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Prevalence of Risk Factors of Metabolic Syndrome in Transgender and Gender Diverse Individuals Receiving Gender-Affirming Hormone Therapy

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ACCEPTANCE

This thesis, PREVALENCE OF RISK FACTORS OF METABOLIC SYNDROME IN TRANSGENDER AND GENDER DIVERSE INDIVIDUALS RECEIVING GENDER-AFFIRMING HORMONE THERAPY, by Ashley Fischer was prepared under the direction of the Master's Thesis Advisory Committee. It is accepted by the committee members in partial fulfillment of the requirements for th edegree Master of Science in the Byrdine F. Lewis College of Nursing and Health Professions, Georgia State University. The Master's Thesis Advisory Committee, as representatives of the faculty, certify that this thesis has met all standards of excellence and scholarship as determined by the faculty.

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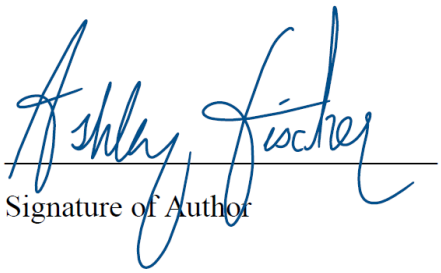

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ABSTRACT

PREVALENCE OF RISK FACTORS OF METABOLIC SYNDROME IN TRANSGENDER AND GENDER DIVERSE INDIVIDUALS RECEIVING GENDER-AFFIRMING HORMONE THERAPY

by

Ashley C. Fischer

Background: The recent increase in the prevalence of metabolic syndrome (MetS) parallels trends in rates of obesity. However, the distribution of weight-related health risks between men and women is not equivalent and the prevalence of risk factors for MetS in adults receiving gender affirming hormone therapy (GAHT) is unknown. The objective of this study is to describe MetS risk status before and after feminizing or masculinizing therapy in an urban transgender/gender nonconforming population.

Methods: A retrospective review of demographic characteristics, anthropometric data, hormone levels, and risk factors for MetS (adiposity, insulin resistance, abnormal triglyceride metabolism, abnormal cholesterol metabolism, and hypertension) was conducted in adults receiving care at a gender clinic in a large urban hospital. The Third Report of the National Cholesterol Education Program on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults was used to determine risk for MetS (low, moderate, high). Differences in MetS risk factor levels and risk scores were examined by therapy type as well as pre- and post-therapy.

Results: Data from 28 adults (median age 30.5 years [Interquartile range; 25.5, 37.5], 68% Black/African American, 4% Hispanic) were included in the analysis. The majority of the population (57%) received feminizing treatment. Of the MetS risk factor levels

examined (BMI, systolic and diastolic blood pressure, glucose, Hemoglobin A1c, triglyceride and high-density lipoprotein [HDL] cholesterol) no significant difference was found between therapy types during either the pre- or post-therapy periods. Significant differences were observed between pre-therapy and post-therapy levels of triglycerides (60.0 ± 7.8 vs. 92.4 ± 7.8, respectively; P=0.003) and HDL cholesterol (54.8 ± 2.1 vs. 44.8 ± 2.5, respectively; P=0.012) for participants in the masculinizing treatment group. Participants in the feminizing treatment group were found to have significant differences in systolic blood pressure (129.8 ± 3.1 vs. 123.9 ± 3.0, respectively; P=0.028) between the pre-therapy and post-therapy periods. An association between HDL cholesterol risk score (determined based on sex assigned at birth) and therapy type was observed in participants post-treatment. The majority of individuals receiving masculinizing therapy (86%) are categorized as high risk after therapy while the majority of individuals receiving feminizing therapy (92%) are at low risk (P=0.002).

