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GUSTAVO DE OLIVEIRA

EFEITOS DA TERAPIA HORMONAL NO PERFIL LABORATORIAL DE PESSOAS TRANSGÊNERO

Florianópolis, SC
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Trabalho Conclusão de Curso apresentado na Universidade Federal de Santa Catarina como requisito parcial para a conclusão do Curso de Farmácia.

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Gustavo de Oliveira

EFFECTS OF HORMONE THERAPY ON THE LABORATORY PROFILE OF TRANSGENDER PEOPLE: A SCOPING REVIEW

Este Trabalho Conclusão de Curso foi julgado adequado para obtenção do Título de Bacharel em Farmácia e aprovado em sua forma final pelo Curso de Graduação em Farmácia

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LISTA DE FIGURAS

LISTA DE TABELAS

List of abbeviations

ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
BMD: bone mineral density
BTM: Bone turnover markers
CI: Confidence interval
DBP: Diastolic blood pressure
E2: 17-b estradiol
FPG: Fasting plasma glucose
FSH: Follicle-stimulating hormone
GAHT: Gender-affirming hormone therapy
GAH: Gender-affirming hormone
GnRHa: gonadotropin-releasing hormone agonist
GnRH1: Gonadotropin releasing hormone
Hct: Hematocrit
Hb: Hemoglobin
HbA1c: Glycated hemoglobin
HDL: High-density lipoprotein
HOMA-IR: Homeostatic model assessment for insulin resistance
HOMA2-I: Homeostasis Model of Insulin Resistance
HT: Hormone therapy
IGF-1: Insulin-like growth factor 1
LH: Luteinizing hormone
LDL: Low-density lipoprotein
SBP: Systolic blood pressure; Results are presented as median (interquartile range).
SHBG: sex hormone binding globulin.
TU: Testosterone undocanate
TE: Testosterone esterases
TD: Transdermal

APRESENTAÇÃO

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SUMÁRIO

EFFECTS OF HORMONE THERAPY ON THE LABORATORY PROFILE OF TRANSGENDER PEOPLE: A SCOPING REVIEW

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1. RESUMO

Dada a intervenção terapêutica para pessoas trans e o impacto nos exames laboratoriais, existe uma grande preocupação com os valores de referência e suas interpretações. Até o momento, não há valor definido para cada teste de parâmetros lipídicos, hematológicos, corporais e metabólicos e um consenso internacional. Nesta revisão de escopo, resumimos as evidências mais recentes sobre os efeitos da terapia hormonal no perfil laboratorial de pacientes transgêneros. O protocolo foi registrado no Open Science Framework (DOI: 10.17605 / OSF.IO / MW4S3). A estratégia de busca e seleção dos estudos foram baseadas na sigla PICOS. Buscamos artigos no PubMed, EMBASE e Scholar Google usando descritores e termos livres combinados por operadores booleanos e publicados de 2018 a 2021. Três blinders e revisores independentes selecionaram estudos aplicando os critérios de inclusão e exclusão. Um total de 27 estudos foram incluídos. Foram estudadas as populações de transgêneros masculinos e femininos. Alterações no hemograma, aumento nos níveis de eritrócitos e hipercoagulação foram relatados por alguns estudos. Além disso, mudanças nos parâmetros lipídicos foram observadas em pessoas trans que receberam terapia hormonal. A terapia hormonal com testosterona parece causar supressão rápida da ovulação em indivíduos transexuais masculinos, mas não há consenso. Consideramos essencial seguir esses parâmetros em pessoas trans que recebem terapia hormonal. Além disso, ensaios clínicos e estudos de coorte são incentivados em pesquisas futuras.

PALAVRAS-CHAVE: Transgênero, Terapia hormonal, Hormônios Esteróides Gonadais, Doenças Metabólicas / diagnóstico, Terapia hormonal de sexo cruzado

1. ABSTRACT

Given the therapeutic intervention for transgender people and the impact on laboratory tests, there is a concern with the reference values and their interpretations. To date, there is no defined value for each test of lipidic, hematological, bodily and metabolic parameters and an international consensus. In this scoping review, we summaried the most recent evidence on the effects of hormonal therapy in the laboratory profile of transgender patients. The protocol was registered in Open Science Framework (DOI:10.17605/OSF.IO/MW4S3). The search strategy and study selection were based on the PICOS acronym. We searched for articles in PubMed, EMBASE and Scholar Google using descriptors and free terms combined by boolean operators and published from 2018 to 2021. Three blinders and independently reviewers selected studies applying the inclusion and exclusion criteria. A total of 27 studies were included. Both male and female transgender populations were studied. Changes in the blood count, increase in erythrocyte levels and hypercoagulation were reported by some studies. Also, changes in lipid parameters were observed in transgender people receiving hormone therapy. Testosterone hormonal therapy appears to cause rapid suppression of ovulation in male transgender individuals, but there is no consensus. We considered it essential to follow these parameters in transgender people receiving hormone therapy. Also, clinical trials and cohort studies are encouraged in future research.

KEYWORDS: Transgender, Hormone therapy, Gonadal Steroid Hormones, Metabolic Diseases/diagnosis, Cross-sex hormone therapy.

2. INTRODUCTION

The transgender population is characterized by people does not identify with the biological sex of birth but with the opposite sex (SAFER et al., 2019). Currently, gender dysphoria is no longer considered a disease by the World Health Organization (WHO, ICD-11, 2019). This change occurred recently in 2018 when the International Classification of Diseases was launched (WHO, ICD-11, 2019) and removed gender identity disorders from the chapter on mental illnesses. With this change, the term came to be called gender incongruence.

Worldwide, access to exercised gender identity in a different way from that assigned to it at birth by the biological sex was considered a pathology. In the Diagnostic and Statistical Manual of Mental Disorders-DSM, trans people are diagnosed as having gender dysphoria. Furthermore, the International Classification of Diseases (ICD-10, 1997) considers that Transvestites and Transsexuals have a gender identity disorder. Even after the depathologization of gender dysphoria, the ICD-10 is still used by many countries as a guarantee of adequate access to their treatment from beginning to end of changes (MAKSOUD et al., 2014).

In all continents, there are countries where it is illegal to have homosexual (lesbian or gay) practices even today, highlighting the African and Asian continent (“INFORME DE MAPEO LEGAL TRANS ilga.org Reconocimiento ante la ley TM”, 2019). For example, in Iran, homosexuals are forced to undergo the transsexualizing process because the condition of relating to people of the same sex is prohibited, having to use hormone therapy medication (SHAKERIFAR, 2011). These people are diagnosed as sick and see it as a way of salvation to stay alive; after all, it is a crime with the death penalty to be homosexual in Iran (SHAKERIFAR, 2011). However, there are also countries with laws that protect and punish this type of practice. It is noteworthy that before performing the gender transition at the surgical level, it is necessary to accept not being in the desired body. Other changes can include social name, judicial name, physiognomy through surgical procedures, hormone therapy, facial hair removal, interventions to modify speech, communication and behavioural adaptations (such as hiding genitals or bandaging the chest). All changes were done to adapt to the person's feelings (KRUGER et al., 2019; UNGER CA 2016; CHEUNG et al., 2019).

