradictory. Overall, most of these studies suggest that crossover hormonization with estrogen is associated with an increase in blood pressure values, with documented increases of up to 4 mmHg in systolic blood pressure and 6.5 mmHg in diastolic pressure after only 1 year of treatment. (25) However, multiple studies that assessed changes in blood pressure did not observe significant differences when comparing these results with those of men in the general population. (26,27) According to a review article, endogenous testosterone in these patients would induce a vasopressor response mediated by the renin-angiotensin-aldosterone system (RAAS). (28,29) Moreover, differences in the distribution of estrogen receptors in the female compared with the male cardiovascular system would contribute to oxidative stress and endothelial dysfunction, mechanisms underlying the development of hypertension. (29)

In relation to the lipid profile, although some studies have shown no variations after treatment initiation (25) most have shown that estrogen therapy in transgender women is associated with favorable changes in lipid parameters, similar to those observed in postmenopausal women using oral estrogens. Among the most representative studies in this regard is the ENIGI study, conducted in four European gender clinics with a total of 144 transgender women. In this study, it was observed that the transwoman population experienced a reduction in total cholesterol of 7.66 mg/dL (95% CI 2.94-12.39) and a reduction of 4.65 mg/dL in LDL-C levels (95% CI 0.74-8.56) compared with baseline values after treatment initiation. (30)

In terms of glucose metabolism, parameters of insulin resistance and reduced incretin response have been observed in transgender women under hormone treatment. (25,31) According to the American Heart Association (AHA), transgender women have a higher prevalence of diabetes compared with cisgender groups. The likelihood of developing diabetes in this group is twice as high as in women in the general population and six times higher than in men. (32) Changes in weight and body mass index (BMI) after initiation of hormone treatment could account for changes in the glycemic profile. (25,33)

In relation to documented cardiovascular events reported in the population of transgender women, a higher incidence of myocardial infarction, venous thromboembolic events, and ischemic stroke has been observed, as in postmenopausal women, com-

pared with the general population. (32) One of the largest studies evaluating the incidence of events in 2842 transgender women, found a higher incidence of thromboembolic events and stroke in transgender women compared with men and women in the general population. In addition, a higher incidence of myocardial infarction was observed in the transwoman population compared with the reference cohort of women, although it was not higher than the incidence observed in the reference male cohort (Table 2). (34) Other studies have obtained similar results, (35-37) and one of them revealed that transgender women had an infarction rate of 7.8%, significantly higher than that of women in the general population. However, this study did not specify whether the patients included were receiving hormone treatment. (38)

Testosterone crossover therapy and cardiovascular health in the transmasculine population

In contrast to what has been observed in the transfeminine population, most studies in transgender men receiving androgen therapy have shown a clear association between hormone treatment with testosterone and an increase in blood pressure values. (28,32,33) An increase of almost 11 mmHg in systolic blood pressure and up to 9 mmHg in diastolic blood pressure has been observed after one year of treatment. (25) Different studies have proposed that impaired endothelial function is an underlying mechanism in the development of hypertension in transgender men receiving androgen crossover treatment. Investigations comparing arterial stiffness, brachial vasodilator response (measured as brachial artery diameter after occlusion with an inflated blood pressure cuff at supra-systolic values) and pulse wave velocity in testosterone-treated transgender men with values obtained in premenopausal women in the general population and in transgender men without hormone treatment, found a decrease in the vasodilator response and an association between androgen treatment and increased vascular system stiffness in these patients. (39,40)

Possible causes of increased blood pressure in this group include altered activity of the endothelin-1 system, due to suppression of a receptor involved in nitric oxide synthesis, together with increased RAAS activity. (29) These mechanisms have also been previously observed in women with hyperandrogenic PCOS. (18)

Several studies have revealed that testosterone treatment in transgender men has an adverse effect on the lipid profile. A retrospective longitudinal study showed a statistically significant increase in plasma total cholesterol levels, with baseline concentrations of 166 ± 35.1 mg/dL and 175.6 ± 38.2 mg/dL at 2 years. An increase in LDL-C levels was also observed, from 103.8 ± 28.7 mg/dL to 112.8 ± 30.3 mg/dL. Triglycerides increased from 70.6 ± 30.7 mg/dL to 102.3 ± 68.5 mg/dL, and HDL-C levels decreased from 52.2 ± 12.2 mg/dL to 45.4 ± 13.8 mg/dL. (33) Other studies obtained similar results. (25,30)

Results on the impact of testosterone treatment on glucose metabolism in transgender men are contradictory. While some studies have observed a statistically significant increase in glycosylated hemoglobin levels associated with treatment, (25) a systematic review suggests that testosterone therapy does not affect insulin sensitivity and, instead, could be associated with an improvement in glycemic control. (41) However, as in transgender women on estrogen therapy, an in-