Conclusions: This study demonstrates the health effects that may result from GAHT, a vital therapeutic practice for this population. MetS risk was similar between treatment types during the pre-therapy and post-therapy periods. However, within group analysis demonstrated significant shifts in triglyceride and HDL levels (masculinizing) and systolic blood pressure (feminizing) over the course of treatment. Twenty-five percent of the participants are living with HIV, which increases the risk of developing MetS. The increased risk of developing MetS in this population may warrant earlier and more thorough lifestyle and dietary interventions to adequately prevent and manage disease progression.

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TABLE OF CONTENTS

List of Tables iv

Abbreviations v

Chapter

I. INTRODUCTION 1

II. LITERATURE REVIEW 6

Sex, Gender Identity and Gender Expression 6

Transgender and Gender Diverse Healthcare 7

Hormone Replacement Therapy – Clinical Application 12

Feminizing Hormone Therapy (FHT) 14

Masculinizing Hormone Therapy (MHT) 16

Health Concerns for the Transgender and Gender Diverse Population 20

Food Insecurity in the Transgender Population 22

Metabolic Syndrome in the Transgender and Gender Diverse Population 24

III. METHOD 27

IV. RESULTS 33

V. DISCUSSION AND CONCLUSIONS 36

REFERENCES 45

APPENDICES 68

LIST OF TABLES

Table 1. Risk Assessment for Metabolic Syndrome 68

Table 2. Demographic Characteristics of Gender Clinic Adults Who Received Gender Affirming Hormone Therapy 70

Table 3. Metabolic Syndrome Risk Factor Scores for Gender Clinic Adults Who Received Gender Affirming Hormone Therapy 71

Table 4. Difference in Metabolic Syndrome Risk Factor Levels between Adults Receiving Masculinizing and Feminizing Therapy (Pre- and Post-Therapy) 72

Table 5. Difference in Hormone Levels between Adults Receiving Masculinizing and Feminizing Therapy (Pre-Therapy, 2-Year Post-Therapy, 5- Year Post-Therapy) 73

Table 6. Difference in Metabolic Syndrome Risk Factor Levels (Pre- and Post-Therapy) by Treatment Type 74

Table 7. Difference in Hormone Levels (Pre-Therapy, 2-Year Post-Therapy, 5 Year Post-Therapy) by Treatment Type 75

Table 8. Body Mass Index Risk Score by Therapy Type 76

Table 9. Blood Pressure Risk Score by Therapy Type 76

Table 10. Glucose Risk Score by Therapy Type 76

Table 11. Hemoglobin A1C Risk Score by Therapy Type 76

Table 12. Triglyceride Risk Score by Therapy Type 77

Table 13. High Density Lipoprotein (based on Sex Assigned at Birth) Risk Score by Therapy Type 77

Table 14. High Density Lipoprotein (based on Treatment Type) Risk Score by Therapy Type 77

Table 15. Number of Participants with Variable Risk Scores of 2 (High Risk), by HDL Variable Used 77

Table 16. Diagnostic Criteria for Metabolic Syndrome 78

Table 17. American Board of Internal Medicine Laboratory Test Reference Ranges 78

Table 18. Comparison of Various Estrogen Therapies Currently Available 79

Table 19. Comparison of Various Testosterone Therapies Currently Available 82

ABBREVIATIONS

AHA	American Heart Association
ART	Antiretroviral therapy
ANOVA	Analysis of Variance
BP	Blood pressure
BMD	Bone mineral density
BMP	Basic metabolic panel
BMI	Body mass index
CBC	Complete blood count
CBD	Complete blood count with differential
CMP	Complete metabolic panel
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DEXA	Dual x-ray absorptiometry
DRE	Digital rectal exam
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
HER	Electronic health record
FHT	Feminizing hormone therapy
GAHT	Gender-affirming hormone therapy
GAT	Gender-affirming therapy
GnRH	Gonadotropin-releasing hormone
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
ICD-10	International Classification of Diseases, Tenth Revision