In addition to the entire process of physical change, there are still problems related to mental health, especially depression and attempted suicide (MAKSOUD; PASSOS; PEGORARO, 2014). Furthermore, stigma and sex discrimination have been identified as an obstacle for the segment for prevention and health care services (MAKSOUD; PASSOS; PEGORARO, 2014).

Therefore, for monitoring transgender patients, it is recommended to perform laboratory tests periodically: blood count, renal function, electrolytes, liver function, fasting glucose, insulin, glycated haemoglobin (diabetic or pre-diabetic), lipid profile, hepatitis B markers (HbsAg, anti-Hbs, anti-Hbc antibodies, hepatitis C (anti-HCV), HIV, syphilis (VDRL, FTA-Abs), luteinizing hormone (LH), stimulating follicle hormone (FSH), estradiol and total testosterone. It is necessary to adjust the time interval between assessments concerning the individual needs of each individual to monitor the development of sexual characteristics and identify adverse effects and possible significant changes in laboratory parameters (SORELLE et al., 2019; MADELINE et al., 2016; ROBERT et al., 2019).

Given the therapeutic intervention for transgender people and the impact on laboratory tests, there is great concern with reference values and their interpretations. Until today, there is no defined value for each test and an international consensus. In some studies, for trans women, it is recommended the reference values of male cisgender are considered (upper limit). When there is a significant change in laboratory results, the lower limit for female cisgender can be regarded (Guidelines for the Primary Care of Transgender and Gender Nonbinary People, 2016). There is a real need to guarantee and improve the access and quality of health services for this population and laboratory diagnosis and monitoring of transgender people. Also, the scarcity of works on the laboratory profile of transgender people is highlighted (GUPTA; IMBOREK; KRASOWSKI, 2016), especially in developing countries, which brings out the need for an approach to the subject for the understanding of the entire population, whether health professionals, laypeople, curious and mainly transgender people. The latter considers itself a very marginalized population, excluded and with various stigmas and prejudices towards our society.

3. METHODOLOGY

We conducted this scoping review according to methodological recommendations (ARKSEY et al., 2007; COLQUHOUN et al., 2014; LEVAC, COLQUHOUN, O'BRIEN, 2010) and Preferred Reporting Items method for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (MOHER et al., 2009; TRICCO et al., 2018). We registered the study protocol in the Open Science Framework database (DOI 10.17605/OSF.IO/MW4S3). The scientific question was based on the PICOS strategy (participants = transgender people of both sexes and any age, intervention = testosterone and progesterone, control = placebo/other/no, results = laboratory profile (biochemical, hematological and others; and study design= (primary and secondary studies) (Supplementary File Table 1). Scientific question: “What are the effects of testosterone and progesterone therapy on the laboratory profile of transgender people?”.

3.1 IDENTIFICATION OF RELEVANT STUDIES

The articles were searched in two databases PubMed and EMBASE, Scholar Google (grey literature), from February to October 2021. The searched were included Boolean operators (AND, OR, NOT) and keywords/descriptors for transgender, testosterone and laboratory tests. We also use the terminology Medical Subject Headings (MeSH) from PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov/). We conducted a pilot of search strategy in PubMed following PICOS acronym and blocks: block 1 (transgender people: Transgender Persons OR Gender Dysphoria OR Gender Identity OR Health Services for Transgender Persons OR Transsexualism); AND block 2 (hormone therapy: Gonadal Steroid Hormones OR Estradiol OR Estrogens OR Androgens OR Testosterone); AND block 3 (diagnosis: Metabolic Diseases/diagnosis OR Metabolic Diseases/drug effects OR diagnosis) (Supplementary File Table 2). The expert reviewers validated the PubMed search. It was used as the basis for other databases. We apply restriction filters to articles published in the following languages: English, Portuguese and Spanish, and publication between 2018-2021.

We transferred the search to reference management software (My Web EndNote, Thomson Reuters) and removed all duplicates. Finally, the study selection was eligible in the Rayyan QCRI mobile and web application (https:// /rayyan.qcri.org/welcome).

3.2 STUDY SELECTION

According to the PICOS strategy, we established the eligibility criteria (O'CONNOR, GREEN, 2008) (Supplementary File Table 1). In this study, we included original studies (primary and secondary) in humans. English, Portuguese, and Spanish articles published so far were selected with free full text. Comments, letters, editorials, in vitro and in vivo studies, conferences, event abstracts, studies in cells and animals, theses and dissertations were excluded. Two students carried out the first stage of selection independently and blindly, who reviewed the titles and abstracts (GO, VOW). In cases of disagreement, the experts determine the final inclusion of the study. The second step for the selection of articles was carried out from the reading of the articles in full text, Portable Document Format (PDF), by the students (GO and GFR), and in case of disagreement, again the experts reached a consensus to determine the final inclusion.

3.3 DATA EXTRACTION

After selecting the articles, the following data was registered in a standard spreadsheet in Excel: author(s), year, country, study objective, type of study, statistical analysis, drug, dosage, treatment time, laboratory parameters evaluated, main outcomes, reference values used, biases and conclusions. Two authors (GO, GFR) extracted the data independently. In addition, to experts (IGD, BGMB, EMD, IFK). Performed peer validation to ensure accuracy before the quality assessment phase of the studies.

3.4 DATA SYNTHESIS

Initially, a narrative synthesis of the results was carried out. It is intended to group the studies according to current gender, age, continent and other variables that are considered important to the topic.

4. RESULTS

4.1 Literature Search

A total of 992 studies were recovered from databases (PubMed= 416 EMBASE= 476, PubMed and Scholar Google= 100). After the Endnote program automatically removed the duplicates. It was selected 966 for reading the title and abstract in RAYYAN. We excluded 818 articles. A concordance between reviewers was superior to 95% in the first phase (Figure 1). In the second stage, the full text of 148 was read by three blinded reviewers (GO, GFR, VOW). It was limiting the publication time results in 27 studies included (Figure 1).

