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CROSS-SEX HORMONE THERAPY AND TRANSGENDER PEOPLE'S HEALTH: AN APPROACH TO METABOLIC IMPACT, CARDIOVASCULAR DISEASE INCIDENCE AND LGTBQ+ DIETARY GUIDELINES

Bachelor's Thesis

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Abstract

Some important differences in health outcomes of women and men are not just due to biological causes but are partly explained by the influence that gender-related factors have on their choices and actions. Transgender individuals who seek a full transition to the gender they identify with may undergo cross-sex hormone therapy (CSHT). The administration of sex hormones must proceed with caution due to its metabolic implications. Also, cardiovascular disease (CVD) risk factors should be precisely screened throughout the process. In this review, little significant metabolic alterations were found either in transgender women or transgender men. CVD incidence was reported higher in transgender women populations. Overall, CSHT was reported safe. Reviewed dietary guidelines came up insufficient to fully address specific dietetic and nutritional requirements of the lesbian, gay, transgender, bisexual and queer (LGTBQ+) community. Dietitian-Nutritionists and the rest of health providers and researchers must broaden their knowledge and awareness on dealing with the health care management of the whole LGTBQ+ community.

Key Words

Transgender; Cross-Sex Hormone Therapy; Metabolism; Cardiovascular Disease; Dietary Guidelines.

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Introduction

In this review we deal with concepts that are usually misconceived by general public and even by health care providers. In this section, it is intended to contextualize and introduce the main concepts regarding transgender people, available sex reassignment therapies and the status of the health care that is currently delivered to this group.

Sex, Gender and Transgender

In the Real Academia Española (RAE) dictionary, "Sex" is defined as an organic condition of animals and plants (1). It is also described as a set of biological, physical, physiological, and anatomical characteristics that define human beings as male or female.

In the same source, "Gender" is defined as the group to which the human beings of each sex belong to, understanding it from a sociocultural point of view instead of exclusively biological (1). Gender is seen as a system that assigns expectations, roles, power and also differential access to all kind of resources according to whether one is perceived as a woman, a man or other.

The word "Transgender" refers to people whose gender identities are different from the sex assigned to them at birth (2). Even though the word is known by many, nowadays we still cannot find this definition in several official dictionaries of the most widely spoken languages such as the Spanish one, and the word Gender continues to appear just as a synonym for the word Sex, as in the Cambridge English Dictionary (3).

Marginalized by political, religious, legal, medical, and other cultural institutions, transgender people encounter levels of discrimination that range from simple misapprehension and exclusion by an uneducated public, to explicit acts of sexual and physical violence (4), thus making exceedingly difficult to estimate the current transgender population in the world since many are not open about it fearing retaliation.

However, demographers from the World Health Organization (WHO) recognize both the importance and the difficulties of collecting meaningful data about groups labelled as sexual minorities. Some authors even tried to estimate the transgender population in

America, reporting there was 1.4 million people non-conforming with their sex assigned at birth in 2019 (5) accounting for the 0.3% of the total population of the country.

Sex and Gender in Medicine

Health outcomes for women and men are known to be different. Some of these differences are biological, referred to male and female sex, while others are related to their gender. Sex- and gender-related issues are different and thus, require different interventions (6).

Some important differences in the exposure of women and men to health-related conditions are not just due to biological causes, but are partly explained by the influence that gender-related factors have on their choices and actions (7).

Sex and gender differences in frequent diseases are more common than one may assume. Moreover, they have significant yet frequently underestimated consequences on the daily clinical practice. Gender medicine is a novel medical discipline concerned about why diseases are expressed differently in the genders and it takes differences between women and men into account, which are often overlooked by traditional medicine (8).

In the past, being transgender was defined by medical sciences as a mental health concern and was categorized as such by the WHO in the International Classification of Diseases-10 (ICD). Luckily, the appreciation of gender identity has lately ensued in a major framework shift. Indeed, the latest WHO ICD-11, published in 2018, changed the concern to "gender incongruence" and reclassified it under conditions related to sexual health (9).

Gender Identity and Gender Dysphoria

Gender identity refers to people feeling themselves to be like others of one gender. Perceiving oneself as female or male is an important basis for interactions with others (10). Usually, gender identity and biological sex characteristics are corresponding. However, incongruence with one's physical characteristics does occur occasionally.

Gender Dysphoria (GD), also known as Gender Identity Disorder (GID), is a psychiatric diagnosis that describes the feeling of discordance between gender identity and sex assigned at birth, with which affected people do not identify or feel as their own.

When a person with a normal somatic sexual differentiation is convinced that he or she is actually a member of the opposite sex, this may be associated with an irresistible urge to be hormonally, surgically, and psychosocially adapted to the desired sex as in transgender individuals.

The first appearance of medical conditions concerning gender identity was in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), in 1980. It included diagnoses such as Gender Identity Disorder of Childhood and Transsexualism for the first time (10). In 2013, DSM-V is published and there, Gender Dysphoria appears as a diagnosis itself.