IQR	Interquartile range
ISCD	International Society of Clinical Densitometry
IM	Intramuscular
LDL-C	Low density lipoprotein cholesterol
LGBTQIA+	Lesbian, bisexual, transgender, queer/questioning, intersex, asexual
MetS	Metabolic syndrome
MHT	Masculinizing hormone therapy
NAFLD	Nonalcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
PCOS	Polycystic ovary syndrome
PI	Principal investigator
PSA	Prostate specific antigen
SBP	Systolic blood pressure
SC	Subcutaneous
TGD	Transgender and gender diverse
TRT	Testosterone replacement therapy
USDA	United States Department of Agriculture
USTS	United States Transgender Survey

CHAPTER 1

INTRODUCTION

Healthcare inequality within the lesbian, gay, bisexual, transgender, queer, intersex, and asexual (LGBTQIA$^+$) population is attributed partially to poorer quality of care and lack of knowledge regarding specific healthcare concerns for this community.[1,2] Various members of the LGBTQIA$^+$ community have noted negative experiences with the healthcare system, including discrimination and lack of LGBTQIA$^+$ inclusive education, but it would be inadvisable to generalize healthcare considerations for all members of this community. The transgender population faces unique barriers to healthcare access that are not ubiquitous to all members of the LGBTQIA$^+$ population, placing these individuals at increased risk for poor health outcomes.[3,4] Current nutrition guidelines fail to address the nuanced experiences and specific healthcare needs of transgender individuals and can further impede patient trust in healthcare professionals.[5] Special considerations should be taken to properly care for members of the transgender community, including the importance and relevance of gender identity and gender expression in patient-centered care.

The prevalence of obesity amongst adults in the U.S. has increased, but trends in obesity prevalence and socioeconomic status vary between cisgender men and women. Data collected from the 2005-2008 National Health and Nutrition Examination Survey (NHANES) reported no significant correlation between obesity prevalence and income among men; however, women with higher income were less likely than women with low

income to be obese.[6] Men and women also demonstrated differences in obesity prevalence based on education, with only women showing a significant increase in obesity prevalence as education decreased.[6] Obesity is strongly associated with the development of comorbidities, including diabetes, cardiovascular disease, cancer, insulin resistance, glucose tolerance, and hypertension.[7] It has also been strongly correlated with anxiety and low-income status.[8-11] However, the distribution of weight-related health risks between men and women is not equivalent. Findings from the 2017-2018 NHANES[12] show no significant difference in the prevalence of obesity between men and women, but severe obesity was higher for women than men. Gender disparities in obesity have been attributed to various environmental and biological factors, including epigenetics, gender-specific societal stressors, sex hormone regulation, socioeconomic status, and nonidentical thresholds of comorbid disease development and progression.[13] Obesity-related disease burden, including medical comorbidities and poorer health-related quality of life (HRQoL), was disproportionately associated with women compared to men.[14,15] Weight-related health risks are more strongly associated with women than men, with overweight women demonstrating "twice the risk of mortality as compared to overweight men" and may be associated with higher risks of poor health-related quality of life.[14]

Discrepancies in the development and progression of chronic illnesses are varied based on the individual's specific health status, sex, age group, and even membership in the LGBTQIA+ community, but very little research is dedicated to understanding these trends in the transgender community.[16-21] In addition, while sex-specific health risks and barriers have been extensively studied, the application of gender-specific measures in

research remains underutilized.[22] Recent analysis of secondary data from the Dutch LifeLines Cohort Study tested the "unique associations of gender and sex with common somatic symptoms and chronic diseases" and found that gender and sex have unique influences over both variables.[22] Of the 152,728 participants in the study (58.5% female, 41.5 % male), 10.1% of the participants' gender indices, which were determined based on the participants' psychosocial variables (unique variables that correlated with specific gender roles and institutionalized gender), did not correspond with the participants' biological sex, highlighting a need for gender-specific research initiatives. With the continuous rise in the prevalence of chronic illnesses in the U.S. related, in part, to increases in adiposity and metabolically unfavorable alterations to body composition, such as loss of lean muscle mass, or increased fat mass, understanding the complex relationship between the development of obesity and chronic illness in the context of gender identity is of the utmost importance.[7,9,23-27]

