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Review

Impact of Hormone Therapy on Serum Lipids in Transgender People

Beatriz Almeida [1], Melissa Mariana [2,3], Margarida Lorigo [1,2], Nelson Oliveira [4] and Elisa Cairrao [1,2,*]

[1] FCS-UBI, Faculty of Health Sciences, University of Beira Interior, 6200-506 Covilha, Portugal; a41970@fcsaude.ubi.pt (B.A.); margarida.lorigo@gmail.com (M.L.)
[2] CICS-UBI, Health Sciences Research Centre, University of Beira Interior, 6200-506 Covilha, Portugal; melissa.r.mariana@gmail.com
[3] FC-UBI, Faculty of Sciences, University of Beira Interior, 6201-001 Covilha, Portugal
[4] IPG-CITUR, Polytechnic Institute of Guarda & Centre for Tourism Research, Development and Innovation, 6300-654 Guarda, Portugal; nelsonoliveira@ipg.pt
* Correspondence: ecairrao@fcsaude.ubi.pt; Tel.: +351-275-329049

Abstract: The term "Transgender" is used to describe individuals whose gender identity is different from their external sexual anatomy at birth. The number of people identifying as transgender has increased in recent years, and consequently, the number of gender affirmation surgeries and the use of hormonal therapies has also increased. A wide range of hormonal therapies has emerged considering the target population, age, and final outcomes, and as such these are becoming increasingly developed and complex in order to be the most appropriate for each individual. However, the side effects of these therapies remain to be fully understood. Therefore, this review aims to assess the impact of hormone therapy, in both transgender men and women of different ages, on the lipid profile. From the studies analyzed, it is possible to conclude that there is a relationship between hormone therapy and the lipid profile, with different outcomes between transgender men and women. There is a reduction in cardiovascular risk for transgender women as opposed to transgender men, in whom cardiovascular risk seems to increase due to lipid changes. It is now necessary to understand the mechanisms involved in order to reduce the consequences of these therapies and promote positive health outcomes.

Keywords: transgender people; transsexualism; hormone therapy; cardiovascular health; lipid profile

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1. Introduction

The term "Transgender" is a very broad concept that is used to describe individuals whose gender identity is different from their external sexual anatomy at birth [1]. It is estimated that there are currently approximately 1.3 million adults and 300,000 young people who identify as transgender in the United States, and this number has doubled since 2017, according to a report released by the Williams Institute at the University of California, Los Angeles. Various hypotheses have been proposed to explain this global exponential increase, including that increased visibility in society that results from a greater exposure of transgender people in the media and the role of activism and public figures; the access to sex education in schools and the availability of information, supported by online groups and communities; the globalization of practices and social norms materialized in political and legal changes; and the role of health systems supported by the growing number of health professionals trained to provide mental and medical support, among others have concomitantly contributed to reducing gender identity stigma and discrimination, allowing more individuals to find a safer environment to explore, accept, and affirm their gender identities [2–6].

Currently, the American Psychiatric Association (APA), in the fifth and most recent edition of the Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (DSM-5),

has changed the diagnosis from gender identity disorder (GID) to gender dysphoria (GD), which has generated a lot of controversy in the scientific community. The DSM-IV diagnosis of GID assumed that various gender identities were inherently disordered which was, consequently, perceived by many as stigmatizing. On the other hand, the DSM-5 reflects an evolution in the understanding of gender identity, attempting to recognize the suffering that can accompany this incongruence and providing support to alleviate patients' suffering. Thus, this new terminology is an important step towards the depathologization and the reduction of stigma surrounding trans people [7]. In addition, trans people may not experience GD but can benefit from different treatments, mainly hormone therapies (HT) and gender affirmation surgeries (GAS).

The use of HT in transgender individuals dates back to the 1930s, when testosterone and diethylstilbestrol were synthesized. Until then, the therapies used were completely inefficient [8]. However, it was only in 1979 that the World Professional Association of Transgender Health (WPATH) published the first edition of the book Standards of Care, which contained the first guidelines for hormonal treatment in transgender people.

According to the guidelines of The Endocrine Society, adapted in the book Standards of Care published in 2022, the best hormonal therapies may vary depending on the target population, the age of the individuals, and the hormone levels needed to achieve the intended secondary sex characteristics, so it is imperative to know more about which regimens are appropriate in each case [9,10]. Different therapies have been applied, according to gender and age, as summarized in Table 1. Specifically, in the case of adolescent transgender women, the appropriate medication to induce female puberty is (a) oral 17β-estradiol started at a dose of 5 μg/kg/day and increased every 6 months by 5 μg/kg/day, up to a maximum of 20 μg/kg/day, when dealing with pre-pubertal individuals, and in the case of post-pubertal adolescents, the dose can be increased more rapidly, starting with 1 mg/day for 6 months and then increasing to 2 mg/day; and (b) initial transdermal 17β-estradiol with a dose of 6.25–12.5 μg/24 h, titrated every 6 months with 12.5 μg/24 h according to the hormonal levels of estradiol. Regarding the therapy of adolescent transgender men, the recommended therapy is 25 mg/m^2/2 weeks, increasing every 6 months until an adult dose and the hormonal target of testosterone are reached [9–11].

For adults, hormone regimes are more complex and offer more options in terms of both formulation and dosage. Transgender women can use any of these options: (a) oral or sublingual estradiol at a dosage of 2 to 6 mg/day; (b) transdermal estradiol patch 0.025–0.2 mg/day; (c) transdermal estradiol gel, which can be applied to the skin in different formulations and with different effects depending on its effectiveness (no specific dosage is known); or (d) parenteral estradiol valerate or cypionate 5–30 mg intramuscularly (IM) every 2 weeks or 2–10 mg IM weekly. In these cases, estrogen therapy can be supplemented with anti-androgens: (a) spironolactone 100 to 300 mg/day; (b) cyproterone acetate 10 mg/day; and (c) Gonadotropin-releasing hormone (GnRH) agonist: 3.75–7.50 mg IM monthly or 11.25–22.5 mg IM every 3/6 months. For adult transgender men, the approved regimens are (a) parenteral testosterone enanthate or cypionate: 50–100 mg IM/subcutaneous weekly or 100–200 mg IM/subcutaneous every 2 weeks; (b) parenteral testosterone undecanoate: 1000 mg IM every 12 weeks or 750 mg IM every 10 weeks; (c) transdermal testosterone gel 50–100 mg/day; or (d) transdermal testosterone patch 2.5–7.5 mg/day [2,9,10,12].

In summary, the range of suitable hormonal therapies is becoming increasingly developed and complex. However, the outcomes of these therapies in the different systems remain to be clarified. In this sense, this review aims to assess the impact of hormone therapy on the cardiovascular health of transgender people in the short, mid, and long term. Initially, the effects on the patients' lipid profiles and, consequently, on cardiovascular risk, were analyzed, taking into account the concentrations used and patient follow-up. It is imperative to understand its impact so that the target population, which is constantly growing, can have accessible healthcare adapted to their needs.

Table 1. Summary of hormone therapy for both transgender women and men at different ages, according to the Endocrine Society guidelines.