4.2 Characteristic of included studies

In this review, nine studies were carried out in the USA (ADELEYE et al., 2019; ANTUN et al., 2020; AUER et al., 2018; CHEW et al., 2018; DELGADO-RUIZ; SWANSON; ROMANOS, 2019; GREENE et al., 2019; MEJIA-OTERO; WHITE; LOPEZ, 2021; SORELLE et al., 2019; TAUB et al., 2020), three in Australia (BRETHERTON et al., 2021; CHEW et al., 2018; LIM et al., 2020), two in Italy (MOTTA et al., 2020; VITA et al., 2018), and one in Germany (MEYER et al., 2020), one Sweden (WIIK et al., 2018), one Israel (AMIR et al., 2020), one Argentina (OTERO et al., 2018) ,one Belgium (SHADID et al., 2020), and Netherlands (STOFFERS; DE VRIES; HANNEMA, 2019). Some studies included other countries in their research such as three in Amsterdam/Belgium (KLAVER et al., 2020; VAN VELZEN et al., 2019, 2020), two Belgium/Netherlands

(DEFREYNE et al., 2018, 2020), one USA/Thailand (KULPRACHAKARN et al., 2020), and one in Amsterdam, Belgium, Italy and Norway (VLOT et al., 2019). Because we are Brazilian researchers, and expecting studies from Brazil, unfortunately, based on the previous steps, no Brazilian studies was included.

The article with the lowest number of participants was (TAUB et al., 2020) with only twenty-two transgender patients and the article with the highest number of participants was (DELGADO-RUIZ; SWANSON; ROMANOS, 2019) with one thousand six hundred and forty participants (Table 1).

Of the twenty-seven articles included, nine studies are retrospective studies (ADELEYE et al., 2019; AMIR et al., 2020; CHEW et al., 2018; MEJIA-OTERO; WHITE; LOPEZ, 2021; MEYER et al., 2020; OTERO et al., 2018; SORELLE et al., 2019; STOFFERS; DE VRIES; HANNEMA, 2019; VITA et al., 2018), which four cross-sectional studies (BRETHERTON et al., 2021; KULPRACHAKARN et al., 2020; LIM et al., 2020; MOTTA et al., 2020). Being one of them a case-control (LIM et al., 2020). Nine were prospective studies(ANTUN et al., 2020; AUER et al., 2018; DEFREYNE et al., 2018, 2020; GREENE et al., 2019; TAUB et al., 2020; VAN VELZEN et al., 2019, 2020), two multicenter prospective (BRETHERTON et al., 2021; CHAN et al., 2018; DELGADO-RUIZ; SWANSON; ROMANOS, 2019; MOTTA et al., 2020; SHADID et al., 2020; VLOT et al., 2019), and one single cohort prospective (WIIK et al., 2018), also we included two systematic reviews (CHEW et al., 2018; DELGADO-RUIZ; SWANSON; ROMANOS, 2019). (Table 1).

Nineteen studies included study both male and female transgender populations (ADELEYE et al., 2019; AMIR et al., 2020; ANTUN et al., 2020; AUER et al., 2018; BRETHERTON et al., 2021; CHAN et al., 2018; DEFREYNE et al., 2018; DELGADO-RUIZ; SWANSON; ROMANOS, 2019; GREENE et al., 2019; KLAVER et al., 2020; MEJIA-OTERO; WHITE; LOPEZ, 2021; MEYER et al., 2020; SHADID et al., 2020; SORELLE et al., 2019; VAN VELZEN et al., 2019, 2020; VITA et al., 2018; VLOT et al., 2019; WIIK et al., 2018). Five articles studied

only the transgender men population (CHEW et al., 2018; DEFREYNE et al., 2020; OTERO et al., 2018; STOFFERS; DE VRIES; HANNEMA, 2019; TAUB et al., 2020) and three articles studied only the transgender woman population (KULPRACHAKARN et al., 2020; LIM et al., 2020; MOTTA et al., 2020) (Table 1).

4.3 Main outcomes

he hematological parameters were the most investigated, nine included studies (ANTUN et al., 2020; DEFREYNE et al., 2018; GREENE et al., 2019; KLAVER et al., 2020; KULPRACHAKARN et al., 2020; LIM et al., 2020; MEYER et al., 2020; OTERO et al., 2018; VITA et al., 2018), followed by a lipidic profile four (CHEW et al., 2018; OTERO et al., 2018; VAN VELZEN et al., 2019; VITA et al., 2018) three are about ovarian parameters (ADELEYE et al., 2019; AMIR et al., 2020; TAUB et al., 2020) .The rest of the studies are divided into changes in metabolism, body and mind (ADELEYE et al., 2019; AMIR et al., 2020; ANTUN et al., 2020; AUER et al., 2018; BRETHERTON et al., 2021; CHEUNG et al., 2019; CHEW et al., 2018; DEFREYNE et al., 2020; DELGADO-RUIZ; SWANSON; ROMANOS, 2019; MEJIA-OTERO; WHITE; LOPEZ, 2021; MEYER et al., 2020; MOTTA et al., 2020; SHADID et al., 2020; SORELLE et al., 2019; STOFFERS; DE VRIES; HANNEMA, 2019; VAN VELZEN et al., 2020; VLOT et al., 2019; WIIK et al., 2018).

4.3.1 HEMATOLOGICAL PARAMETERS

On this topic research, the most discussed subject in all the studies included was blood parameters. Also, alterations in the blood count, increase in erythrocyte levels, in blood pressure, hypercoagulation were reported by some studies (ANTUN et al., 2020; DEFREYNE et al., 2018; LIM et al., 2020; MEYER et al., 2020).

One study about to gender dysphoria treatment in Sweden, provided new and deeper insight into the effects of cross-sex hormone treatment on skeletal

muscle, adipose tissue, skin, heart, immune system, and endothelial function (WIIK et al., 2018). This is important for improving gender-affirming treatment and future care and will further define the role of sex hormone treatment and its relationship to the development of metabolic complications and cardiovascular disease (WIIK et al., 2018). Serum hematocrit levels can be found in the perceived gender reference range from three months after starting the gender-affirming hormone treatment (DEFREYNE et al., 2018). Their results support previous recommendations that the hematological parameters of transgender persons receiving hormone therapy (HT) should be interpreted based on their stated gender rather than their documented gender at birth. (ANTUN et al., 2020; DEFREYNE et al., 2018; GREENE et al., 2019). Low rates of erythrocytosis in trans men on testosterone treatment, with a maximum measured hematocrit level of 54.0%.(DEFREYNE et al., 2018). They did not observe any serious risk of health problems with the use of HT in transsexual women. In addition, HT therapy is likely to have some positive effects on the carotid artery wall in transgender women (KULPRACHAKARN et al., 2020).

Their results (MEYER et al., 2020), taken from a valid cohort of individuals with gender dysphoria, confirm the decreased risk of side effects using a modern guideline-based gender-affirming hormone therapy (GAHT). The incidences such as metabolic side effects and erythrocytosis in trans men and venous thromboembolic in trans women are impressively decreasing compared to previous data (MEYER et al., 2020). In addition, HT therapy is likely to have some positive effects on the carotid artery wall in transgender women (KULPRACHAKARN et al., 2020).