It is noteworthy that GD is no longer categorized as a mental disorder since 2018 after the WHO's ICD-11 publication. Now it is fortunately detached from sexual dysfunctions and paraphilias such as exhibitionism or paedophilia.

In the first place, the most common treatment for gender dysphoria is provided by mental health professionals to help deal with mental issues such as depression or anxiety often caused by GD. A following step in treatment, if the individual's distress persists, would be to seek medical treatment that might include feminizing or masculinizing surgery, to change the breasts or chest, external and internal genitalia, facial features and body contouring.

Another way of treatment would be to undergo a Cross-Sex Hormone Therapy (CSHT) mainly with testosterone or estrogen derivates(11). Treatments are based on the patient's goals, as well as in an evaluation of the risks and benefits of medication use, the presence of any other conditions, and consideration of social issues (12).

Testosterone and Estrogen

Testosterone is an anabolic steroid and the main male sex hormone. It plays a key role in the development of male reproductive system such as testes and prostate but also in carbohydrate, fat and protein metabolism. It is synthesized from cholesterol primarily

in the testes (13).

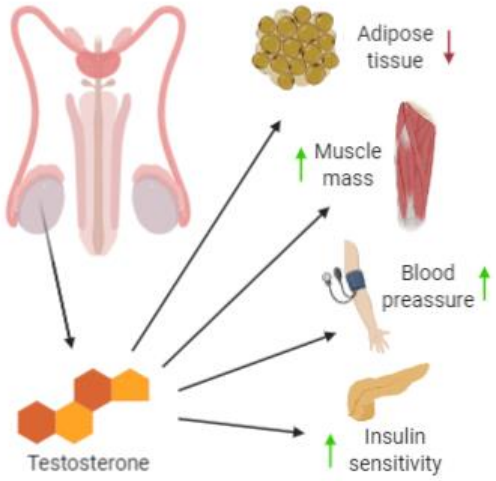

Figure 1. Testes-produced testosterone acts mainly on adipose and muscle tissue and increases blood pressure and insulin sensitivity (13).

It has been known for some time that testosterone has a major influence on body fat composition and muscle mass in the male, as seen in Figure 1. Furthermore, deficiency of testosterone is associated with impaired insulin sensitivity, increased percentage of body fat, obesity, dyslipidemia, hypertension and also cardiovascular disease (CVD) (14).

Estradiol, also known as 17β-estradiol or estrogen (E2), is the most common form of circulating estrogens and is considered the primary female hormone (15). Estrogens are mainly synthesized and secreted by the ovaries in premenopausal cisgender women. Ovary-produced estrogens mostly functions as an endocrine factor affecting the distal tissue. Extragonadal-produced estrogen acts locally as a paracrine or intracrine factor in the tissue where it is synthesized.

E2 acts on many types of tissue, as in Figure 2, including brain, bone and fat tissue, as well as in the vascular endothelium and smooth muscle cells of the aorta. In peripheral tissues estrogens are produced by converting androgens such as testosterone into E2 via the aromatase enzyme. Local production of E2 in these tissues plays an important role in their physiological functions (16).

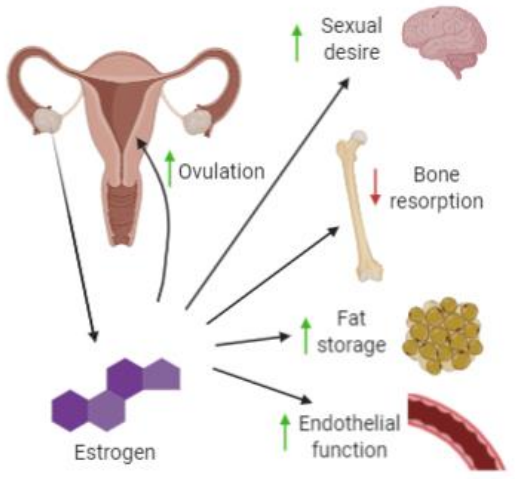

Figure 2. Ovary-produced estrogens act on the uterus, brain, bone and adipose tissue and enhances endothelial function (15).

Administration of estrogen therapy in CVD has shown some beneficial effects in animal models, but the use of estrogens in humans as a hormone replacement therapy stays controversial (17).

The Cross-Sex Hormone Therapy

Sex reassignment is a multidisciplinary treatment. It requires five processes: diagnostic assessment, psychotherapy or counselling, real-life experience (RLE), cross-sex hormone therapy (CSHT), and finally surgery (oophorectomy for transgender men or orchiectomy for transgender women) (18). It is essential for all caregivers to be aware of the contributions of each discipline and to communicate with each other throughout the whole process.

Treatment of transgender people, previously limited to ineffective pseudotherapies and implants, became reasonable with the accessibility to stilbestrol (an agonist of estrogen receptors) in 1938 and after the isolation of testosterone back in 1935. Still, before 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender people.