Table 2. Incidence of cardiovascular events in the transwoman population

Cohort and event of interest	Transwoman cohort		Adjusted HR (95% CI)*	
	Cardiovascular events (n)	Incidence† (95% CI)	vs. men in the general population	vs. women in the general population
Overall transwoman cohort (n=2842)				
Venous thromboembolism	61	5.5 (4.3-7.0)	1.9 (1.4-2.7)	2.0 (1.4-2.8)
Ischemic stroke	54	4.8 (3.7-6.3)	1.2 (0.9-1.7)	1.9 (1.3-2.6)
Myocardial infarction	33	2.9 (2.1-4.1)	0.9 (0.6-1.5)	1.8 (1.1-2.9)
Transwoman estrogen initiation cohort (n=853).				
Venous thromboembolism	17	6.6 (4.1-10.6)	3.2 (1.5-6.5)	2.5 (1.2-5.0)
- At 0-2-year follow-up	6	4.3 (1.9-9.6)	1.5 (0.5-5.1)	1.7 (0.5-5.5)
- At >2-year follow-up	11	9.3 (5.2-16.8)	5.1 (2.1-12.6)	3.2 (1.3-7.6)
Ischemic stroke	17	6.6 (4.1-10.6)	2.3 (1.2-4.3)	2.9 (1.5-5.5)
- At 0-6-year follow-up	9	3.8 (2.0-7.3)	1.3 (0.6-2.9)	2.3 (1.0-5.4)
- At >6-year follow-up	8	36.2 (18.1-72.4)	9.9 (3.0-33.1)	4.1 (1.5-11.4)
Myocardial infarction	4	1.5 (0.6-4.1)	1.0 (0.3-3.2)	2.4 (0.6-9.4)

HR, hazard ratio; CI, confidence interval; vs, versus.
*Comparison with reference cohorts. Adapted from Getahun et al. (34)
†Calculated as number of cases per 1000 patients/year.

crease in BMI has also been observed in testosterone-treated transgender men, though this increase could be attributed to the fact that testosterone therapy increases the lean mass and decreases the fat mass. (25,41,42) On the other hand, the ENIGI study found no significant variation in BMI with hormonization. Although transgender men showed a higher long-term risk of cardiovascular disease than the optimum calculated according to biological sex, as estimated by the Framingham risk calculator based on this index, these results did not change after two years of androgen treatment. (30)

Regarding cardiovascular events in transgender men, the first observational study, published in 1989, found no statistically significant differences in infarction rates or infarction-associated mortality compared with the general population. (26) Another study showed incidence curves for venous thromboembolism, stroke, and myocardial infarction with similar patterns in transgender men on hormone treatment (n=2118) and the general population. In relation to myocardial infarction, HR values were 0.7 (95% CI 0.3-1.8) relative to men in the general population and 1.3 (95% CI 0.5-3.9) relative to women. (34) These results partially differ from those observed in other studies. (26,38) Alzahrani et al. found that the transmasculine population had a probability of myocardial infarction twice that of men in the general population (OR 2.53; 95% CI 1.14-5.68; p=0.02) and almost five times that of women (OR 4.90; 95% CI 2.18-10.90; p<0.01), after adjusting for other CVRF. (38)

Cardiovascular risk stratification in transgender patients.

Cardiovascular disease is the second leading cause of mortality among the transgender population, exceeded only by suicide in overall all-cause mortality. (43) Studies that sought to stratify transgender patients according to their cardiovascular risk encountered notable difficulties and limitations. The ENIGI study, which estimated the 30-year cardiovascular risk of transgender patients using the Framingham score based on the lipid profile according to their biological sex, (1) demonstrated a significant increase in risk after GAHT initiation. The study revealed that both transgender men and women have a higher baseline cardiovascular risk (i.e., pre-hormonization) than the general population, suggesting the presence of cardiovascular risk factors in addition to the traditional ones. In the case of transgender men, such risk increased after initiation of hormone treatment, whereas in the case of transgender women it was slightly decreased after GAHT initiation but not statistically significant . (30)

According to a retrospective study that estimated cardiovascular risk in 427 transgender patients without hormone treatment, employing the ASCVD risk calculator system, the transgender population would be the majority in the highest cardiovascular risk categories compared with the general population (Figure 1). (44) Furthermore, the mean values of the calculated risk for the transgender population aged 45-65 years using the QRISK3 and ASCVD risk calculator scores were 12.2% and 8.3%, respectively. The difference observed between the two risk calculators could be explained in part by steroid use, high rates of mental health disorders, and substance use in this population, factors that are only considered in the QRISK3 score