Several studies[28-31] have attempted to identify weight trends within the transgender community, but nutritional guidelines designated for this population have yet to be established.[5,28,32-35] While the availability of nutrition-related transgender research has steadily increased over the last ten years, there is limited information regarding the association between gender and obesity in the transgender community. Consequently, the prevalence of risk factors for metabolic syndrome (MetS) in urban transgender populations is relatively unknown.[28] The cumulative aim of this retrospective chart review is to determine the prevalence of obesity and other risk factors for the development of MetS, namely cholesterol levels (total, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, calculated

cholesterol/HDL ratio), blood pressure (BP), and serum blood glucose, in transgender patients at a large urban hospital. Data collected from this study will also be used to compare the prevalence of overweight and obesity and other risk factors of between participants receiving either feminizing or masculinizing hormone therapy. The objectives for this study are as follows:

Objective 1: Investigate the prevalence of overweight/obesity and other risk factors for metabolic syndrome in the transgender and gender diverse (TGD) population at a large urban hospital.

Research Hypothesis: The prevalence of overweight/obesity and oth er risk factors for metabolic syndrome in the TGD population will be higher than in the non-transgender patient population.

Null Hypothesis: The prevalence of overweight/obesity and other risk factors for metabolic syndrome in the TGD population does not differ from the general population.

Objective 2: Assess the relationship between the diagnosis of metabolic syndrome and gender-specific hormone laboratory values for participants by their specified gender identity (woman, man, gender nonconforming) and therapy type (utilization of feminizing or masculinizing hormone therapy).

Research Hypothesis: Participants receiving masculinizing hormone therapy will have a higher prevalence of metabolic syndrome than participants receiving feminizing hormone therapy.

Null Hypothesis: The prevalence of metabolic syndrome in the TGD population does not differ between participants receiving masculinizing hormone therapy and participants receiving feminizing hormone therapy.

The observational data obtained from this study can be used to identify nutrition-related risks that exist for the TGD population. Understanding the unique health risks and barriers TGD patients face can help healthcare professionals improve client-centered care plans to enhance this population's overall health, well-being, and quality of life.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Sex, Gender Identity, and Gender Expression

The development of gender identity is a complex process involving introspection and integration of lived experiences from various social, biological, and environmental conditions.[36,37] Gender identity, gender expression, and assigned sex at birth can influence the development of individual identity and one's sense of self. Sex, also referred to as sex assigned at birth can include male, female, or intersex.[38] Sex is used to summarize aspects of reproductive function, like chromosomal sex and external genitalia, but it is not limited to a purely biological definition. Gender socialization, or the process of integrating behaviors that align with the social expectations of one's gender, is notably influenced by an individual's assigned sex at birth. As such, sex can also be viewed as a societal metric attributed to individuals based on their perceived gender. However, this commonly assumed simplification cannot encompass the components that determine one's sex. At a minimum, sex is comprised of the following components: (1) chromosomal sex, (2) gonadal sex, (3) fetal hormonal sex, (4) internal morphological sex, (5) external morphological sex, (6) hypothalamic sex, (7) sex of assignment and rearing, (8) pubertal hormonal sex, and (9) gender identity and role.[37] Fetal sex determination occurs either in utero, in which an ultrasound procedure is used to identify the directionality of the genital tubercle and sagittal sign, or more commonly, at birth.[39,40] As

such, assigned sex at birth is determined primarily by the physical presence of external genitalia.

In contrast, gender identity refers to the internal, personal sense of one's gender, which cannot be identified through external observation.[38] Gender expression is the set of individual personal, behavioral, and physical characteristics that allow for the communication of gender to others. Gender perception, or how others perceive one's gender, can be influenced by culturally or socially determined expectations of assigned sex.[38] Gender expression and gender identity may appear interchangeable, but they are separate, interdependent entities that characterize individual experiences of gender. As such, normative forms of gender expression do not necessarily correlate with a specific, designated gender identity. The same holds true for the relationship between gender identity and perceived sex.