One of the studies compared transgender women to cisgender men (LIM et al., 2020) and trans women on estradiol therapy demonstrated a profile of hypercoagulable thromboelastographic and thrombin generation compared to cisgender male controls with a shift towards the parameters of cisgender female controls. In contrast, there was evidence of increased overall fibrinolytic potential compared to cisgender male controls (LIM et al., 2020).

4.3.2 LIPIDIC PROFILE

Three studies investigated the impact of HT in lipidic profile. Based on results, it is possible to observe slight increases in low density lipoprotein (LDL) and triglycerides, and these slight variations could not pose a short-term risk to suspend testosterone. They observed that HDL levels increased significantly after one year of treatment and remained stable with a mean greater than 50 mg/dL. Their large, prospective observational study of transmen and transwomen undergoing HT showed no relevant changes in blood pressure (BP) (VAN VELZEN et al., 2019) but did show unfavorable increases in cholesterol levels during testosterone therapy in transmen. Also, it decreased cholesterol levels during estrogen plus cyproterone acetate therapy, along with a decrease in HDL-C levels in transwomen. This seemed more pronounced in transdermal application of estrogen (VAN VELZEN et al., 2019). The main changes concerned blood pressure, hemogram and lipid profile in transgender women patients, and hemogram, glycemia, creatinine and liver enzymes in transgender men patients. However, despite the changes, values still appeared to be generally within the normal range (VITA et al., 2018).

4.3.3 OVARIAN PARAMETERS

Four studies investigated about ovarian parameters (ADELEYE et al., 2019; AMIR et al., 2020; CHEW et al., 2018; TAUB et al., 2020). Suggested that testosterone may cause rapid suppression of ovulation in male transgender individuals receiving testosterone. Another study that looked at prolonged exposure to testosterone hormone therapy in transgender males showed an excellent response to ovulation stimulation (AMIR et al., 2020). The levels being comparable to fertile cisgender women of the same age (AMIR et al., 2020). Showing that the use of hormonal therapy in transgender patients may not negatively impact the results of ovarian stimulation. Clinical pregnancy is possible from oocytes from transsexual men with a history of transgender hormone therapy (ADELEYE et al., 2019).

Therefore, cryopreservation of oocytes and/or embryos can be considered an effective way to preserve their fertility for future biological parents (AMIR et al., 2020). Testosterone therapy in transgender men across a wide

range of doses and over many years did not result in the abnormalities in glycated hemoglobin or dyslipidemia seen with polycystic ovary syndrome. Instead, treatment of transgender men with testosterone resulted only in a shift of metabolic biomarkers toward the average physiologic male body (CHEW et al., 2018).

4.3.4 OTHERS METABOLIC PARAMETERS AND BONE HEALTH

Many effects of GAHT on the components of the metabolic syndrome to be directly attributable to changes in the sex steroid milieu (AUER et al.,2018). However the authors did not observe indirect sex-specific effects involving mediators such as changes in body composition and metabolic cytokine secretion, or a combination of both of these factors (AUER et al., 2018). Their study highlighted the importance of lean and fat mass and the correlation with insulin resistance among transgender individuals and the relatively stronger correlation of insulin resistance with android over gynoid fat. Significantly higher levels of fat mass and lower lean mass in trans women is associated with insulin resistance, and whilst there is some degree of higher fat mass in trans men on established GAHT. The significantly higher lean mass relative to fat mass appears to be protective. These findings provide insights into sex hormone action and suggest a predominantly indirect mechanism of action (via changes in body composition) in mediating insulin resistance (BRETHERTON et al., 2021). Obesity was more prevalent in a subset of young adult transwomen and transmen compared with the young adult general population. Therefore, body weight management should be an important part of the endocrinological treatment in transgender adolescents and young adults (KLAVER et al., 2020).

One year of hormone therapy (HT) did not result in deleterious effects on bone health in transgender people (VLOT et al., 2019). Despite these results, the effects after multiple years of HT, particularly for younger transmen, are of great interest for future study. Given the still increasing incidence and the need for the treatment of transgender people, additional studies should be performed to

evaluate the longer-term relationships between change in bone turnover, bone mineral density (BMD), and fracture risk during HT in transgender people (VLOT et al., 2019). Even after two years of HT, body composition changes are still progressing. However, there is a large inter-individual variation, with a total of 20% of transmen and 9% of transgender women without measurable effects even after two years (VAN VELZEN et al., 2020). Transgender Women on estrogen replacement therapy, and five years after gender-confirming surgery, have a high prevalence of low bone mass, significantly associated with low estradiol levels and low compliance to therapy replacement estrogen. Thus, major efforts have to be made to keep transgender women on estrogen replacement therapy after gender confirming surgery (MOTTA et al., 2020).

Considering other hormonal parameters, the testosterone administration in transgender men resulted in lower serum estradiol levels compared with baseline (DEFREYNE et al., 2020). The most likely due to suppression of endogenous estradiol production. Their hypothesis was supported by the observed comparable serum estradiol levels in people with versus without hystero-oophorectomy or contraceptives after the first year of HT. Therefore, the need for estradiol-lowering agents (e.g., aromatase inhibitors) seems unlikely. They did not assume that testosterone therapy in transgender people on testosterone therapy (AFAB). transgender people could be a risk factor for undesired estrogenic effects. They also concluded from previous research that the observed decrease in serum estradiol levels does not lead to adverse outcomes, unlike in hypogonadal females. However, serum estradiol levels after initiation of testosterone therapy in their population remained higher than those observed in the male control group (DEFREYNE et al., 2020). Their study showed that gonadotropin-releasing hormone agonist (GnRHa) are effective in suppressing the HPG axis in transgender youth. Their finding has relevant clinical implications as GnRHa are recommended to suppress puberty in children and adolescents with gender dysphoria (MEJIA-OTERO; WHITE; LOPEZ, 2021).

One study observed that liver enzymes remained without significant variations, and as mentioned in other publications, there were only small increases (OTERO et al., 2018).

5. DISCUSSION

In this scoping review, the included studies highlighted changes in hematological, lipidic and ovarian parameters. Changes can occur in several common laboratory parameters inpatients receiving hormone therapy (SORELLE et al., 2019). Some laboratory values changed to match the gender identity, whereas others remained unchanged or were intermediate from the baseline values (SORELLE et al., 2019).

The European Network for the Investigation of Gender Incongruence (ENIGI) has a partnership of currently five gender identity clinics in Amsterdam (the Netherlands), Ghent (Belgium), Oslo (Norway), Florence (Italy) and Tel Aviv (Israel). ENIGI was initiated to obtain more insight into the potential of diversity in diagnostics and treatment of transgender individuals. Although we have a limitation in terms of time, studies considered to be of good quality were included in the research.