CSHT is a gender-affirming therapy. The main objectives of CSHT are to induce the appearance of sexual characteristics consistent with gender identity and to suppress endogenous hormone levels and secondary sexual characteristics associated with biological sex (18).

The number of transgender individuals seeking CSHT has risen over the years (19). Many transgender men pursue therapy for virilization where the core treatment is administration of exogenous testosterone. Transgender women look for suppression of androgenic effects and use estrogen therapy combined with antiandrogenic drugs (20). Administration of hormone therapy must also consider the patient's comorbidities and the risks associated with hormone use such as CVD, cancer, and metabolic alterations as previous literature has shown (21, 22).

Nowadays, standards for hormone therapy in adult transgender men are mostly extrapolations from recommendations of treatments of hypogonadal natal men.

Estrogen therapy for adult transgender women is mainly based on treatments also used in postmenopausal women (23).

Masculinizing hormone therapy for transgender men

For transgender men who are seeking to suppress female secondary sex characteristics and enhance masculinization, testosterone therapy is used and most of the administrated drugs are testosterone esters.

The most commonly used oral formulation in Europe is testosterone undecanoate, a long-acting testosterone that can be administered every 12 weeks and its off-label use in transgender men was approved by the Food and Drug Administration (FDA) in 2014. This option though, continues to not be available in some countries due to concerns about metabolic effects from the drug. Transdermal and intramuscular options are also good alternatives for some people (20). Another way of administration is via a subcutaneous implant of testosterone pellets. Recommended administration regimen proposed by the International Journal of Transgenderism is described in Table 1 (24).

After the first three months on testosterone therapy, patients are already expected to present amenorrhea, increased facial and body hair, skin changes and acne, changes in fat distribution, increases in muscle mass and increased libido. Later effects include deepening of the voice, atrophy of the vaginal epithelium, and increased clitoral size (25).

Still, in most adult transgender men, there is some degree of feminization after puberty that cannot be reversed with exogenous testosterone. As a result, many transgender

	Intramuscular injection (esterified testosterone)		Transdermal gel	Transdermal patch
Agent	Testosterone cypionate	Testosterone enanthate	Testosterone crystals dissolved in gel	
Pre-oophorectomy	25-40 mg[a] every week (or 50-80 mg every two weeks); gradually increase each month until blood testosterone is within normal male range or there are visible changes (typically 50-100 mg every week, or 100-200 mg every 2 weeks)		5-10 g qd; start with 2.5 g qd if there are comorbid conditions that may be exacerbated by testosterone	5-10 mg/24 hours, applied daily; start with 2.5 mg patch if there are comorbid conditions that may be exacerbated by testosterone
Maintenance (after 2 years) or post-oophorectomy	Reduce to level needed to keep serum free testosterone within the lower-middle end of the male reference interval. Monitor risk of osteoporosis.			

[a]Ensure patient knows how much to inject–there are 100 mg/ml and 200 mg/ml preparations.

Table 1. Basic masculinizing regimen proposed by the International Journal of Transgenderism (22).

men are shorter, have some feminine subcutaneous fat distribution and often have wider hips than biologic males.

Feminizing hormone therapy for transgender women

Estrogens are the main therapy for transgender women. Estrogen therapy changes fat distribution, induces breast formation, and reduces male pattern hair growth after 18 months on treatment (26). Estrogens alone are often not enough so, usually, an anti-androgenic therapy is also administrated so that desired goals can be achieved (27). This therapy suppresses gonadotropin secretion, leading to a reduction in androgen production.

The main formulation used in this therapy was ethinyl estradiol until some years ago. Now, there are strong recommendations against the use of this drug in transgender women due to an association of deep venous thrombosis incidence and this hormone administration (28). Oral and transdermal estradiol and parenteral estradiol valerate are currently the preferred formulations in CSHT (20).

Spironolactone and Cyproterone are the most common drugs used to suppress endogenous testosterone in transgender women. When administrated, hyperkalemia and hyponatremia should be monitored due to relatively high incidence associated to this drug usage (20). Recommended administration regimen proposed by the International Journal of Transgenderism is described in Table 2 (24).The extent of feminizing changes varies across patients. Providing also an anti-androgenic therapy is theorized to help to reach maximum change in a shorter period of time (29).

Agent	Estrogen			Androgen antagonist		
	17β-estradiol			Spironolactone	***and/or***	Finasteride
	Transdermal[a]	***or***	Oral	Oral		Oral
Pre-orchiectomy	Start at 0.1 mg/24 hrs, applied twice per week; gradually increase up to maximum of 0.2 mg/24 hrs, applied twice per week.		Start with 1-2 mg qd; gradually increase up to maximum 4 mg qd.	Start with 50-100 mg qd; increase by 50-100 mg each month up to average 200-300 mg qd (maximum 500 mg qd). Modify if there are risks of adverse effects.		Use 2.5-5.0 mg qd for systemic anti-androgen effect; use 2.5 mg every other day if solely for alopecia androgenetica.
Post-orchiectomy	0.375-0.1 mg/24 hrs, applied twice per week.		1-2 mg qd	25-50 mg qd		2.5 mg qd

[a]Use transdermal estradiol if the patient is > age 40 or is at risk for DVT. Oral estradiol is an option if the patient is < age 40 and is low risk for DVT.