2.2 Transgender and Gender-Diverse Healthcare

Transgender or trans is an umbrella term often used to describe persons whose gender expression and/or identity differs from their assigned sex at birth.[38,41,42] The compilation of the various possible gender identities can be represented as points along a continuum. Transgender individuals may identify with gender normative terms like man (transman) or woman (transwoman), but gender identity is not limited to this binary methodology.[38] Some transgender individuals may identify as both a man and a woman, neither, or nonbinary, in addition to other terms not explicitly identified in this paper.[38,43] Transgender persons may experience gender dysphoria, symptoms of distress that arise from incongruency between assigned sex and gender identity, but this is not a universal experience for all persons in the trans community.[43,44] The American Psychiatric

Association[42] uses the term gender dysphoria, which is included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as a diagnostic term for the characterization of gender incongruence experienced by transgender individuals.[42,45] Though not a universal desire amongst patients, some trans individuals may seek gender-affirming therapies to develop the "physical characteristics of the affirmed gender."[42] Gender incongruence does not dictate sexual orientation, external gender expression, gender dysphoria, or the desire to undergo gender-affirming medical interventions. As such, healthcare professionals should assess individual preferences of self-expression and specific medical needs to develop personalized health care plans for patients.

Gender-affirming therapy (GAT) aims to alleviate the distress associated with gender dysphoria/gender incongruence and improve patient well-being.[42,46] This type of intervention for transgender individuals requires multidisciplinary management, and the types of interventions can vary greatly depending on the patient's individual needs. As such, in-depth knowledge of transgender-specific diagnostic criteria, therapy options, health disparities, and health risks are needed.[42] Medical interventions for transgender patients include non-surgical interventions like gender-affirming hormone therapy, laser hair removal, speech modification, chest binding, and genital tucking.[47,48] Gender-affirming surgical procedures can also be performed to aid in the transition process and reduce gender dysphoria. While some patients may decide to undergo medical interventions that aim to create observable alterations to the body, the desire to alter structural and physical characteristics should not be assumed as a universal goal of care for all transgender and gender diverse (TGD) individuals. Current standards of care

permit each TGD patient the autonomy to decide the types of interventions that would allow them to express their identified gender.

Gender incongruent individuals, with or without the presence of gender dysphoria, may undergo hormone therapy to develop the physical characteristics of their affirmed gender.[42] Endocrinologists who provide hormonal interventions for this population should know the diagnostic criteria for gender-affirming therapies, possess sufficient training and experience with this population, and be willing to provide continuous care for the entire duration of expected treatment. Gender-affirming hormone therapies (GAHT) are considered partially irreversible, so informed consent and understanding are required to begin the intervention process. For adolescents, sufficient mental capacity for informed consent has been determined to be possible at the age of 16, but those younger than the age of 16 may present with special circumstances that warrant earlier medical involvement.[42] The current standards of care recommend that adults receiving gender-affirming hormone therapies also receive the supervision of mental health professionals in conjunction with GAHT. Adolescents require professional involvement from mental health professionals. Once the multidisciplinary team can establish the persistence of gender dysphoria/gender incongruence and the individual can provide informed consent, hormonal therapies can be implemented.[42]

Clinicians are advised to "evaluate and address medical conditions exacerbated by hormonal depletion and therapy with sex hormones of the affirmed gender before beginning GAHT."[42] During GAHT, clinicians will measure hormone levels to monitor the status of both endogenous hormone production and administered sex steroids. For hormonal therapy to produce the desired physiological effects, endogenous sex hormone

levels should be suppressed while achieving and maintaining normal physiologic levels of administered sex hormones for the affirmed gender.[42] Patients should also be educated on the potential onset of changes and duration of hormone therapy necessary for developing the desired gender-affirming physical traits.