Women and men transgenders were investigated in the included studies, and testosterone and estradiol were the main intervention of hormone therapy. In trans women, masculinizing hormone intervention develops male secondary sexual characteristics. It can also promote suppression/minimization of female secondary sexual characteristics. General effects include facial hair development, virilizing voice changes, a redistribution of subcutaneous facial and body fat, increased muscle mass, increased body hair, change in sweat and odour patterns, frontal and temporal hairline recession, and baldness (IRWIG, 2017). There are hormone therapy regimens by different international consensuses that define the minimum initial dose, the desired initial dose or the maximum dose. Medicines that appear in different regimens are androgen blockers: Finasteride, Spironolactone, Dutasteride, Cyproterone acetate and GnRH agonists (UNGER, 2016). As the transgender population needs to use this medication, it is necessary to pay special attention to possible adverse reactions due to hormone therapy. However, possible drug intoxications, inappropriate use and long-term physiological changes cannot be ruled out, considering that our organism ends up producing physiological hormones according to our birth sex (UNGER, 2016).

Estrogen is presented as an oral, intramuscular, transdermal tablet.

When using hormone therapy, the patient must be aware that all drugs can cause various adverse/undesirable effects regardless of their formulation. Therefore, it is essential to monitor the hormone levels in the laboratory to check the evolution of therapy in each patient since we are unique individuals, and our bodies act in different ways. For example, oral estrogen can significantly increase triglyceride levels, which is related to the increased risk of pancreatitis and cardiovascular events, venous thromboembolic events (VTE), risk of cholelithiasis (gallstones) and subsequent cholecystectomy, risk of type II diabetes mellitus and hypertension. Regarding the use of testosterone, there is interference in reducing HDL levels, but it affects in different ways LDL and triglycerides, which may increase hypomanic, manic or psychotic symptoms (WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH, 2012). According to the results obtained in the articles selected in this work, it was noticed that we should use as reference laboratory parameters, the values of the patient's current gender after the hormonal transition. It is not compatible to try to use the reference values of the patient's biological sex. Over time, possible changes in the health of the transgender population are being increasingly investigated in various clinical areas from their quality of life, mental health, blood changes, lipid profile, ovulation and body changes, glycemic markers, hormonal values, which may change even change the semen (Adeleye et al. 2019). Any research should continue to be carried out to clarify doubts and extinguish any prejudice.

Looking for any change during life, the transgender population through monitoring laboratory tests, biological markers, lipid profile and changes in metabolism. Seeking to ensure quality of life and health. In addition to being able to make the general population aware of the long-term risks of using hormone therapy.

6. Strengths and limitations

We performed this review in pairs and validated data by expertises. We have searched in main databases and also included some study types. We did not evaluate the risk of bias of included studies, and it was considered a limitation

of this study. Also, we limited the time of publication, thus, some studies could contribute to evidence.

7. CONCLUSION

In this scoping review, the study's results highleted a slight change in the hematological and lipid parameters of transgender people receveing hormone therapy. Also, testosterone therapy appears to cause rapid suppression of ovulation in male transgender individuals, but there is not a consensus. It is essential to follow these parameters in transgender people receiving hormone therapy. Considering our nationality, we are encouraging more studies in the Brazilian transgender population to identify laboratorial parameters changes. We should be mirrored in Europe and in the future, who knows how to set up an investigation network on transgender people.

8. Contributors

IGD and GO carried out the bibliographical research, elaborated the data extraction form. GO, VOW, GFR blindly selected the studies, and GO and GFR performed data extraction. GO and IGD performed data analysis. IGD and BIA critically reviewed the analyzed data. GO E IGD wrote the article and critically reviewed subsequent drafts. All authors approved the final version of the manuscript for submission. All authors had full access to the data and were responsible for the integrity and accuracy of data analysis.

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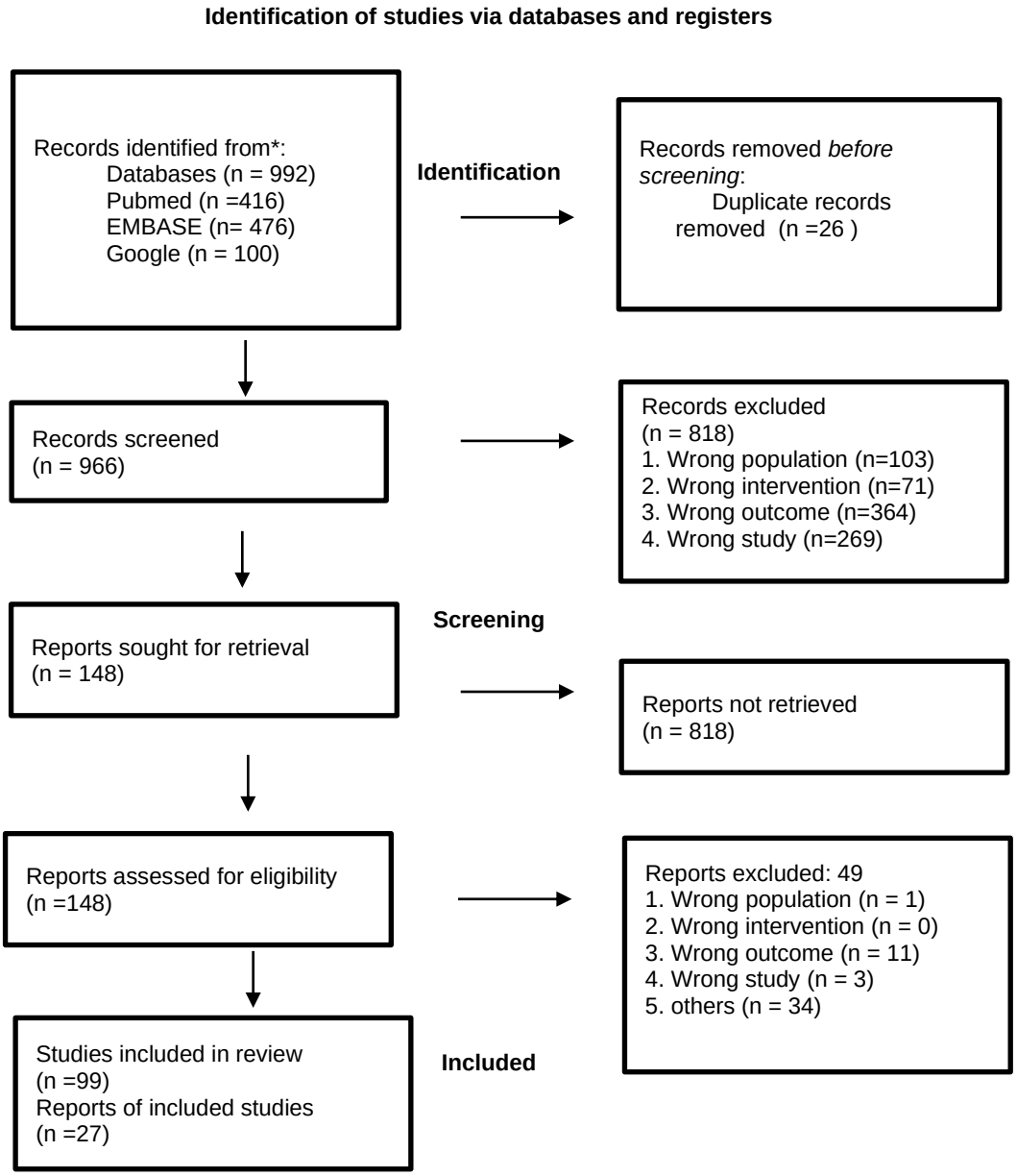
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary File Table 1. PICOS strategy.