Table 2. Basic feminizing regimen proposed by the International Journal of Transgenderism (22).

Objectives

The aim of this review is to assess the safety of Cross-Sex Hormone Therapy for transgender people specifically regarding:

- Its metabolic impact and consequences.
- Cardiovascular disease incidence and risk factors within transgender population who have followed this gender reassignment treatment.

Existing dietary guidelines aimed at the LGTBQ+ community will also be reviewed, specially focusing on the transgender issues.

Materials and Methods

A digital research was conducted to compose this review. Full text articles, considering the impact factor of its publication site, were chosen from PubMed, Scopus and Web of Science databases.

For the first part of the review, regarding the metabolic impact of CSHT, research keywords used were "CSHT", "hormone therapy", "metabolism" and "metabolic impact", all cross-referenced with "transgender" or "transsexual".

For the second part, aiming the cardiovascular disease risk, keywords used were "CVD incidence", "cardiovascular risk factors" and "transgender", cross-referenced with "CSHT".

Dietary guidelines where searched using "diet", "nutrition" and "guideline" as key words, cross-referenced with "hormone therapy" or "LGBT".

The general limitation by date of publication was 10 years from now. However, some key articles were older and were also included. Some other information was also extracted from assistance to scientific congresses and conferences where transgender medicine and LGTBQ+ health care were addressed.

Results

Standard practice in transgender intervention studies include measurements of blood pressure, BMI, testosterone, estradiol, glucose, lipid profile, electrolytes (mostly sodium and potassium), liver and renal function tests, hematocrit and hemoglobin recorded at baseline and in follow up visits. The presence of other pharmacological treatment and comorbidity at the start of the study are also addressed in most of the reviewed papers. The majority of the included subjects presented a normal and healthy panel before the hormonal intervention.

Metabolic impact of CSHT

A set of studies have looked at the effects of cross-sex hormone administration on metabolic markers in transgender people. A key factor to be considered is the route of administration of hormones (30). The mean duration of CSHT treatment was not significantly different between affirmed female and affirmed male subjects in any of the reviewed literature although the absence of an adequate control group is a limitation in some of them.

Affirmed female subjects

Transgender women under treatment with estrogen therapy do not present any overall changes in their fasting plasma glucose levels from baseline (31). Although some studies have found different levels of glucose in patients during the follow-up, these changes were not statistically significant and vanished after some control visits.

Many authors have shown that the effects of CSHT on lipid profile are likely to vary dose-dependently (32). In an Italian cohort study, 17β-estradiol levels were negatively correlated with total cholesterol (33). A retrospective study found that total cholesterol, high density lipoprotein (HDL), and triglycerides tend to increase over time in affirmed female subjects treated with oral or transdermal estrogens and cyproterone acetate (34).

Furthermore, compared to transdermal estradiol, oral estradiol was associated with higher triglycerides and lower HDL levels (35). Two other studies have shown that HDL levels increase, while low density lipoprotein (LDL) levels decrease on estrogen therapy (34, 35) while, in opposition, another multicentre study showed that total cholesterol, HDL, LDL and triglyceride levels were lower after CSHT (38).

Some retrospective data also suggest that estrogen therapy in transgender adults is associated with higher triglycerides than in both male and female cisgender adults (39).

Concerning the lipid profile, although estrogen therapy does not show significant changes in overall lipid levels, their levels do vary according to hormone concentration. Indeed, HDL seems to be the only lipid parameter that shows a statistically significant increase, as there are non-significant trends towards a decrease in total cholesterol, triglycerides and LDL levels from baseline (40).

After the first month since the initiation of estradiol therapy, a reduction in red blood cell count (RBC), hematocrit and hemoglobin is seen (26) but, in the majority of studies, with no statistical significance. Erythropoiesis seems to be affected mostly by the reduction in serum testosterone rather than by the increase in serum 17β-estradiol (41). 17β-estradiol is reported to enhance iron absorption in the intestine and to inhibit hypoxia-induced erythropoietin synthesis in the kidney (38). However, the mechanism underlying the relation between estrogen and testosterone levels on erythropoiesis is yet not completely understood.

Some studies that have also focused on skeletal muscle, have shown that there is a statistically significant decrease in creatinine levels from baseline (42) but again, it is yet not clear if it is due to the rising estradiol levels or the decrease in testosterone.

There have been some concerns regarding the safety of the use of antiandrogens in the literature (43). However, the use of antiandrogenic drugs like spironolactone or cyproterone has eventually been reported safe in individuals with no comorbidities. Nonetheless, if a patient undergoing CSHT presents any health issue or polymedication, especially in human immunodeficiency virus (HIV), the intervention should proceed

without antiandrogens so that outcomes such as hyperkalemia or hyponatremia can be avoided.