		Hormone	Route	Dosages	Specifications
Transgender Women	Adolescent	17β-estradiol	Oral	5 μg/kg/day	Pre-puberty: dose increased every 6 months by 5 μg/kg/day to a maximum of 20 μg/kg/day; Post-puberty: dose increased 1 mg/day for 6 months to a maximum of 2 mg/day.
			Transdermal	6.25–12.5 μg/24 h	Titrated with 12.5 μg/24 h every 6 months
	Adult	Estradiol	Oral	2–6 mg/day	Can be supplemented with anti-androgens: - spironolactone 100 to 300 mg/day; - CPA: 10 mg/day; - GnRHa: 3.75–7.50 mg IM monthly or 11.25–22.5 mg IM every 3/6 months.
		Estradiol	Transdermal-patch	0.025–0.2 mg/day	
		Estradiol	Transdermal-gel	Daily to skin with no specific dosage	
		Estradiol valerate or cypionate	Parenteral (IM)	5–30 mg/2 weeks or 2–10 mg weekly	
Transgender Men	Adolescent	Testosterone esters	Parenteral (IM)	25 mg/m^2/2 weeks	Increased every 6 months until an adult dose and the hormonal target of testosterone are reached
	Adult	Testosterone enanthate or cypionate	Parenteral (IM, subcutaneous)	50–100 mg weekly or 100–200 mg every 2 weeks	
		Testosterone undecanoate	Parenteral (IM)	1000 mg every 12 weeks or 750 mg every 10 weeks	
		Testosterone	Transdermal-gel	50–100 mg/day	
		Testosterone	Transdermal patch	2.5–7.5 mg/day	

CPA, cyproterone acetate; GnRHa, Gonadotropin-releasing hormone agonist; IM, intramuscularly.

2. Methods

Advanced research was initially carried out on the PubMed and Scopus platforms for published articles, using the Boolean operators AND and OR and the following keywords: "Transgender Person", "Transsexualism", "Cardiovascular", and "Lipids". As the terms "Transgender Person" and "Transsexualism" are synonyms, the Boolean operator OR was used between them, and the Boolean operator AND was used between the aforementioned terms and the terms "Lipids" and "Cardiovascular" (example: ((Transgender Person) OR (Transsexualism)) AND ((Cardiovascular) OR (Lipids)). This search brought together 336 articles.

The inclusion criteria used in this review were: (1) articles in English; (2) original articles; (3) articles published after the year 2000; (4) articles referring to the formulation and dosage of the hormone therapy used during the study. Regarding the exclusion criteria, these were: (1) articles not written in English; (2) non-original articles; (3) articles outside the search time frame; (4) articles that do not include the formulation and dosage of the hormonal therapy used during the study; (5) articles that did not address the change in lipid profile associated with hormonal therapy; (6) duplicate articles; (7) text with restricted access.

After applying all these criteria, a total of 14 articles were included in this review. In addition, an article obtained by consulting different systematic reviews was also included, due to its relevance and framing of the topic, making a total of 15 articles. This literature review process is schematized in Figure 1.

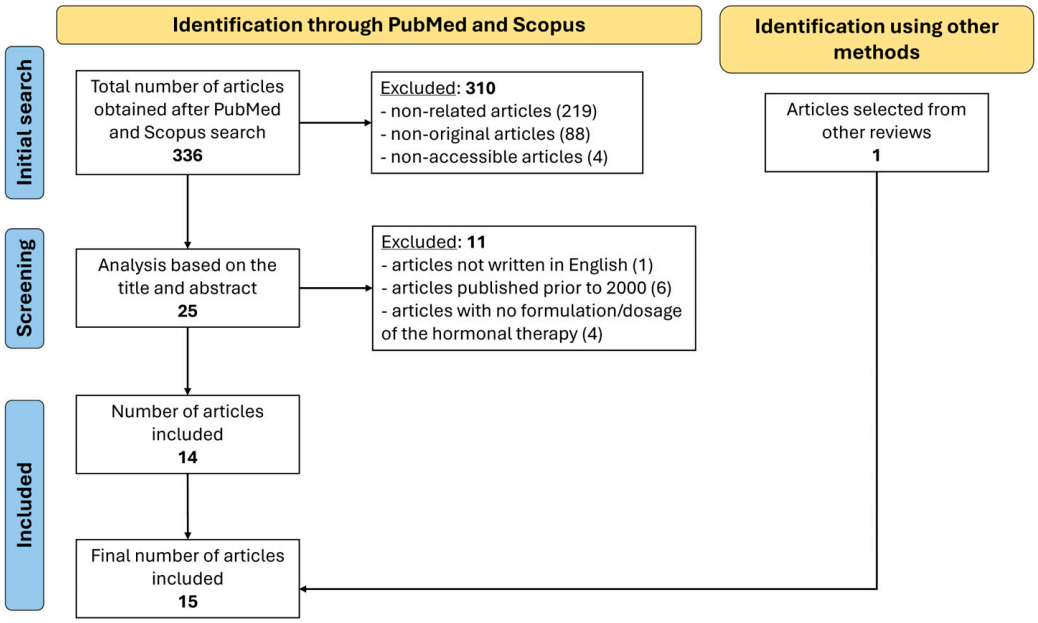

Figure 1. Flow diagram of the literature review process.

3. Hormone Therapy and Cardiovascular Outcomes

Although there are already several studies on this topic, the effect of hormone therapy is still insufficiently understood. Furthermore, there is a great deal of heterogeneity in these studies, which can be subdivided into different categories depending on the population studied. In this review, the studies will be analyzed according to the age of the participants and sorted into the categories of adolescents and adults. The studies analyzed in this review are summarized in Table 2.

Of the 15 articles retrieved from the search platforms, only 3 addressed this issue in adolescents. Two of them analyzed a population ranging from 12 to 24 years old, and another did not specify the age of the study participants, mentioning only that the start of the treatment was around 11.8 years old.

3.1. Adolescents

The first study was published in 2019 by Stoffers and collaborators. This Dutch observational study set out to evaluate the efficacy and safety of testosterone in the treatment of transgender male adolescents [13].

Participants were selected between November 2010 and August 2018, and 62 transgender men were included in the study. They were all treated with 3.75 mg of gonadotropin-releasing hormone agonists (GnRHa) every 4 weeks to inhibit puberty for at least 6 months before starting hormonal therapy. After the age of 15–16 years, participants who did not demonstrate psychological, medical, or social problems were eligible to begin testosterone therapy. This started with 25 mg/m^2/2 weeks, increasing every 6 months to 50 mg/m^2/2 weeks and then to 75 mg/m^2/2 weeks, until reaching a total dose of 125 mg every 2 weeks. If, at the time of entry into the study, the adolescent was already over 16 years old, T doses could be increased more quickly, starting with an initial dosage of 75 mg/2 weeks and increasing to 125 mg/2 weeks after 6 months. The results of this study demonstrated a significant decrease during the first 6 months in total cholesterol from 4.59 $\pm$ 0.92 mmol/L to 4.24 $\pm$ 0.92 nmol/L (n = 39; p = 0.001), but then it slowly increased again and did not differ significantly at 12 and 24 months. Regarding HDL cholesterol levels, they decreased significantly during the first 6 months from 1.58 $\pm$ 0.28 mmol/L to 1.33 $\pm$ 0.24 mmol/L (n= 39; $p < 0.001$) and remained unchanged. However, there were no changes in the levels of LDL cholesterol and triglycerides [13]. It is important to take into account that it was not possible to monitor the established population during the 24 months, meaning that the results obtained for the 12-month period include only 37 trans-

gender people from the initial population, and those for the 24 months only include 15. Considering these results and the duration of the study, possibly a greater follow-up would be necessary to provide more accurate results and to understand the long-term effects of this therapy. Another limitation of this study was the lack of a control group, considering that some of the changes that occurred may be related to the adolescence period.