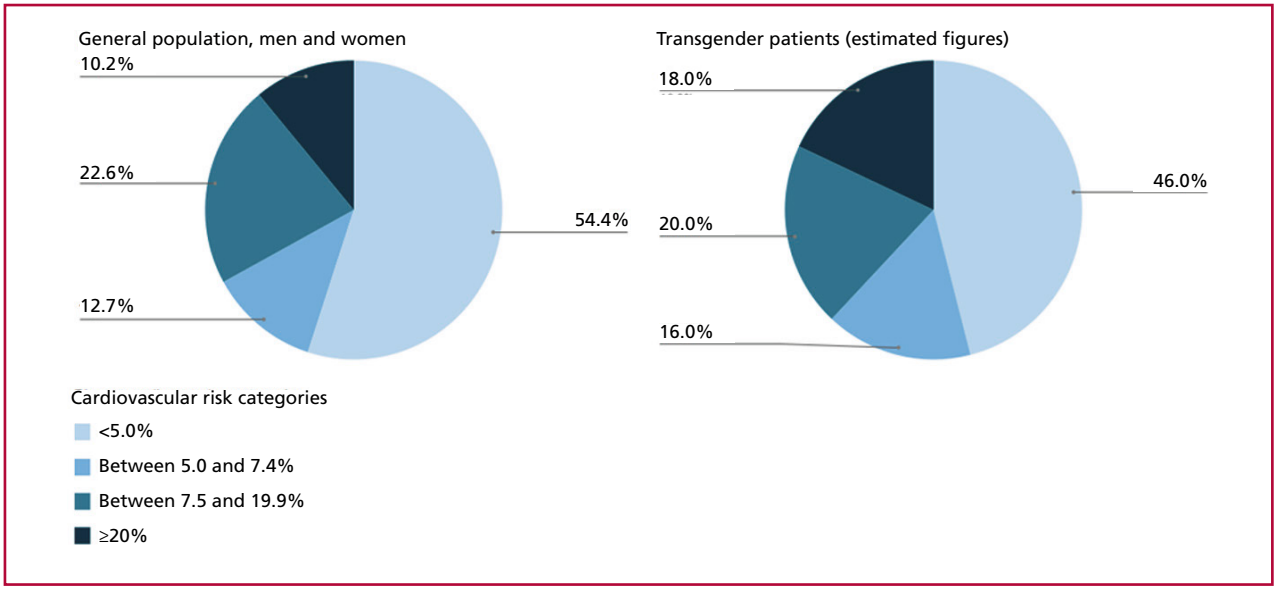

Fig. 1. Proportion of transgender patients and the general population (aged 40-79 years) in the different risk categories (*QRISK3* system). Adapted from Denby et al.(44)

Final reflections and conclusions

The influence of sex hormones on cardiovascular health is complex. The impact of crossover hormonization in transgender patients has been evaluated in numerous studies, but these have clear methodological limitations, as they tend to be retrospective studies and, in many cases, with small number of patients. Based on the effects of hormonization described for the general population in large randomized clinical trials, a key question arises: can these results be directly extrapolated to the transgender population receiving crossover hormone treatment? It has been recognized that there are sex differences in cardiovascular health, attributable both to genetic variations associated with biological sex and to the dynamic interaction between hormones. Epigenetic mechanisms play a crucial role in this context and could explain the differences in the response of the heart and blood vessels to sex hormones observed in individuals of male and female biological sex. (45)

When determining the cardiovascular risk of patients receiving GAHT, both the physiological mechanisms of the hormones and the effects of crossover treatment and nontraditional CVRF associated with their minority status come into play. In this regard, there are no studies that have evaluated how traditional risk scores apply to this population. Therefore, rethinking the tools for cardiovascular risk stratification in this specific population, through the development of adapted estimators, represents a major challenge for current cardiology.

In recent years, there has been an increase in the number of transgender patients seeking access to hormone therapies to improve their well-being and reduce the stress and nonconformity associated with gender dysphoria. The metabolic effects of gender-affirming hormone therapy, combined with the effects of crossover treatment and the nontraditional CVRF associated with their condition, notably impact on the cardiovascular health of these individuals.

In this context, it is essential to implement a specialized cardiological follow-up program for these patients. The formation of multidisciplinary teams with expertise in the subject could contribute to the development of better recommendations in future cardiovascular prevention guidelines, since the general recommendations are not fully applicable to this very particular population.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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M. Camila Bartolomé Roca, Walter Masson, Mariano Falconi, Juan M. Iroulart, Rocío Blanco, Rodolfo Pizarro

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