In fact, in recent studies, there were no significant changes in potassium levels among subjects taking spironolactone (37). In the absence of preexisting medical conditions and medications, hyperkalemia and hyponatremia are unlikely to appear during feminizing therapy, despite the previous concerns about them on antiandrogen administration.

Regarding liver health, no significant alterations in aspartate aminotransferase (AST) nor alanine aminotransferase (ALT) enzyme levels have been reported in relation with estrogen therapy (30).

In summary, as seen in Table 3, estrogen therapy is reported to mainly affect metabolism by increasing HDL levels. Also, a decrease in hemoglobin, hematocrit and creatinine is seen but this seems to be due to a decrease in testosterone levels rather than by the action of estrogen therapy.

Affirmed male subjects

Although estrogen therapy does not induce any changes in fasting plasma glucose levels, testosterone therapy is reported to decrease them in affirmed male subjects (33). Glucose uptake was found to be reduced in another study, where endogenous glucose production was also measured, but with no statistical significance and though decreased, glucose level maintained in normal healthy ranges (44).

A set of studies have shown that while testosterone does not significantly affect total cholesterol and LDL levels, it does lead to a reduction in HDL levels and to an increase in triglyceride levels (30, 42, 43).

In some studies, an increase in mean total cholesterol and LDL levels was reported after initiation of testosterone administration, but these changes were not statistically significant and disappeared after 3 months of therapy (31, 44).

In a small clinical trial, testosterone was associated with decreased plasma cholesterol and LDL levels, with no changes in HDL levels in affirmed male subjects (48). In opposition, a longitudinal study reported a small increase in total cholesterol levels in

affirmed male adults during the follow-up (49). In another study, a decrease in HDL, increase in LDL, and decrease in triglycerides levels was seen, however, none of these changes reached statistical significance besides the decrease in HDL (33).

As expected from the effects of testosterone on erythropoiesis, RBC, hemoglobin and hematocrit levels rise significantly from baseline. Hematocrit levels are reported to significantly increase right after initiation of testosterone therapy. Increase in hemoglobin levels is also rapidly noted (41).

After starting testosterone therapy, creatinine levels rise significantly from baseline. In affirmed male subjects, CSHT causes a significant increase in creatinine levels, which turn up higher than in cisgender men, and positively correlate with serum testosterone levels (42). This effect is not unexpected, since testosterone treatment is reported to increase muscle mass in both cisgender and transgender people (50).

The Endocrine Society recommends a check on liver enzymes at least once per year in both transgender female and transgender male because CSHT has been reported to worsen liver dysfunction in some cases (51).

Unlike the oral 17-alphaalkylated androgens, which are no longer used because of their hepatotoxicity, testosterone esters do not undergo first-pass metabolization in the liver, and therefore they are free of liver toxicity (52). In all of the recent studies, ALT and AST levels both trended downward but with no statistical significance in a short- and medium-term.

Another study examining the administration of long-acting testosterone and its effects on various sex hormones found a significant decrease in luteinizing hormone, prolactin and sex hormone binding globulin (53) in transgender men after CSHT.

Metabolic impact of CSHT	
Transgender female	= glucose, ↑ **HDL**, ↓ LDL, ↓ cholesterol and triglycerides
	↓ hemoglobin, hematocrit and RBC, ↓ creatinine
Transgender male	↓ glucose, ↓ HDL, ↑ LDL, ↑ cholesterol and triglycerides
	↑ **hemoglobin**, **hematocrit** and **RBC**, ↑ **creatinine**

Table 3. Metabolic impact of CSHT. In bold, statistically significant changes.

In summary, as seen in Table 3, testosterone therapy seems to lead to a small reduction in HDL levels and a little increase in other lipid levels but more importantly to an increase in hemoglobin, hematocrit and creatinine levels. Other metabolic parameters remain with no significant changes.

Incidence of cardiovascular disease after CSHT

Since last decade, an increase in CVD research have ensued focusing on CVD morbidity and mortality in the transgender community. Some reviews and meta-analysis have already been performed too (35, 47). However, there is still limited research available to properly establish CVD outcomes due to long-term hormone use among transgender persons provided most of the carried-out studies were mainly on a young population who additionally is not yet at high risk of CVD.

Affirmed female subjects

The thrombogenic effect of estrogen derivates is well known in cisgender people (54). Recent studies confirm a similar risk of venous thrombosis and pulmonary embolism in transgender women who receive CSHT (52, 53).

In a Dutch retrospective study that included more than 300 transgender women on CSHT (a combination of ethinyl estradiol and cyproterone acetate), the incidence of venous thromboembolism (VTE) increased 45-fold compared with the expected in a group of cisgender women (57). In another study with on the same set conditions, an overall reduction was seen in VTE events when transdermal estradiol was used instead of oral ethinyl estradiol, but compared with general population estimations, a 20-fold increase in VTE was still noted (58).