PICOS	Inclusion Criteria	Exclusion criteria
P*opulation*	Transgender people (any age and gender)	Non-transgender people In Vivo and in vitro 1.wrong population
***I**ntervention*	Hormone therapy (testosterone and progesterone)	Non-hormone therapy use Use of the synthetic compounds 2.wrong intervention
***C**omparator*	Any control or none	Not applicable
***O**utcomes*	Hematological, immunological and biochemical parameters (reference values, cut-off, and other) and outcomes	Non-laboratory diagnostics (Hematological, immunological and biochemical) Image diagnosis, Clinical diagnosis 3.wrong outcome
S*tudy design*	Clinical trial and observational studies (cross sectional, case-control, cohort studies), systematic or meta-analyzes and clinical guidelines / clinical practice record	Case-report, Case series, brief communication, Narrative or Integrative Reviews, letter, conference summary, editorial, thesis, correspondence, dissertations, In Vivo and in Vitro 4.wrong study 5.others (duplicate, unavailable)
Research question:	What are the effects of hormone therapy on the laboratory profile of transgender people?	

PICOS strategy for studies of intervention (Needleman IG, 2002; Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. England: John Wiley & Sons, Ltd; 2011).

Supplementary File Table 2. Search strategy.

Busca	**Query/ Pubmed (Mesh or free term)**	**Embase/ Emtree (PICO Search®)**
Block 1 Ttransgender persons #1	Transgender Persons OR Gender Dysphoria OR Gender Identity OR Health Services for Transgender Persons OR Transsexualism	transgender'/exp OR 'gender identity'/exp OR 'gender dysphoria'/exp
Block 2 Hormone therapy #2	Gonadal Steroid Hormones OR Estradiol OR Estrogens OR Androgens OR Testosterone OR Estradiol Congeners OR Testosterone Congeners OR Hormone Replacement Therapy OR Cross-sex hormone therapy (free term)	'sex hormone'/exp OR 'steroid hormone'/exp OR 'testosterone'/exp OR 'hormone substitution'/exp
Block 3 Diagnosis #3	Metabolic Diseases/diagnosis OR Metabolic Diseases/drug effects OR diagnosis OR Lipids / blood OR Lipids/analysis OR lipids/metabolism OR Cholesterol/analysis OR "Cholesterol/blood OR Cholesterol/metabolism OR Blood Glucose/analysis OR Blood Glucose/metabolism OR biomarkers OR reference interval	*'metabolic disorder'/exp OR 'diagnosis'/exp
Combination	(#1 AND #2 AND #3) = 416	(#1 AND #2 AND #3) = 476

Google Scholar (Gray Literature): (Transgender persons OR Gender Dysphoria OR Gender Identity) AND Steroid Hormones AND Diagnosis filetype:PDF = 625 (100 first, most relevance)

Supplementary File **Table 3 -** Summary of characteristics of included studies (n=27).

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
OTERO *et al.* 2018; AR	**Retrospective observational and analytical study**	**Transgender men**	**TD gel testosterone (50mg), Testosterone-undecanoate (1000mg) IM, testosterone-enanthate (250mg) IM.**	**Not**	**Hb, Hto, Colesterol, TG, LDL, HDL, GOT and GPT.**	**It did not present significant changes in the short term; slight increases in LDL and triglycerides, and these small variations could not pose a short-term risk to suspend testosterone. We observed that HDL levels increased significantly after one year of treatment and remained stable with a mean greater than 50 mg / dl. Liver enzymes remained without significant variations.**
Adeleye *et al.* 2018; USA.	**Retrospective chart review between**	**Transgender men and cisgender women**	**Testosterone cypionate 150 mg, 200 mg (IM)**	**Yes**	**FSH, LH, Peak Estradiol, Peak estradiol per oocyte**	**HRT use may not negatively impact ovarian stimulation outcomes. Clinical pregnancies are possible from the oocytes of transgender men with a history of HRT.**
Amir *et al.* 2020; IL.	**Retrospective cohort study**	**Transgender men and cisgender**	**The route of administration and dosage were not reported**	**Yes**	**FSH, LH, Peak Estradiol, Peak estradiol per oocyte**	**Even after longterm exposure to testosterone, transgender men have an excellent response to ovulation stimulation similar to age-matched fertile cisgender women. Therefore, oocyte and/or embryo cryopreservation can be considered an effective way for them to preserve their fertility for future biological parenting. In addition, their data indicate that an antagonist-based protocol for ovarian stimulation triggered by a GnRH agonist for oocyte maturation is a feasible means of ART in this population.**
Antun et *al.* 2019; USA	**Longitudinal observational study**	**Transgender men and women**	**TM: testosterone esters, undecanoate (IM) or gel TW: cyproterone acetate with diol estravalerate or transdermal estradiol**	**Yes**	**HT, Hct, anemia and erythrocytosis**	**The results support previous recommendations that hematological parameters of transgender people receiving HT should be interpreted based on their affirmed gender, rather than their sex documented at birth. The clinical significance of erythrocytosis following testosterone therapy, as well as anemia following feminizing HT, requires further investigation.**