While GAHT has proved lifesaving[49] for many transgender individuals, this form of therapy is not without risks and warrants proper monitoring and evaluation by qualified healthcare professionals. The Endocrine Society Clinical Practice Guideline recommends that patients receiving GAHT be evaluated for "physical changes and potential adverse changes in response to sex steroid hormones."[42] Laboratory testing of sex hormone levels is recommended every 3 months during the first 12 months of GAHT to monitor the need for dosing changes. However, this may prove challenging to implement in practice due to the numerous healthcare barriers this population faces. Following the initial year of GAHT, patients are recommended to obtain sex hormone laboratory values once or twice annually.[42] TGD individuals receiving exogenous hormones should also be evaluated for cardiovascular and osteoporosis risk factors. Cardiovascular disease risk factors can be assessed by laboratory testing (fasting lipid profiles, blood glucose, and hemoglobin A1c) and blood pressure readings, in addition to diagnostic screening tools like electrocardiograms (ECG or EKG), Holter monitor, echocardiogram, exercise stress tests, cardiac catheterization, and cardiac computed tomography (CT) or magnetic resonance imaging (MRI) scans.[42]

The variations in recommended bone density screening for cis women, and lack of consensus for cis men, makes it difficult to determine the appropriate screening periods for transgender patients. Current recommendations for bone density screenings

are based on sex and age (female over 65 years of age). However, individuals with the following risk factors may need earlier initial or more frequent bone density screenings: Caucasian or Asian race, higher chronological age, frequent intake of alcohol (>10 drinks per week), low body mass index, smoking, vitamin D deficiency, positive human immunodeficiency virus (HIV) status, chronic corticosteroid use, and presence of rheumatoid arthritis, hypogonadism, and hyperparathyroidism.[50,51] Transgender individuals who discontinue hormone therapy after a gonadectomy are at higher risk for osteoporosis, and these patients are recommended to receive bone mineral density (BMD) measurements via dual energy X-ray absorptiometry (DEXA).[42,50] The International Society of Clinical Densitometry (ISCD) and the Endocrine Society indicate that medical providers consider testing BMD in TGD patients prior to initiating hormone therapy.[42,52] Based on the results, follow-up BMD testing is recommended for TGD individuals and BMD testing should be conducted every 1 to 2 years until stabilization of care is achieved.[52] Additionally, transgender women receiving feminizing hormone therapy (FHT), specifically estrogen, should obtain periodic prolactin laboratory readings and are advised to follow the breast-screening guidelines recommended for non-transgender women.

To obtain gender-affirming surgery, both the clinician responsible for endocrine transition therapy and the designated mental health professional must agree on the medical necessity for surgery resulting in overall health and well-being benefits for the patient.[42] Patients must adhere to their GAHT regimen for a minimum of 1 year before they can be approved for surgical intervention options, with exceptions being made for patients who do not desire hormone therapy or where hormone therapy is medically

contraindicated.[42] Like GAHT, surgical interventions for transgender patients are often classified as masculinizing or feminizing, and their integration into the gender-affirming care plan is determined on an individual basis.

Some common transgender surgery procedures include facial reconstructive surgery, chest or "top" surgery, and genital or "bottom" surgery. Facial reconstructive surgeries involve altering the cheekbones, chin, jawline, and nose to create the desired feminizing or masculinizing features. "Top" surgery is a type of mammoplasty that involves the surgical removal (subcutaneous (SC) mastectomy) or enhancement (transgender breast augmentation) of breast tissue, resulting in chest masculinization or feminization, respectively. Similarly, "bottom" surgery can alter a person's genitalia to reflect their gender identity.[53-55] Transgender genital procedures include feminizing genitoplasty (clitoroplasty, vaginoplasty, and labiaplasty), and masculinizing phalloplasty/metoidioplasty and scrotoplasty, with or without urethral lengthening.[53,56] Surgical procedures that are not specific to the transgender population but may also be incorporated into gender-affirming care plans include hysterectomy/oophorectomy, orchiectomy, and vaginectomy.[46,53] Recovery time after gender-affirming surgery can vary depending on the type and combination of procedures performed, with some treatments requiring follow-up procedures to achieve the desired result.