In opposition, a later study on middle-aged transgender women receiving transdermal 17β-estradiol therapy did not report any venous thrombosis or pulmonary embolism events during follow-up (55). But in this study, the mean CSHT administration time to screened individuals was under 5 years.

In an observational study among transgender women who received CSHT for more than 7 years, the prevalence of myocardial infarction (MI) was higher than in the control

group of cisgender women, 30% of whom were also receiving some form of exogenous hormones (59). However, the prevalence of MI was similar to that in cisgender men. The prevalence of cerebrovascular accidents was also greater in transgender women than in cisgender men (59).

Most recently, a Dutch analysis of more than 2500 transgender women using estrogen CSHT found that transgender women had twice as many strokes and MIs as cisgender women (60).

It is worthy to mention that some studies have pointed out that risk factors for CVD, such as type 2 diabetes mellitus (T2DM), are more frequent among transgender women receiving CSHT than in cisgender women or cisgender men (43, 58).

Compared with baseline, systolic blood pressure but not diastolic blood pressure is reported to decrease significantly while on CSHT in transgender women. In a German retrospective study, CSHT was associated with a 6 mmHg decrease in systolic blood pressure, but seemed to be more related to the reduction in serum testosterone rather than to the increase in 17β-estradiol (61).

In another Dutch study though, no statistically significant changes were reported in transgender women's blood pressure. However, trends towards decreased blood pressure from baseline were observed but with no statistical significance (32). Another study has hypothesized that lower blood pressure may also be due to the reduction of an individual's psychological stress as they progress with their gender affirming transition (62).

No remarkable body mass index (BMI) changes in relation to CSHT are reported in transgender women who have followed this therapy though downward trends can be observed (46).

As seen before, the lipid profile of transgender women after CSHT is not really altered besides the increase in HDL levels. These results were also found in studies on cisgender postmenopausal women in estrogen therapy suggesting that estrogens may have a protective role in CVD (29). However, its extrapolation to transgender women was eventually refuted by clinical trial data (63).

There have been some reports suggesting that the timing of initiating hormone therapy is a key determinant for the onset of CVD in transgender women (64). It is also noteworthy that the observed delay in CVD onset that cisgender women have compared to cisgender men is lost in transgender women on CSHT.

Synthetic ethinyl estradiol and equine conjugated estrogens were commonly used in Europe up until 2003. Due to safety concerns regarding prothrombotic potential of this drug (65), most providers now prefer to use oral and transdermal estradiol and parenteral estradiol valerate formulations which appear to be safer.

In summary, as Table 4 shows, some CVD risk factors, such as T2DM, in transgender women are reported to be more prevalent than in the cisgender population, while other CVD risk factors seem to be unchanged. Despite, estrogen therapy has been reported with a higher potential thrombogenic risk in transgender women. Transdermal formulations are preferred over oral estradiol administration provided its lower incidence of CVD outcomes.

Affirmed male subjects

There are not plenty of studies in transgender men on the direct effect of CSHT on CVD incidence and risk factors. Though, existing evidence indicates that CVD risk is similar in transgender men receiving CSHT compared to cisgender women (61).

In a retrospective analysis, Dutch transgender man who received CSHT with various testosterone formulations, CVD morbidity and mortality did not increase significantly compared with that expected in a comparable group of cisgender individuals (28).

These findings were corroborated by another retrospective cohort study that did not reveal a significant difference between transgender men who received CSHT and the cisgender male population (50). In these studies, transgender men tended to start undergoing CSHT at a younger age than transgender women, which may account to their reduced morbidity and mortality during the follow-up.

A case-control study comparing CVD outcomes in transgender men with those in cisgender women and cisgender men found that transgender men receiving CSHT did

not have an increased prevalence of MI, cerebrovascular accidents or transient ischemic attacks (TIAs) (36).

Both transgender women and transgender men are reported to have higher prevalence of T2DM than cisgender individuals. Transgender persons being carefully screened by endocrinologists before starting of CSHT may be the cause of the frequent diagnosis of T2DM. The incidence of T2DM during hormone therapy is also reported higher in transgender men than in the controls of cisgender individuals or transgender women (66).

Also, regarding other CVD risk factors, a prospective study assessing levels of endothelin, which is associated with vasoconstriction and hypertension, in transgender men found significantly increased levels of this hormone after CSHT with testosterone esters (67).

A meta-analysis assessing lipid levels and blood pressure in transgender persons found that transgender men who received CSHT had an increase in triglyceride levels, a statistically significant increase in systolic blood pressure and a decrease in HDL levels (35), in the same direction of what has been pointed out in a previous section of this review. A significant increase in BMI has also been reported (45).

Again, another cross-sectional observational study that examined over 100 transgender men receiving testosterone esters found that those receiving CSHT had higher systolic blood pressure and higher total cholesterol levels compared to transgender men not receiving CSHT (68).

In short, as Table 4 illustrates, transgender men who received CSHT do not show an increased incidence of CVD, despite the potentially increased risk factors for CVD due to the effects of CSHT. Also, literature is limited by the small size of the study population and the young age of transgender men when starting CSHT.