Table 3- Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Auer *et al.* 2019; USA	Longitudinal observational study	Transgender men and women	TM: TO undecanoate 1000mg IM TW: 50 mg cyproterone acetate, E2 TD patch releasing 100 mg	Not	Lipids, Glucose metabolism, Sex hormones, Metabolic Cytokines	One of the most in-depth analyses to date has, in their study, succeeded in further disentangling the direct and indirect effects of GAHT on the components of the MS in transgender individuals. Many effects of GAHT on the components of the MS seem to be directly attributable to changes in the sex steroid milieu. However, weal so found indirect sex-specific effects involving mediators such as changes in body composition and metabolic cytokine secretion, or a combination of both factors.
Brethert on *et al*. 2021; AU	Cross-sectional	Transgender men and women	TM: TU, TE (IM), gel1% TW: oral valerate E2, ethinyl E2, TD E2 cyproterone acetate, spironolactone, progestogens	Yes	E2, testosterone, SHBG, HOMA2-IR, IGF-1	Their study highlighted the importance of lean and fat mass and the correlation with insulin resistance among transgender individuals and the relatively stronger correlation of insulin resistance with android over gynoid fat. Significantly higher levels of fat mass and lower lean mass in trans women is associated with insulin resistance, and whilst there is some degree of higher fat mass in trans men on established GAHT, the significantly higher lean mass relative to fat mass appears to be protective. These findings provide insights into sex hormone action and suggest a predominantly indirect mechanism of action (via changes in body composition) in mediating insulin resistance.
Chan *et al*. 2018; USA	retrospective anonymous chart review	Transgender men	TC and TE are used interchangeably, a typical maximum of 125 mg	Yes	TG, Testosterone, HDL, LDL	Testosterone therapy in transgender men across a wide range of doses and over many years did not result in the abnormalities in HbA1c or dyslipidemia seen with PCOS. Instead, treatment of transgender men with testosterone resulted only in a shift of metabolic biomarkers toward the average physiologic male body
Chew *et al*. 2018; AU	Systematic review	Transgender men and women	GnRHas, estrogen, testosterone, antiandrogen (cyproterone acetate) and progestin	Yes		Low-quality evidence suggests that hormonal treatments for transgender adolescents can achieve their intended physical effects, but evidence regarding their psychosocial and cognitive impact are generally lacking. Future research to address these knowledge gaps

Table 3- Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Defreyne *et al.* 2020; BE and NL	prospective cohort	Transgender men	TG 50mg TU 1000mg (IM) TE 250mg (IM)	Yes	E2, Serum testosterona, LH, FSH.	Testosterone administration in AFAB transgender people resulted in lower serum estradiol levels compared with baseline, most likely due to suppression of endogenous estradiol production. This hypothesis was supported by the observed comparable serum estradiol levels in people with versus without hystero-oophorectomy or contraceptives after the first year of HT. Therefore, the need for estradiol-lowering agents (e.g., aromatase inhibitors) seems unlikely. They did not assume that testosterone therapy in AFAB transgender people could be a risk factor for undesired estrogenic effects. They also concluded from previous research that the observed decrease in serum estradiol levels does not lead to adverse outcomes, unlike in hypogonadal females. However, serum estradiol levels after initiation of testosterone therapy in this population remained higher than those observed in the male control group.
Defreyne *et al.* 2018; BE and NL	prospective cohort	Transgender men and women	TM: TU 1000mg TE 250mg , TG 50mg TW: TD E2 50ug/100ug, EG, E2 valerate 2mg	Not	Hct, E2 TM/TW, Testosterone TM/TW	Serum hematocrit levels can be found in the reference range of the perceived gender as from 3 months after the initiation of gender-affirming hormonal treatment. They suggested consulting the reference range for men in trans men after the initiation of testosterone treatment and the reference range for women in trans women in whom effective androgen deprivation has been established. Low erythrocytosis rates in trans men on testosterone treatment, with a maximum measured hematocrit level of 54.0%, and as none of the trans men in their study cohort experienced a thromboembolic event during follow up, they have no reasons to assume that the observed mild increase in serum hematocrit levels is associated with an increased thrombotic risk on short term. Trans men on testosterone undecanoate exhibit lower erythrocytosis rates compared to trans men on testosterone esters or gel. Changing the treatment to testosterone undecanoate seems a valid option if the hormone prescribing physician and/or the patient are concerned about elevated serum hematocrit levels.
DELGADO-RUIZ; SWANSON; ROMANOS, 2019; USA	Systematic review	Transgender men and women	TM: TE 250mg, TD100 mg, TU 1000 mg, TG 50mg TW:E2 valertate 2-4 mg, TD E2 40mg. CA 100mg anti-androgens until gonadectomy		ALP, Calcium, Phosphate, Osteocalcium	Long-term pharmacotherapy for transgender patients does not alter the calcium, phosphate, alkaline phosphatase, and osteocalcin bone markers. Long-term pharmacotherapy for transgender patients will slightly increase the bone formation, expressed with increased PINP turnover markers. Long-term cross-sex pharmacotherapy for M to F transgender patients will produce a slight reduction in bone mineral density.

Table 3- Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Greene et al., 2019; USA	Prospectively	Transgender men and women	TW: Testosterone (IM or SC) TM: E2 valerate (IM or SC), Spirolactone, finasteride.	Yes	Testosterone, E2, RBC, HB, HCT,PTL, MCV, MCHC, RDWCV	The hematology parameters for transgender men and women receiving stable hormone therapy should be evaluated against the cisgender male and cisgender female reference ranges, respectively and does not require concurrent sex hormone analysis. Care providers can utilize this observation to aid in interpretation of hematology laboratory values for transgender people.
KLAVER et al., 2020	Retrospective cohort study	Transgender men and women	TW (E2) 2 mg TM: TE 250 mg GnRHas E2 daily or 75 mg of TE IM. to 2 mg of E2 or 250 mg of TE		Glucose, LDL, HDL, Insulin, Total Cholesterol, TG, HOMA-IR, Testosterone, GAH, GnRHa, E2	Treatment with GnRHas and GAHs in transgender adolescents is generally safe regarding cardiovascular risk factors. However, obesity was more prevalent in a subset of young adult transwomen and transmen compared with the young adult general population. Therefore, body weight management should be an important part of the endocrinological treatment in transgender adolescents and young adults
Kulprachakarn et al;2020 USA	Cross-sectional study	Transgender women or men	Testosterone and estradiol	Yes	TG, E2, LDL, HDL, Cholesterol total	Their present study demonstrated no severe risk of health problems with HT use in transgender women. Also, HT therapy is likely to have some positive effects on carotid artery wall in transgender women.
Lim *et al*. 2020; AU	Cross-sectional case-control study	Transgender women	Antiandrogens, testosterone, estradiol	Yes	E2, cholesterol, testosterone, Hb, Platet	Transgender women on estradiol therapy demonstrated a hypercoagulable thromboelastographic and thrombin generation profile compared with cisgender male controls with a shift towards the parameters of cisgender female controls. In contrast, there was evidence of increased overall fibrinolytic potential compared with cisgender male controls.
Mejia-Otero, J, D.; White, P.; Lopez, X.. 2020. USA	Retrospective review	transgender men and women	Oral contraceptives, testosterone, estradiol, or spironolactone	Not	FSH, LH, Testosterone and Estradiol	Their study showwer that GnRHa are effective in suppressing the HPG axis in transgender youth. This finding has relevant clinical implications as GnRHa are recommended to suppress puberty in children and adolescents with gender dysphoria