2.3 Hormone Replacement Therapy – Clinical Application

Gender-affirming hormone therapy assists TGD individuals in the development of the secondary sex characteristics associated with their affirmed gender. Initiation of hormone therapy for adults typically begins with an "informed consent" pathway or a referral letter from a mental health professional.[57] Qualified prescribers of GAHT include

primary care physicians, obstetricians-gynecologists, endocrinologists, advanced practice nurses, and physician assistants, preferably with experience working with this population. The 2022 Standards of Care for the Health of Transgender and Gender Diverse People[58] states the following regarding gender-affirming hormone therapy for adults:

1) Does not recommend the use of ethinyl estradiol
2) Does not recommend the use of conjugated estrogens (when estradiol is available)
3) Does recommend the use of transdermal estrogen for individuals at higher risk of developing venous thromboembolism based on age > 45 years or previous history
4) Does recommend the use of testosterone-lowering medications for individuals whose goal is to achieve close to circulating sex hormone concentrations like those found in cisgender women
5) Does recommend monitoring hematocrit or hemoglobin in patients receiving testosterone therapy
6) Does recommend laboratory monitoring of sex hormones every 3 months during the first year of therapy, with dose changes, until stable adult dosing is reached. This should be followed by clinical and laboratory testing once or twice a year to ensure maintenance.

No single method of GAHT is recommended for all TGD individuals. Hence, prescribers need to consider each patient's tolerance of various therapy options and potential access limitations due to financial constraints or availability at designated pharmacies.

2.3.1 Feminizing Hormone Therapy (FHT)

Feminizing hormone therapy (FHT) is implemented to develop female secondary sex characteristics by using a combination of estrogen, specifically estradiol, and an androgen blocker to suppress male secondary sex characteristics. Androgen blockers include spironolactone, cyproterone acetate, gonadotropin-releasing hormone (GnRH) agonists, or GnRH agonist depot formulation.[58] Taking androgen blockers without estrogen will only have a mild effect and is insufficient to yield the desired physical changes of GAHT. The combination of exogenous estrogen and anti-androgens is associated with the softening of the skin, redistribution of facial and subcutaneous body fat, reduction of body hair, potential increases in scalp hair growth, and reduction in muscle mass.

Various forms of estrogen are used in pharmaceutical interventions for both cisgender and transgender/gender-diverse populations. Estrogen in the conformation of 17-β estradiol, known as estradiol, is one of the most common estrogens used in FHT. Other pharmaceutical forms of estrogen used in FHT include estradiol valerate and estradiol cypionate, prodrug esters of estradiol.[59] Estrogens can be prescribed in various forms, including a transdermal patch/gel/spray, oral or sublingual tablet, vaginal insert, and intramuscular administration.[60,61] Oral or sublingual estradiol dosages for FHT range from 2.0 to 6.0 mg/day, with transdermal estradiol patches ranging from 0.025-0.2 mg/day[42,58] Estradiol gels can vary in concentration based on the brand and compounding prescription, but are typically applied to the skin daily. Intramuscular (IM) administration of estradiol valerate or cypionate is dosed at 5 to 30 mg every two weeks or 2 to 10 mg weekly. Route of estrogen administration can have different effects on

serum sex hormone concentrations, and serum estradiol levels are not directly proportional to their administered dose, so it is essential to monitor hormonal levels to ensure the safe and effective therapeutic administration of estrogen.[42,58,62]