In 2020, a prospective longitudinal study was developed with the aim of evaluating the physiological impact of hormonal therapy for gender dysphoria in transgender adolescents [14]. Monitoring was carried out between February 2011 and June 2013 of 59 adolescents aged between 12 and 24 years old (34 transgender men and 25 transgender women). Initially, transgender women were medicated with oral spironolactone (100–200 mg/day) or GnRHa with 17β-estradiol (oral estradiol—1–6 mg/day; injectable estradiol—20–30 mg IM every 2 weeks). Since antiandrogens were not reimbursed, 28% of participants chose not to use them, being treated only with estradiol. Regarding transgender men, they received testosterone cypionate subcutaneously with doses between 12.5 and 75 mg/week. Two of the participants were simultaneously taking GnRHa, since they had already started taking it before entering the study. Participants were followed for 21–31 months after starting therapy, and the majority had never used hormone therapy before or, in some cases, had used it for a maximum of 3 months. After 24 months of follow-up, there was only a statistically significant increase in HDL values (43.83 mg/dL vs. 50.91 mg/dL, $p < 0.001$) in adolescent transgender women; however, this remained within normal values for cisgender women. In the case of transgender male adolescents, there were significant changes in the HDL values (51.74 mg/dL vs. 44.49 mg/dL, $p < 0.001$) and triglyceride values (109.86 mg/dL vs. 144.40 mg/dL, $p < 0.05$). Overall, the authors concluded that, despite the differences found, there was no clinical significance [14]. However, this study is not free of limitations, including difficulties in collecting data and correctly adhering to therapy and monitoring, as it concerned a younger population. Moreover, it is not representative of the general population, considering that the population studied was almost all Caucasian and Latino [14].

Lastly, through a cross-sectional cohort study, the lipoprotein subtypes were analyzed in the profile of 17 transgender male adolescents (12–23 years old) treated with testosterone [15]. To analyze the lipid profile, plasma was collected between January 2017 and August 2020, and, subsequently, the samples were analyzed using nuclear magnetic resonance (NMR) spectroscopy. All individuals taking medication associated with lipid-metabolic effects or with medical conditions associated with abnormal cholesterol values were excluded from the test. The participants were treated with testosterone cypionate subcutaneously (average time of 1.2 ± 0.8 years); 12 adolescents received 50 mg/week, 4 adolescents received 60 mg/week, and 1 adolescent received 80 mg/week, all the same formulation. Before the study, none of the teenagers had been medicated with GnRHa. This group of adolescents was then compared with two groups: a group of 32 cisgender female adolescents and a group of 33 cisgender male adolescents. These control groups had similar average age, blood pressure values, and percentages of racial distribution, but with different body mass index (BMI) values, which were higher in the transgender adolescents, so all data were adjusted for this difference. The results obtained showed that the lipid profile of transgender adolescents was similar to those of cisgender male adolescents and more atherogenic compared to the lipid profile of cisgender female adolescents, as they had higher values of small LDL particles (435 ± 222 nmol/L vs. 244 ± 163 nmol/L, $p = 0.008$). However, due to this increase in small LDL particles, the transgender adolescent group had a higher concentration of LDL than cisgender women (81 ± 27 mg/dL vs. 67 ± 19 mg/dL), but this change was not statistically significant when controlled for BMI. Furthermore, the transgender group presented lower concentrations of large HDL particles when compared to cisgender females (1.5 ± 1.3 μmol/L vs. 2.7 ± 1.2 μmol/L, $p = 0.003$), with no change in small or medium HDL particles, which, consequently, caused decreased HDL concentration values in general when compared to cisgender women (45 ± 12 mg/dL vs. 57 ± 11 mg/dL, $p = 0.007$). Regarding the cisgender men, the values were similar. Moreover, there were

no significant changes in triglycerides in the transgender group compared to the other two groups [15]. In this study, the authors showed that transgender male adolescents treated with testosterone have lipoprotein profiles more similar to those of cisgender male adolescents than female adolescents, concluding that testosterone seems to be the main factor promoting the more atherogenic lipoprotein subtype profiles found in males [15]. However, it was not possible to exclude external variables such as tobacco consumption, dietary habits, and physical activity that may have influenced the results, as well as the fact that the samples were not all obtained in a fasting state. In addition, it is difficult to understand which of the hormones is affecting the lipid profile, since hormone therapy with testosterone increases the values of this hormone but decreases the values of estrogen.

Overall, these studies show that hormonal treatment in adolescents seems to decrease total cholesterol and HDL cholesterol and increase LDL cholesterol levels, mostly in transgender men. However, research in such young populations is still taking its first steps, and caution must be made considering the normal hormone changes in adolescence. Thus, according to the three articles presented, the question remains: since these changes can already be seen at such a young age and with little treatment time, can the impact of these therapies be even more pronounced at older ages and for longer periods of time?

3.2. Adults

The remaining 12 articles analyzed the hormonal therapy effects in adult populations. Some of them focused only on transgender populations of a certain gender, transgender women [16] or transsexual men [17,18], while others studied the hormonal impact on both groups [19–27].

The study conducted by Even Zohar and colleagues analyzed the effectiveness of different doses of cyproterone acetate (CPA) in transgender women [16]. This retrospective cohort study was developed in Israel, between January 2003 and October 2018. A total of 64 transgender women were included in the study, which was divided into two groups: (1) 38 participants on low doses of CPA (10 or 20 mg/day) and (2) 26 participants on high doses of CPA (50 or 100 mg/day). In addition to CPA, transgender women were treated with 17β-estradiol in the form of a transdermal patch (83.7 $\pm$ 36.5 mg estradiol/day), transdermal gel (3.8 $\pm$ 1.2 g/day), or orally (4.1 $\pm$ 1.7 mg/day, with higher doses for group 2). The patients were evaluated for serum liver enzymes, hormonal values, and lipid profiles using assay kits, and data regarding their age, weight, height, and blood pressure values were collected. Follow-up for these patients was carried out every 3–6 months in the clinic, and the parameters were collected again. The results obtained demonstrated that, in both groups, the triglyceride value decreased, from 75.8 mg/dL to 63.8 mg/dL ($p = 0.049$) in group 1 (low doses of CPA), and 113.7 mg/dL to 92.5 mg/dL in group 2 (high doses of CPA). Furthermore, there were no significant changes in total cholesterol, HDL, and LDL during treatment [16]. Thus, since there is still no concrete evidence that establishes a dose-dependent cause–effect relationship, we can conclude that, regarding the lipid profile, none of the doses is safer than the other. However, it has been demonstrated that lower doses of CPA are safer in other parameters, which is in line with the values presented by The Endocrine Society [9]. This study presented some inherent limitations. As this is a retrospective study, the data were collected beforehand and may be incomplete or incorrect. In addition, the blood tests were carried out in different laboratories over the years and may differ in reference or cut-off values.