Table 3 - Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Meyer et al/2020. Frankfurt, Germany	Cohort study of medical file	Transgender men and women	TM: TU 1000mg (IM) And GnRH TW: TD E2 1,5mg/6mg, Valerate E2	Not	GGT, ALT, AST, LDL, HDL-C, TG, Hb, Hct	The results were raised in a valid cohort of gender dysphoric individuals, confirm a decreasing risk of side effects using a modern, guideline based GAHT. Especially, incidences like metabolic side effects and erythrocytosis in transmen and venous thrombembolisms in transwomen are impressively declining compared to former data.
Motta 2020/Turin, Italy	cross-sectional study	Transgender women (TW)	cyproterone acetate 25–100 mg/day or spironolactone 100–200 mg/day in combination with oral estradiol valerate 2–6 mg/day or TD hemihydrate 1.5–3 mg/day	Not	17ß-estradiol (pg/ml), LH, 25OHD (ng/ml), Ca and phosphate	TW on ERT, 5 years after GCS, have a high prevalence of low bone mass, signifi cantly associated with low estradiol levels and low compliance to ERT. Thus, major efforts have to be made to keep TW on ERT after GCS.
Shadid 2019/Ghent, Belgium	multicenter prospective cohort study	transgender men (TM) and transgender women (TW)	TW: cyproterone acetate 50 mg once daily with oral estradiol valerate 2 mg twice daily. TM: TO via IM 1000mg/12 weeks	Not	E2, total and free TO, sex hormone–binding globulin, and albumin, plasma glucose, TC, free fatty acids, HDL, LDL levels calculated; HOMA; GIP and GLP-1	The insulin sensitivity but also post-OGTT incretin responses tend to increase with masculinization and to decrease with feminization.
Sorelle et al 2019/r, Dallas, TX	retrospectiv e chart review	transgender women (TW) transgender men (TM)	TW (84%) took oral estradiol, from 2 to 8 mg daily TM (98%) took TO IM, from 35 to 300 mg/1or 2 weeks	Not	complete blood count, complete metabolic panels, liver function tests, lipids, total TO, and E2.	Changes occur in several common laboratory parameters for patients on HT. Some laboratory values changed to match the gender identity, whereas others remained unchanged or were intermediate from the baseline values.

Table 3- Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Stoffers et al., 2019. Leiden, the Netherlands;	Observation aretrospective	Transgendermen and women	GnRHa (Decapeptyl-CR; 3.75 mg every 4 weeks s.c.) Testosterone (Sustanon; 250 mg IM)	Not	androstenedione, ALP, DHEAS, E2, FSH, GnRHa, Hb, HDL, Hct, LDL, LH, PRL, SHBG	Testosterone treatment using a dosing schedule as recommended by current guidelines effectively induces virilization in transgender boys, with increased hair growth and voice change noted within 3 months of therapy in the majority
Taub et al/2020. Seattle, Washington	Prospective observational study	Transgendermen and women	All individuals injectable testosterone cypionate at a dose of 50-100mg either (IM or SC).	Not	TO, E2, SHBG. urinary PdG	Their study suggested that testosterone may cause rapid suppression of ovulation in transmasculine individuals on testosterone.
Vanvelzen et al/2020. Amsterdam and Ghent	Prospective	Transgendermen and women	TM: TG 50 mg once daily), (IM) TE mixture 250 mg (IM) of TU 1000 mg. TW: oral or transdermal E2, cyproterone acetate (25 or 50 mg daily)	Not	LH, E2, Testosterone	Even after two years of hormone therapy, body composition changes are still progressing. However, there is a large inter-individual variation, with a total of 20% of transmen and 9% of transwomen without measurable effects even after two years.
Vanvelzen et al/2019. Amsterdam or Ghent	Prospective observational	Transgender women (TW) transgendermen (TM)	TW: cyproterone acetate 50 mg, estradiol valerate 2 mg, TD E2 100 mg TM: In Ghent TU 1000 mg. In the Netherlands, TG 50 mg, TE in 250-mg (IM)	Not	Hct, CR, TC, triglycerides, HDL-C, LDL, E2 and TO	This large, prospective observational study of transmen and transwomen undergoing HT showed no relevant changes in BP, but did show unfavorable increases in cholesterol levels during testosterone therapy in transmen and decreases in cholesterol levels during estrogen plus CPA therapy, along with a decrease in HDL-C levels in transwomen, which seemed more pronounced in transdermal application of estrogen.

Table 3- Continued

Author, Year; Country	Study design	Population	Intervention	Control Yes or not	Laboratorial parameters	Fiddings
Vita et al/2017. Messina, Italy	Retrospective cohort study	Transgendermen and women	TW: cyproterone acetate 50 mg, estradiol valerate 2 mg, TD E2 100 mg TM: In Ghent TU 1000 mg. In the Netherlands, TG 50 mg, TE in 250-mg (IM)	Not	Total TO, E2, SHBG, CR, hemogram, fasting plasma glucose, TC, HDL, TC to HDL, LDL, TG	The main changes concerned blood pressure, hemogram and lipid profile in MtF patients, and hemogram, glycemia, creatinine and liver enzymes in FtM patients. However, despite the changes, values still appeared to be generally within the normal range
Vlot et al/2019. Belgium, Norway, Italy and Amsterdam	Prospective observational multicenter cohort	Transgendermen and women	TW: cyproterone acetate 50 to 100 mg, estradiol valerate (2 to 4mg TD E2 50 to 100 µg. TM: TG 50 mg, TE 250 mg, (IM), or TU 1000 mg (IM).	Not	ALP; Sclerostin, 25OHD, TO, E2	1 year of HT does not result in deleterious effects on bone health in transgender people. Despite these results, the effects after multiple years of HT, particularly for younger transmen, are of great interest for future study. Given the still increasing incidence and the need for the treatment of transgender people, additional studies should be performed to evaluate the longer term relationships between change in bone turnover, BMD, and fracture risk during HT in transgender people.
Wiik et al/2018. Sweden	Prospective observational single cohort	Transgendermen and women	GnRH antagonist 240mgsc (IM) Transgender men: TU 1000 mg i.m. TW: TD E2 or (IM) estradiol polyphosphate	Not	Lipids, hematology, sex hormones, insulin sensitivity	The long-term effects of cross-sex hormone treatment is not fully understood and have not been studied at all in some areas such as adipose and skin. Thus, the GETS study will provide novel and deeper insight into the effects of cross-sex hormone treatment on skeletal muscle, adipose, skin, heart, immune system and endothelial function. This is important in order to improve gender-affirming treatment and future care and will further define the role of sex-hormone treatment and its relation to development of metabolic complications and cardiovascular disease.

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	2
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	11, 12
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	11,12, 13, 14
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	11
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	11, 12,
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	11,14
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	16
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	13,14,15
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	13,14,13
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	15
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	15, 32
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	------

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	15, 16
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	30
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	33, 34, 35, 36, 37, 38, 39
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	------
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	33, 34, 35, 36, 37, 38, 39
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	17, 18, 19, 20, 21, 22 ,23 ,24
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	23, 24, 25
Limitations	20	Discuss the limitations of the scoping review process.	25
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	26
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	------

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.