Cardiovascular Disease incidence after CSHT	
Transgender female	↓ blood pressure, ↓ BMI, ↓ total cholesterol
	↑ **venous thromboembolism**, ↑ MI, ↑ stroke, ↑ **T2DM**
Transgender male	↑ **blood pressure**, ↑ **BMI**, ↑ total cholesterol
	= venous thromboembolism, = MI, = stroke, ↑ **T2DM**

Table 4. Cardiovascular disease after CSHT. In bold, statistically significant changes.

Dietary Guidelines for the LGTBQ+ community

Previous studies have shown significant differences in the health status of lesbian, gay, transgender, bisexual and queer (LGTBQ+) people, such as higher rates of cancer, HIV, acquired immunodeficiency syndrome (AIDS) and mental health conditions, exacerbated by limited access to quality and specific health care (69).

In the literature on nutrition and dietetics, differences in gender-specific and nutrition-related considerations have been traditionally framed just within cisgender heterosexual individuals. However, studies start to reveal the differences in many aspects of nutrition for sexual minorities of the LGTBQ+ community (70).

A recent study revealed significant differences in food behaviour and management of health risks in each subcategory of sexual orientation (71), indicating the need to study various dietary considerations of sexual minorities. Indeed, the transgender population is of special importance, given the hormonal interventions for the transition from one gender to the other.

LGTBQ+ adults are reported to have higher prevalence of malnutrition. While many queer people receive support and care from friends, family and LGTBQ+ organizations, they are twice as likely as heterosexual adults to live alone, and much less likely to have children to provide care and companionship (72). Living alone with few social relations can reduce enjoyment of food preparation, leading to skipped meals, eating less healthy, and thus resulting in a poorer nutrition status.

Other examples of nutritional differences in the LGTBQ+ community have been noted in previous literature and summed up in Table 5. Gay men have been reported to have increased body concerns and eating disorders (73). Lesbians and bisexual women are more likely to be obese (69) and transgender women have been reported to have the lowest vegetable and fruit consumption and lowest levels of exercise among LGTBQ+ populations (71).

Although certain dietary considerations for the transgender population are known, a marked gap exists in both research and nutrition care guidelines for this population. The

present digital research of dietary guidelines resulted just in recommendations from nursing, dental, and medical programs where LGTBQ+ issues appeared in a few chapters.

Literature on prevention and primary care for LGTBQ+ people focuses mainly on HIV prevalence and risk behaviours (74). Unfortunately, no literature have yet exclusively focused on dietary and nutritional concerns in regard of the transgender group.

Regarding transgender population, specific side effects of CSHT can be dealt within the professional practice of Dietitian-Nutritionists (D-Ns). These side effects include weight gain, changes in body composition, altered lipid profiles, and changes in bone composition and other metabolic factors and CVD risk factors, reviewed in previous sections of this review, thus requiring specialized nutrition counselling.

Also, LGTBQ+ populations have the highest rates of substance abuse for tobacco, alcohol, and other drugs, all of which may affect their nutrition status (75) and heavily impact on their health outcomes. Based on current evidence, dietary considerations for transgender people are both clinical and psychosocial and D-Ns are able to provide adequate, patient-centred care to this population.

Today, the few considerations found in guidelines in regard of the LGTBQ+ community are mainly focusing on the prevention of sexual diseases and aiming to improve CVD risk factors prevalence among this community (70). Also, in some, recommendations on eating disorders management and healthy eating habits are starting to be found.

Although the full extent of the role of D-Ns in treating transgender individuals and other members of the LGTBQ+ community is yet far to be well-stablished, it is clear that D-Ns can play an important role in reducing health disparities and providing them an appropriate and inclusive nutritional care.

Food-related issues in the LGTBQ+ community	
Gay people	Eating disorders, body image distortion, malnutrition
Lesbian people	Obesity, binge-eating, malnutrition
Bisexual people	Obesity, malnutrition
Transgender people	Low vegetable and fruit consumption, malnutrition

Table 5. Food-related issues in the LGTBQ+ community.

Discussion

Plenty of terms in transgender medicine carry overlapped definitions, which cause confusion among health care providers involved in transgender care. The terminology used in the literature can be confusing and uninformed authors often swap gender terms, especially in older publications. Such missteps are now the outliers, although they continue to raise discomfort within the transgender community.

Eventually, education of all medical professionals, including D-Ns, will play an important role in improving health outcomes for LGTBQ+ people or gender nonconforming individuals.

As seen before, CSHT plays an important role in the transition process for transgender individuals. Even though some recommendations exist to help providers prescribe and monitor this therapy, more studies need to be conducted on this field and education of all health professionals needs to be extended regarding this community health care management.

Hormone therapy has been shown to be associated with positive outcomes for transgender people, but there are also important related medical concerns that must be carefully considered when treating these subjects.