Two different studies were conducted resorting to a population of only transgender men [17,18]. The first study, carried out in Bologna, Italy, had the purpose of evaluating the effect of testosterone as a hormonal treatment on the serological lipid values of transgender men [17]. For this, 16 participants were selected, all without a family history of hypercholesterolemia or dyslipidemia and with a BMI between 19 and 30 kg/m^2. As an inclusion criterion, participants needed to undergo hormonal treatment with 100 mg of testosterone enanthate with 25 mg of testosterone propionate (intramuscular) every 10 days for 6 months, at which point they would be assessed again. Blood samples were collected

after an overnight fasting, stored at −20 °C, and analyzed only at the end of the study. The results from this observational study showed a significant decrease in HDL levels after 6 months of treatment, from 1.7 ± 0.4 mmol/L at baseline to 1.5 ± 0.4 mmol/L after 6 months ($p < 0.005$). Regarding LDL, total cholesterol, and triglycerides levels, there were no significant changes [17]. Similarly, Tangpricha et al. also found a significant decrease in the HDL levels (from 52 ± 11 mg/dL to 40 ± 7 mg/dL after 12 months of testosterone, $p < 0.001$), with no changes in the remaining lipid parameters. In this retrospective cohort, 12 transgender men who had never received testosterone therapy were included, and the therapy consisted of testosterone esters, cypionate, or enanthate in a dosage that varied between 50 and 125 mg every 2 weeks for 12 months. The authors also demonstrated an increased atherogenic lipid profile considering the reduction in HDL and leptin levels [18]. Despite being different populations, with different treatment designs, regarding the duration and doses, the results of these two studies were similar. However, we must point out the lack of control groups for these two population samples, which are very small and may not be representative of the general population. In addition, longer-term studies are needed to determine the impact of these changes on cardiovascular health.

As previously mentioned, most of the studies analyzed in this review focus on hormonal therapy effects in both transgender women and men. Thus, in a Dutch prospective longitudinal study, a population of 37 transgender subjects, 20 transgender women and 17 transgender men, aged between 16 and 36 years old, was analyzed [19]. All participants were eugonadal, non-obese, and considered healthy with no signs of cardiovascular disease, diabetes mellitus, or kidney disease, and with no hormone therapy ever received. The recommended therapy in this study was 100 µg/day of ethinyl estradiol + 100 mg/day cyproterone acetate for transgender women, while for transgender men it was 250 mg/2 weeks (intramuscular) of testosterone esters. All participants provided an overnight fasting blood sample and were measured for blood pressure, insulin sensitivity, and anthropometric parameters at baseline after 2 and 12 months of therapy. Regarding the lipid profile, the authors found that testosterone therapy caused a significant decrease in HDL levels (20%) and its sub-fractions HDL2 (40%) and HDL3 (15%). Furthermore, there was an increase in triglyceride levels (33%) and a small decrease in the size of the LDL molecules (0.4%). In the case of transgender women, there were opposite results, with an increase in HDL levels (24%), which was more pronounced in HDL2 (84%) than HDL3 (11%). Moreover, the triglyceride levels increased by 86% and the LDL levels decreased significantly (12%), and, similar to transgender men, their particle size decreased by 1.1% [19]. According to these results, the authors suggested, even if not unequivocally, that the possibility of developing a cardiovascular event increases with testosterone administration since the lipid profile becomes more atherogenic. Contrarily, in transgender women, the administration of estrogen seems to be cardioprotective [19]. These results should be analyzed with caution, and the therapy used in this study should be re-examined, since, according to the current guidelines, the doses were too high and unapproved formulations were used, which are not recommended for this population.

In 2012, Wierckx and co-workers published a study on the long-term effects of hormone therapy in transgender people that was divided into two phases [20]. The first took place in 2007 and included 50 transgender women who had already been exposed to hormonal therapy for least 2 years and after 6 months after sex reassignment surgery (orchidectomy and phallectomy in combination with vaginoplasty). Before surgery, the hormonal therapy used began with antiandrogens, with 50–100 mg/day of CPA for a maximum of 1 year and, subsequently, exogenous estrogen was added in different formulations (22 participants used 1.5 mg/day of 17β-estradiol gel, 3 of them opted for the transdermal estradiol patch at 50 µg/day, 19 used 2 mg of oral estradiol valerate, 1 used 2 mg of estriol, and the remaining participants used 50 µg or 120 µg of ethinyl estradiol). The second phase included 50 transgender men who were on hormone therapy between 1987 and 2009 and underwent sex reassignment surgery (hystero-oophorectomy and mastectomy) at least 2 years prior to the study. The participants used testosterone hormone therapy (35 of

them used 250 mg of parental testosterone esters IM every 2–3 weeks, 7 used testosterone undecanoate at 1000 mg/12 weeks, and the remaining 7 used transdermal testosterone gel at 50 mg/day). In addition to answering questionnaires about their medical history, body changes, and surgical results, the participants also provided venous blood samples for subsequent biochemical analysis. The results obtained for the lipid profile demonstrate lower triglyceride levels in the transgender women group; however, the cardiovascular risk was similar in both groups [20]. Like all cross-sectional studies, one of the limitations is the inability to establish causal relationships. Moreover, the average age of the transgender women was approximately 6 years higher than that of the transgender men, increasing their susceptibility to CV events.

A different retrospective study gathered a population of 33 transgender women and 19 transgender men undergoing hormone therapy for the first time. The volunteers were followed up for over 18 months, with monitoring visits at 3–6 months and between 6 and 18 months after hormone therapy initiation. For transgender women, the therapy instituted was oral estrogen (1.44 mg/day in the first visit and 1.71 mg/day in the second visit), intramuscular estrogen (1.21 mg/day in the first visit and 1.18 mg/day in the second visit), or transdermal estrogen (0.1 mg/day in both visits). Furthermore, the majority used spironolactone at an average of 100 mg/day. Transgender men were medicated with testosterone in average doses of 10.71 mg/day in the first visit and 11.36 mg/day in the second visit. The results of the study demonstrated a statistically significant change in transgender women, with increased HDL in the first visit compared to baseline, while the second visit showed no changes. Although it is considered necessary that these populations have greater monitoring due to the lack of knowledge about the potential effects of hormonal therapy, in this case, regarding the lipid profile, this therapy seems to be safe [22].

Using a small cohort of transgender patients, Vita et al. also demonstrated the safety of hormonal therapy [23]. Twenty-one transgender women were treated with oral estradiol valerate 2–6 mg/day (n = 21) and CPA 50–100 mg/day. The 11 transgender men were medicated with testosterone enanthate IM every 2–4 weeks (n = 10) or testosterone undecanoate (n = 1). In transgender women, the results showed a negative correlation between total cholesterol and HDL levels and the quantification of estradiol, that is, estradiol treatment decreased total cholesterol and HDL levels (r = −0.341, p = 0.04; −0.338, p = 0.05, respectively), with more changes observed in participants taking estradiol valerate at 6 mg/day. In the case of transgender men, there was a positive correlation between 17β-estradiol and HDL levels, since the decrease in 17β-estradiol value led to a sharp decrease in HDL [23].

The previous studies have presented results relating to very small population sizes, making it difficult to reach a definitive conclusion regarding the safety of these therapies. Thus, using a larger population sample, SoRelle and collaborators evaluated the impact of hormonal therapy on biochemical parameters in transgender people [24]. A total of 302 participants (183 transgender women and 119 transgender men) were included and divided into two groups: (1) those who had already undergone 6 months of hormone therapy and (2) those who had never taken hormone therapy before the study. Transgender women were prescribed oral estradiol at 2–8 mg/day and transgender men were prescribed 35–300 mg of parental testosterone IM every 1–2 weeks. The results obtained demonstrated no statistically significant changes in the case of transgender women taking estrogen. On the other hand, transgender men treated with testosterone had an increase in triglycerides (p = 0.0009) and a decrease in HDL levels (p < 0.0001) [24]. However, it is important to point out that the hormonal treatments used in this study had different doses, so caution must be made regarding these results. In conclusion, more studies must be carried out to concretely evaluate the impact of different therapies, taking into account dosages and formulations.

In 2010, a European partnership between several gender identity clinics from the Netherlands, Belgium, Norway, and Italy, was formed, called the European Network for the Investigation of Gender Incongruence (ENIGI). The purpose was to understand the diversity in diagnostics and treatment used for transgender people. The volunteers were included in the study when they started hormone therapy for the first time, and all the

inclusion and exclusion criteria can be found in the studies by Dekker et al. and Kreukels et al. [26,28,29]. Four different studies resorted to the ENIGI to understand the effects of transgender hormonal treatment on lipid profiles and cardiovascular risk [21,25–27].

A population of 53 transgender women and 53 transgender men participated in the study developed by Wierckx and co-workers [21]. For 1 year, transgender men were treated with testosterone undecanoate at 1000 mg/6 weeks IM or testosterone esters (testosterone decanoate 100 mg, testosterone isocypionate 60 mg, testosterone phenylpropionate 60 mg, or testosterone propionate 30 mg/mL) every 2 weeks. Regarding transgender women, the treatment was divided according to age; those under 45 years (n = 40) were medicated with 50 mg of CPA combined with 4 mg of estradiol valerate daily, and those over 45 years old (n = 13) were medicated with 50 mg of CPA daily in combination with a transdermal patch of 17β-estradiol 100 µg/day, transdermal 17β-estradiol gel at 2 mg twice a day, or 4 mg intravenously. In transgender women, the results obtained were favorable in terms of lipid profile, with a decrease in the concentration of total cholesterol and LDL-C during therapy with oral and transdermal estrogen, with no significant change in triglyceride levels. Hormone therapy in transgender men induced a less favorable lipid panel. Although there was no significance for total cholesterol and LDL values, triglyceride values increased (69.0 mg/dL vs. 81.1 mg/dL, $p < 0.001$), while HDL values decreased (56.3 ± 12.7 mg/dL vs. 47.8 ± 10.7 mg/dL, $p < 0.001$) during treatment [21]. Overall, these results seem to present an unfavorable lipid profile for transgender men.

In 2019, van Velzen et al. found similar results, with adverse changes in lipid profiles observed in transgender men but not in transgender women [25], in the same timeline as the Wierckx et al. study [21]. In this case, only individuals followed in the ENIGI from the Netherlands and Belgium were included, with 242 transgender women and 188 transgender men. Transgender women under 45 years old (n = 144) were medicated with oral estradiol valerate 2 mg/twice a day, accompanied by CPA 50 mg/day, while for those over 45 years of age, oral estradiol was substituted by transdermal patch estradiol 1 mg/day (n = 98). The 79 transgender men followed in Belgium received a therapeutic regimen with testosterone undecanoate 100 mg/every 12 weeks, while those followed in the Netherlands received testosterone gel 50 mg/day (n = 47) or testosterone esters IM 250 mg/2 weeks (n = 62). After blood analytical measurements at the baseline and upon 12 months of therapy, LDL levels increased by 0.32 mmol/L (95% CI, 0.22 to 0.42), HDL decreased by 0.17 mmol/L (95% CI, 0.12 to 0.21), and triglycerides increased by 0.26 mmol/L (95% CI 0.21 to 0.31) in transgender men. In transgender women, there was a decrease in LDL of 0.16 mmol/L (95% CI, 0.09 to 0.22), HDL-C decreased by 0.13 mmol/L (95% CI, 0.10 to 0.16), and triglyceride levels also decreased by 0.09 mmol/L (95% CI, 0.05 to 0.13). It was not possible to establish a direct correlation between the different hormone treatments and the change in lipid profile in either of the groups, either transgender men or women. Thus, it appears that testosterone seems to have an unfavorable effect on the lipid profile, while estrogens seem to have opposite effects [25].

A prospective observational study collected data from 309 participants of the ENIGI (144 transgender women and 165 transgender men) and assessed the long-term cardiovascular implications of hormone therapy after two years [27]. The treatment used by transgender women was oral estradiol valerate between 2 and 6 mg/day in the case of 102 participants, transdermal estrogen 25–50 mg/day in 25 participants, and transdermal estradiol valerate gel 1 to 3 mg/day for 17 participants. Additionally, 136 transgender women were medicated with CPA 50–100 mg/day. Transgender men were administered with IM testosterone undecanoate 1000 mg/12 weeks (n = 156), used testosterone enanthate 250–500 mg/28 days (n = 6), and used transdermal testosterone gel 5–6 mg/day (n = 3). Data were collected at baseline and after 12 and 24 months, and, using information on gender, age, hypertensive drugs, smoking habits, history of diabetes, systolic pressure, and BMI or total and HDL cholesterol values, the Framingham CV risk calculation formula was used to assess the CV risk in people between 20 and 59 years of age. This is divided into general CV events, defined as coronary insufficiency, angina pectoris, TIA, intermittent

claudication, and congestive heart failure, and major CV events, referred to as coronary death and acute myocardial infarction [30]. Cocchetti and collaborators concluded that both transgender men and women experienced significant changes in lipid values. In transgender women, the lipid profile showed a decrease in total cholesterol, triglycerides, and LDL levels ($p < 0.003$, $p < 0.006$, $p < 0.03$, respectively). In transgender men, the lipid profile became less favorable, with increased levels of total cholesterol, triglycerides, and LDL ($p < 0.005$, $p < 0.0001$, $p < 0.0001$, respectively), while HDL values decreased ($p < 0.0001$) over the course of the 24 months. According to the Framingham risk score, an increased risk of general (1.44%) and major (0.68%) CV events was found for transgender men when comparing the 24-month follow-up to the baseline, with no significant effects found for transgender women [27]. The results of this study are in accordance with the previous two resorting to the ENIGI data, with adverse effects found for transgender men using testosterone-based hormone therapy. However, this study presented some limitations, including the use of psychotropic drugs, which was not evaluated and which may have effects on the metabolic profile; the absence of a control group without medication; and the Framingham CVD risk score in an algorithm that has only been validated in cisgender populations.