Provided this field in medicine is all but new, further research is still needed to provide ultimate evidence-based guidelines made up from specific transgender subjects' data. Though, researchers must proceed with caution to avoid making things more difficult for a group that is already stigmatized. This requires consultation with transgender people on their priorities and sometimes, putting these ahead of questions that are simply scientifically interesting.

Social norms on gender-roles constantly change over time thus making it even more difficult to include gender as a variable in metabolic research. Up until now, gender has been rarely factored into studies concerning its influence on biological processes such as metabolism.

Also, it is unreasonable to assume transgender people to have baseline values that would be normal for the gender they identify with and therefore, laboratories are advised to empirically determine the reference ranges specifically for subjects on CSHT when included in their studies.

Longer term studies and larger cohorts are needed to determine the full effect on metabolism of CSHT in transgender people.

Regarding the safety of antiandrogenic drugs use, as a potassium-sparing diuretic, spironolactone is known to be a potential cause of hyperkalemia. However, in the reviewed literature, no statistically significant changes in potassium after initiation of CSHT were found unless the subject presented other medical issues beforehand, confirming recent data refuting those concerns claimed in older papers.

Current research regarding CVD among transgender adults receiving CSHT is mainly limited by a lack of large cohort studies, appropriate control populations, and inadequate collection of gender identity information in clinics and surveys, mostly due to a deficient training of data collectors in this regard.

The lack of valuable research, such as randomized controlled trials, comparing different routes of administration and various formulations in different-aged populations to fully characterize CVD and CVD risk factors in transgender people receiving CSHT limits appropriate primary and specialty care protocols and limits knowledge of any associations between CSHT and CVD.

Therefore, to successfully address cardiovascular events in a transgender population, longer follow-ups than those described in the literature are required to overcome these limitations.

Heteronormativity is deeply rooted in the policies and day-to-day practices of all the health care systems of the world thus leading in many cases of homophobia, stigmatization, and marginalization of LGTBQ+ individuals.

Due to the lack of appropriate guidelines, if a person opens up about their gender identity during nutrition counselling, D-Ns need to ask additional screening questions to assess whether the subject has any unique nutritional needs. Dietitians may also need

to widely address weight management issues for transgender subjects undergoing CSHT and look for any signs of eating disorder when treating an LGTBQ+ individual. In general, health care providers need to make themselves more aware of the special nutrition needs of the LGTBQ+ community members.

Another important focus point for the forthcoming edited guidelines should be malnutrition within the elderly LGTBQ+ community. Provided malnutrition is highly prevalent among the cisgender elderly it is reasonable to think that malnutrition prevalence rates in transgender older adults will also be significantly high due to social and physical impairments.

There is a deficiency of evidence identifying best practices to estimate specific nutrient needs in the different age groups of the transgender population. Further research investigating the impact of hormone therapy on the calorie needs of transitioning individuals would allow D-Ns to work more effectively on weight management strategies with their transgender patients.

It is noteworthy to mention the ongoing European Network for the Investigation of Gender Incongruence (ENIGI) study. It is the largest study of transgender people in the world. They will start publishing their results on hormone therapy implications in a couple of years.

ENIGI study and a handful of other emerging studies will provide very useful information regarding transgender health care management. Some hints are already beginning to emerge about the respective roles of hormones and genetics in gender identity and these results are beginning to clarify the medical and psychological implications of the transitioning process.

Recently, there has been a dramatic increase in public awareness of transgender individuals due to mainstream media exposure. The increased visibility may also increase the patient population size through educating people about the existence of gender dysphoria and about treatment options. Therefore, it is vital to continue educating health providers about the care and treatment of transgender and LGTBQ+ individuals.

The main limitations of this review were the little published data on specific transgender interventions regarding CSHT. Also, in many reviewed papers the population sample was not big enough to fully represent the reality of the whole transgender population and could not lead to general extrapolations.

Although some conclusions can already be drawn from what has been published up until now, and as said before, larger cohorts and follow-ups are needed to fully clarify the exact impact of CSHT on the several metabolic routes and on cardiovascular disease incidence in the transgender community.

Conclusions

CSHT appears to be safe as a gender-affirming therapy for transgender individuals provided the main studied metabolic parameters show little to no statistically significant variance in their levels. However, some issues must be taken into consideration when individuals present comorbidities or polymedication.

Estrogen therapy is reported to increase CVD incidence in transgender women but has little effect on its risk factors such as blood pressure, total cholesterol and lipid profile or BMI. However, an increased prevalence of T2DM is noted in transgender women as in transgender men.

Antiandrogens are also safe to use when the individual present a healthy profile from baseline. Testosterone therapy may exacerbate CVD risk factors, but this is reported to have very limited impact on cardiovascular disease incidence in transgender men.

Dietary guidelines aimed at the LGTBQ+ community are very insufficient and further research is needed to expose the real nutritional requirements derived from hormonal interventions in transgender individuals. Health providers, including D-Ns, need a better education and a wider awareness on the specific needs that this community requires.

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