A slightly different perspective was carried out by van Velzen and colleagues evaluating the impact of hormonal therapy on the efflux capacity of cholesterol (CEC)-HDL [26]. CEC is the ability of HDL to remove cholesterol from the artery walls and, as such, is an excellent predictor of cardiovascular risk. Conversely, cholesterol carrying capacity (CLC) refers to the ability of macrophages to store more cholesterol in their walls, which is a poor indicator of CV risk. In this observational study, carried out between June 2010 and November 2017, 15 transgender men and 15 transgender women were included form the ENIGI cohort. Participants were followed for 12 months, with transgender women taking, besides CPA 50 mg/day, oral estradiol valerate 2 mg/2 times a day or transdermal patches 100 µg/day every 2 weeks. In the case of transgender men, they could opt for testosterone gel 50 mg/day, testosterone esters (intramuscular) 250 mg every 3 weeks, or 1000 mg of injectable testosterone undecanoate every 12 weeks. The results demonstrated that, in transgender men, there were no significant changes in total cholesterol or LDL levels, but there was a significant increase in the value of triglycerides (0.72 mmol/L vs. 0.90 mmol/L, $p < 0.05$), and HDL-C decreased by 19.6% at 12 months of treatment. In transgender women, total cholesterol and LDL levels decreased (4.8 mmol/L vs. 4.47 mmol/L, $p < 0.05$, and 2.97 mmol/L vs. 2.84 mmol/L, $p < 0.05$, respectively), HDL decreased by 14.3%, and there were no changes in triglyceride levels. In the case of serum CLC, there were no changes in both groups. Regarding the HDL-CEC values, no significant differences were proven in transgender men; however, in transgender women, there was a decrease in its value by 10.8% after 12 months of treatment. The authors suggested that these lipid profile results might contribute to a higher CVD risk [26].

Table 2. Summary of the studies analyzed regarding the connection between hormone therapy and cardiovascular outcomes in transgender adolescents and adults.

Authors, Year	Country	Population	Treatment and Dosages	Main Results
			Adolescents	
Stoffers et al., 2019 [13]	The Netherlands	62 transgender men	- GnRHa 3.75 mg every 4 weeks for at least 6 months before starting hormonal therapy with T. - After age 15–16, T therapy began (25 mg/2 weeks), increasing the dose every 6 months to a total of 125 mg/2 weeks. - For adolescents over 16 years of age at the start of the study, T doses could be increased more rapidly, starting at 75 mg/2 weeks, increasing to 125 mg/2 weeks after 6 months.	- Decreased total cholesterol in the first 6 months (4.59 vs. 4.24 mmol/L, $p < 0.001$), then slowly increased and did not differ significantly at 12 and 24 months. - Decreased HDL during the first 6 months (1.58 vs. 1.33 mmol/L; $p < 0.001$) and remained unchanged in the remaining months.

Table 2. *Cont.*

Authors, Year	Country	Population	Treatment and Dosages	Main Results
Olson-Kennedy et al., 2018 [14]	USA	59 transgender teenagers (25 transgender women and 34 transgender men)	Transgender women: - Spironolactone 100–200 mg/day orally or GnRHa with 17-β estradiol (oral estradiol—1–6 mg/day; injectable estradiol—20–30 mg IM every 2 weeks). Transgender men: - T cypionate subcutaneously with doses from 12.5 to 75 mg/week (most of them from 50 to 75 mg/week). - Two of the participants were simultaneously taking GnRHa.	Transgender women: - Increased HDL levels (43.83 vs. 50.91 mg/dL, $p < 0.001$), that remained within the normal range for cisgender women. Transgender men: - Decreased HDL levels (51.74 vs. 44.49 mg/dL, $p < 0.001$). - Significant changes in TG, with no clinical value.
Millington et al., 2021 [15]	USA	17 transgender men	Subcutaneous T cypionate: - 50 mg/week ($n = 12$) - 60 mg/week ($n = 4$) - 80 mg/week ($n = 1$)	- Increased small LDL particles compared to cisgender females (435 ± 222 nmol/L vs. 244 ± 163 nmol/L, $p = 0.008$). - Increased LDL concentration than cisgender women (81 ± 27 mg/dL vs. 67 ± 19 mg/dL). - Decreased large HDL particles (1.5 ± 1.3 µmol/L vs. 2.7 ± 1.2 µmol/L, $p = 0.003$) and HDL values (45 ± 12 mg/dL vs. 57 ± 11 mg/dL, $p = 0.007$) compared to cisgender females.
			Adults	
Even Zohar et al., 2021 [16]	Israel	64 transgender women (38 in the low-dose CPA group and 26 in the high-dose CPA group)	Low-dose CPA group: - 10 mg/day ($n = 32$) - 20 mg/day ($n = 6$) High-dose CPA group: - 50 mg/day ($n = 20$) - 100 mg/day ($n = 6$) 17β-estradiol: - Transdermal patch (83.7 ± 36.5 mg/day) - Transdermal gel (3.8 ± 1.2 g/day) - Orally (4.1 ± 1.7 mg/day)	- Decreased TG levels in both groups (low-dose group: from 75.8 mg/dL to 63.8 mg/dL, $p = 0.049$; high-dose group: from 113.7 mg/dL to 92.5 mg/dL). - No significant changes in total cholesterol, HDL, and LDL values.
Berra et al., 2006 [17]	Italy	16 transgender men	100 mg T enanthate + 25 mg T propionate (IM) every 10 days for 6 months	Decreased HDL levels after 6 months (1.7 ± 0.4 mmol/L vs. 1.5 ± 0.4 mmol/L, $p < 0.005$)
Tangpricha et al., 2010 [18]	USA	12 transgender men	50–125 mg T esters, cypionate, or enanthate every 2 weeks for 12 months	Decreased HDL levels after 12 months (52 ± 11 mg/dL vs. 40 ± 7 mg/dL, $p < 0.001$)
Elbers et al., 2003 [19]	The Netherlands	37 transgender people (20 transgender women and 17 transgender men)	Transgender women: 100 µg/day of ethinyl estradiol + 100 mg/day CPA Transgender men: 250 mg/2 weeks (IM) of T esters	Transgender women: - Increased HDL levels (24%), HDL2 (84%), HDL3 (11%). - Decreased LDL levels (12%) and particle size (1.1%). - Increased TG levels (86%). Transgender men: - Decreased HDL levels (20%), HDL2 (40%), HDL3 (15%). - Decreased LDL particle size (0.4%). - Increased TG levels (33%).
Wierckx et al., 2012 [20]	Belgium	100 transgender people (50 transgender women and 50 transgender men)	Transgender women: 50–100 mg/day of CPA for 1 year and exogenous estrogen: - 1.5 mg/day of 17β-estradiol gel ($n = 22$) - 50 µg/day transdermal estradiol patch ($n = 3$) - 2 mg of oral estradiol valerate ($n = 19$) - 2 mg of estriol ($n = 1$) - 50 or 120 µg of ethinyl estradiol ($n = 5$) Transgender men: - 250 mg of parental T esters (IM) every 2–3 weeks ($n = 35$) - 1000 mg/12 weeks of T undecanoate ($n = 7$) - 50 mg/day of transdermal T gel ($n = 7$)	- Decreased TG levels in transgender women compared to men. - CV risk similar in both groups.

Table 2. *Cont.*

Authors, Year	Country	Population	Treatment and Dosages	Main Results
Fernandez et al., 2016 [22]	USA	52 transgender people (33 transgender women and 19 transgender men)	Transgender women: 100 mg/day of spironolactone and: - Oral estrogen (1.44 mg/day on the 1st visit, 1.71 mg/day on the 2nd visit) - Intramuscular estrogen (1.21 mg/day on 1st visit, 1.18 mg/day on the 2nd visit) - Transdermal estrogen (0.1 mg/day in both visits) Transgender men: T in average doses of 10.71 mg/day in the 1st visit and 11.36 mg/day in the 2nd visit.	Increased HDL levels in transgender women in the first visit compared to baseline.
Vita et al., 2018 [23]	Italy	32 transgender people (21 transgender women and 11 transgender men)	Transgender women: Oral estradiol valerate 2–6 mg/day and CPA 50–100 mg/day. Transgender men: - T enanthate IM every 2–4 weeks (n = 10) - T undecanoate (n = 1).	Transgender women: - Negative correlation between quantification of estradiol and total cholesterol and HDL levels (r = −0.341, p = 0.04; −0.338, p = 0.05, respectively), more pronounced for estradiol valerate at 6 mg/day. Transgender men: - Decreased HDL levels
SoRelle et al., 2019 [24]	USA	302 transgender people (183 transgender women and 119 transgender men)	Transgender women: 2–8 mg/day of oral estradiol Transgender men: 35–300 mg of parental T (IM) every 1–2 weeks	Transgender women: No significant changes Transgender men: - Increased TG levels (p = 0.0009) - Decreased HDL levels (p < 0.0001)
Wierckx et al., 2014 [21]	ENIGI (Belgium, Norway, the Netherlands)	106 transgender people (53 transgender women and 53 transgender men)	Transgender women: - <45 years: 50 mg of CPA with 4 mg of estradiol valerate daily (n = 40); - >45 years: 50 mg of CPA daily with a transdermal patch of 17β-estradiol 100 µg/day, transdermal 17β-estradiol gel at 2 mg twice a day or 4 mg intravenously (n = 13) Transgender men: - T undecanoate at 1000 mg/6 weeks (IM) - T esters (T decanoate 100 mg, T isocypionate 60 mg, T phenylpropionate 60 mg, or T propionate 30 mg/mL) every 2 weeks.	Transgender women: - Decreased total cholesterol and LDL-C during therapy with oral and transdermal estrogen. Transgender men: - Increased triglyceride levels (69.0 mg/dL vs. 81.1 mg/dL, p < 0.001) - Decreased HDL levels (56.3 ± 12.7 mg/dL vs. 47.8 ± 10.7 mg/dL, p < 0.001).
van Velzen et al., 2019 [25]	ENIGI (Belgium, the Netherlands)	430 transgender people (242 transgender women and 188 transgender men)	Transgender women: - <45 years: CPA 50 mg/day with oral estradiol valerate 2 mg/twice a day (n = 144) - >45 years: CPA 50 mg/day with transdermal patch estradiol 1 mg/day (n = 98) Transgender men: - From Belgium (n = 79): T undecanoate 100 mg/every 12 weeks - From the Netherlands: T gel 50 mg/day (n = 47) or T esters (IM) 250 mg/2 weeks (n = 62)	Transgender women: - Decreased LDL, HDL, and TG levels Transgender men: - Increased LDL levels - Decreased HDL levels - Increased TG levels
Cocchetti et al., 2021 [27]	ENIGI (Belgium, Norway, the Netherlands)	309 transgender people (144 transgender women and 165 transgender men)	Transgender women: CPA 50–100 mg/day (n = 136) and: - Estradiol valerate 2–6 mg/day (n = 102) - Transdermal estrogen 25–50 mg/day (n = 25) - Transdermal estradiol valerate gel 1–3 mg/day (n = 17). Transgender men: - T undecanoate 1000 mg/12 weeks (IM) (n = 156) - T enanthate 250–500 mg/28 days (n = 6) - Transdermal T gel 5–6 mg/day (n = 3)	Transgender women: - Decreased total cholesterol, TG, and LDL levels (p < 0.003, p < 0.006, p < 0.03, respectively). Transgender men: - Increased total cholesterol, TG, and LDL levels (p < 0.005, p < 0.0001, p < 0.0001, respectively) - Decreased HDL levels (p < 0.0001) - Increased risk of general (1.44%) and major (0.68%) CV events

Table 2. *Cont.*

Authors, Year	Country	Population	Treatment and Dosages	Main Results
van Velzen et al., 2021 [26]	ENIGI (Belgium, Norway, the Netherlands)	30 transgender people (15 transgender women and 15 transgender men)	Transgender women: - CPA 50 mg/day and: - Oral estradiol valerate 2 mg/2 times a day - Transdermal patches 100 µg/day every 2 weeks Transgender men: - T gel 50 mg/day, - T esters (IM) 250 mg every 3 weeks - T undecanoate 1000 mg of injectable every 12 weeks	Transgender women: - Decreased total cholesterol levels (4.8 mmol/L vs. 4.47 mmol/L, $p < 0.05$) - Decreased LDL levels (2.97 mmol/L vs. 2.84 mmol/L, $p < 0.05$) - Decreased HDL levels by 14.3% - Decreased HDL-CEC values by 10.8% Transgender men: - Increased TG levels (0.72 mmol/L vs. 0.90 mmol/L, $p < 0.05$) - Decreased HDL-C by 19.6%.

BMI, body mass index; CPA, cyproterone acetate; ENIGI, European Network for the Investigation of Gender Incongruence; HDL, high-density lipoprotein; IM, intramuscular; LDL, low-density lipoprotein; T, testosterone; TG, triglyceride.

4. Discussion

This review summarizes the existing literature on the impact of hormonal therapy, in both transgender men and women, from adolescence to adulthood, on the lipid profile and, as a consequence, on cardiovascular risk. The transgender population is currently growing, with an estimated 0.5% of adults and 3% of adolescents identifying as transgender in the United States of America (USA) and Europe [31–33], and around 75% of them are undergoing hormone therapy in the USA [8]. However, despite the exponential growth observed, the transgender population, as well as the long-term effects of hormonal therapy, remain very little studied. However, although there are several treatment options, with different dosages and formulations, for specific age ranges, very little has been studied about the real impact of this therapy, in the short and long term, at the cardiovascular level [8,10]. As it is known, the increase in LDL, total cholesterol, and triglycerides favors the creation of an atherogenic environment and, consequently, increases the cardiovascular risk [34]. Conversely, increased HDL levels have a protective function in the cardiovascular system, as HDL removes cholesterol from the arteries and has antioxidant, anti-inflammatory, antithrombotic, anti-apoptotic, and vasodilatory properties [35–38]. In this sense, evaluating the increase or decrease in different lipids allows us to infer their effect on CV risk. The 15 articles analyzed demonstrated that hormonal therapy with estradiol, testosterone, antiandrogens, and GnRH analogs caused statistically significant changes in the individuals' lipid profiles.

Regarding the effect of hormonal treatment on adolescents, hormonal treatment in adolescents seems to decrease total cholesterol and HDL cholesterol and increase LDL cholesterol levels, mostly in transgender men [13–15]. In transgender women, only an increase in HDL levels was demonstrated when subjected to hormonal therapy [14]. Understandably, there are few epidemiological studies on this matter in such young populations, so the results obtained in these have to be compared with those from older populations. Moreover, normal hormonal changes in adolescence must be taken into account.

Regarding transgender women, some studies demonstrated an improvement in the lipid profile, which may lead to a reduction in CV risk or to keeping a lower CV risk. Of the articles analyzed, four observed a decrease in the LDL values [19,25–27], two demonstrated a decrease in total cholesterol [26,27], four showed a decrease in the triglyceride value [16,20,25,27], and two demonstrated an increase in the HDL value [19,22], although Fernandez et al. showed that this increase only occurred in the first visit, normalizing during the remaining period of the study. Some of the results obtained are in agreement with other existing articles, with some of the lipid parameters being significantly altered [22,39,40]. However, there are also studies that demonstrate opposite results, revealing increased triglyceride values and no changes in the remaining parameters [39,41,42].

The diversity of existing results does not allow us to determine the true impact of hormonal therapy on lipid parameters. Based on the results obtained, lipid changes were suggestive of a lower cardiovascular risk. However, some studies demonstrate an increased cardiovascular risk in transgender women compared to cisgender women [43–45]. These studies demonstrated an increased incidence of venous thromboembolism and cerebrovascular accidents (CVA) in transgender women when compared to the cisgender population, either men or women. Also, de Blok et al. demonstrated an increase in mortality in the transgender population due to an increase in cardiovascular diseases [46]. A positive correlation between the use of estrogens as hormonal therapy and increased risk of hypertension was shown by Pyra and collaborators [47]. However, it is necessary to evaluate and standardize the dosage and formulation used in the studies so that the results are not biased. As mentioned previously, many transgender women take estrogen and anti-androgen therapy in order to suppress male characteristics. The CPA dosage recommended in the guidelines is 10 mg/day; however, in all studies, the dosages were between 50 and 100 mg/day, and in the study conducted by SoRelle et al. oral estradiol was given between 2 and 8 mg/day when a maximum of 6 mg/day is recommended [24]. On the other hand, the study by Even Zohar et al. was fundamental, as they showed that lower doses of CPA, according to the guidelines, have the same impact on the lipid profile as the higher doses used in the past. Therefore, more studies are needed to understand if the same occurs for other hormonal treatments, and to determine if lower dosages are sufficient for transition while, at the same time, reducing the occurrence of the associated adverse effects [16]. In addition, it could be interesting to compare the results obtained with the effect that hormonal contraceptive methods and hormone replacement therapy have on women's lipid profiles. Specifically, in cisgender women, it was observed that postmenopausal hormone therapy could produce a regression in atherosclerosis. Some studies have documented a reduction in intimal thickening [48,49] and a reduction in atherosclerotic plaque length and thickness [50]. These cardioprotective effects have been comparable to those induced by a lipid-lowering drug [48–50]. Contrarily, the HERS study conducted by Hulley et al. demonstrated that hormonal therapy in cisgender women with established coronary disease showed that the oral conjugated estradiol and progesterone did not reduce cardiovascular events. In fact, the authors observed an increase in thromboembolic events and gallbladder disease [51]. Therefore, based on this study, the clinical recommendations were changed. However, according to other authors, the results obtained in this study cannot be extrapolated to healthy women since the characteristics of the study population were very different [52,53]. In summary, although it is not possible to directly determine the effects of hormone therapy on CV risk associated with the lipid profile, taking into account the controversy of results and the different populations under study, we can suggest that, in the case of healthy transgender women, the administration of hormone therapy seems to produce results more similar to healthy cisgender women than cisgender women with cardiovascular pathologies. However, it is urgent to increase the number of studies with a considerable number of people (healthy and with different pathologies) with different types of hormone therapy to have a clear idea of the effect of these therapies on the general population.

The results were less divergent regarding transgender men. Of the studies analyzed, 2 showed an increase in LDL [25,27], 1 of them demonstrated an increase in total cholesterol [27], 6 indicated an increase in triglycerides [19,21,24–27], and 10 showed a decrease in HDL [17–19,21–27]. According to these results, there seems to be an increased risk of CV, as from the population studied, hormonal therapy led to the development of an atherogenic lipid profile. These results are in accordance with previous ones where decreased HDL levels were found [42,54,55], as well as increased LDL levels [42], total cholesterol, and triglycerides [39,55], which were later confirmed in a meta-analysis [41]. Although lipid changes can be a good starting point to infer changes in CV risk in the transgender population, they depend on numerous variables. For example, several studies have already demonstrated that hormone therapy can have an impact on body fat distribution [19,56], increased body fat [57], increased BMI [54,58,59], and blood pressure [25,47,54,58], and

all of these are risk factors for cardiovascular diseases. However, as mentioned in the case of transgender women, some of the studies used dosages and formulations different from those recommended. According to the Standards of Care guidelines, the maximum recommended values for testosterone esters is 100–200 mg (intramuscular) every 2 weeks for enanthate and cypionate and 1000 mg/12 weeks for undecanoate [10]. However, in some of these articles, in addition to not specifying the esters used, dosages higher than the recommended were prescribed [19,20,26,27], while others were administered with lower doses [18]. Therefore, the question remains whether the results obtained with these dosages are reliable and safe and whether the guidelines must be updated to standardize hormonal therapy. Finally, it is important to compare these results with the effects on the lipid profile of the supraphysiological doses of androgens used by athletes to understand whether, in different circumstances, the results are similar. In athletes, it was already demonstrated that testosterone and testosterone esters administration decrease HDL values [60,61], which is in agreement with the studies on transgender hormone therapy. However, no changes in the levels of LDL and triglycerides were observed [60–62]. Regarding total cholesterol, as in the results presented in this article, there is still no consensus on the results; some authors demonstrated an increase [63], while others demonstrated a decrease [64].

Like most epidemiological studies, those presented here are also prone to limitations. Most of the studies resorted to small population samples from Europe and the United States of America, and they were exposed to different external variables, which makes these studies not representative of reality, nor can the results be generalized to the world population. Moreover, the lack of control groups did not allow us to understand if the outcomes were caused by the treatment or by other variables, as well as the fact that this was a retrospective study and it was not possible to control external factors such as physical exercise, diet, smoking status, or alcoholism, which can alter cardiovascular risk. Another issue is the follow-up time. Most of them were around 12 months and no longer than 24 months. Considering the therapy was only instituted upon entry into the cohorts, the effects were only observed during the follow-up time. It is essential to analyze much longer periods so that the long-term impacts can be ascertained.

This review shows that there is still very little and sometimes contradictory information on the subject, which makes it difficult to draw conclusions and, subsequently, adapt healthcare for this population in light of the changes that hormonal therapy can cause. For the future, it is essential to conduct studies with larger and more representative samples of the world population, initially establishing specific entry criteria that would make bias by external variables impossible. Furthermore, it is imperative to evaluate the impact of hormonal therapy on other variables that affect cardiovascular risk.

5. Conclusions

The effect of hormonal therapy on transgender people continues to be insufficiently understood; however, several studies suggest that it has an impact on the lipid profile and, consequently, on cardiovascular health. According to this analysis, there appears to be a positive relationship between the use of hormonal therapy in transgender women and a reduction in cardiovascular risk, inversely to what is seen in transgender men, in which cardiovascular risk increases due to changes in the lipid profile. Yet, the mechanisms are still unknown. Therefore, it is imperative to continue studying the effects of these treatments on the transgender population, so that clearer and more targeted guidance can be given, reducing the negative consequences and improving their health and quality of life.

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