Different routes of estrogen administration are associated with various health risks, so the potential health complications of the therapy method should be considered by both prescribers and anyone receiving GAHT. While oral administration in the form of estradiol pills is considered relatively cheap and effective methods of FHT, this avenue poses increased risks of blood clots for individuals who smoke or are older than 35. Injectable estrogen administration is associated with greater fluctuations in estrogen levels and higher overall estrogen levels. Rapid fluctuation in hormonal concentrations and/or elevated estrogen can result in unwanted side effects like hot flashes, mood changes, and weight gain. Since injectable forms of estrogen administration are rarely used outside of gender-affirming therapy, very little information regarding their risks has been studied, and fewer companies produce it. Reduced availability of injectable estrogens can make it difficult for TGD individuals to locate an appropriate pharmacy that can supply this form of estrogen, making it challenging for patients to receive their GAHT consistently.

In contrast with menopausal hormone therapy and contraception, FHT utilizes only estradiol and estradiol prodrugs (estradiol valerate and cypionate). Ethinyl estradiol is not considered for FHT because the therapeutic dosage used in cisgender populations cannot elicit the desired physiological levels of female sex hormone concentrations. Similarly, the use of estrogen to address menopausal symptoms utilizes much lower dosages of estrogen compared to FHT. In addition, ethinyl estradiol and conjugated

estrogens are both associated with an increased risk of blood clots, so oral intakes higher than those prescribed for contraception or menopausal hormone therapy are not advised.[63] A summary of recommended estrogen dosages is shown in Table 1.

Anti-androgens are used in conjunction with estrogen to decrease the production of endogenous testosterone. Use of anti-androgens has been shown to impair sperm production, with re-initiation of spermatogenesis occurring after discontinuation of the medication.[58] As such, anti-androgens are used to reduce the masculinizing effects of testosterone, such as facial hair growth. The 2022 Standards of Care for the Health of Transgender and Gender Diverse People[58] outlines the following hormone regimen options for anti-androgens: spironolactone 100-300 mg/day, cyproterone acetate 10 mg/day, GnRH agonist 3.75-7.50 mg SC/IM monthly, or GnRH agonist depot formulation 11.25/22.5 mg SC/IM every 3/6 months.

Laboratory monitoring for sex hormone concentrations of testosterone and estradiol is recommended every 3 months (with dose changes) during the first year of GAHT, and once or twice yearly thereafter.[58] In addition, individuals receiving spironolactone should have their serum electrolytes and kidney function (creatinine) monitored.[64] The recommended sex hormone concentration ranges for transgender females or transfeminine individuals receiving FHT are:

1) Serum testosterone < 500 ng/dL
2) Serum estradiol in the range of 100-200 pg/mL

2.3.2 Masculinizing Hormone Therapy (MHT)

Testosterone therapy recommendations for transgender males and transmasculine individuals are like those designated for cisgender males. The primary forms of testosterone therapy are transdermal gels and intramuscular (IM) injections, but subcutaneously (SC) inserted testosterone pellets have become more popular in recent years.[65-67] Both unmodified (non-esterified) and esterified forms of testosterone are available in the U.S. in various formulations, with injectable versions containing exclusively esterified forms of testosterone (enanthate, cypionate, and undecanoate). Unmodified testosterone, also referred to as non-esterified testosterone, possesses an elimination half-life of only 10 minutes, making its application as an IM injection impractical.[68] As such, esterification of testosterone prevents its rapid metabolism, permitting slower release into circulation and prolonging its availability in the body.[69] Readily reversible testosterone administrations, like oral capsules and topical therapies, require more frequent applications than long-acting SC/IM injections. Transdermal testosterone (non-esterified) applied to the skin is absorbed within 5-10 minutes, but full absorption may take upwards of 6 hours. Testosterone levels reach their associated reference range within 2-4 hours after application, so testing is recommended at least 2 hours after application, avoiding the application site.[65] Similar to IM estrogen injections, testosterone injections can cause fluctuations in serum testosterone levels, with greater fluctuations seen in shorter-acting ester formulations (testosterone enanthate and cypionate) compared to longer-acting formulations (testosterone undecanoate).[70] Serum testosterone peaks are seen shortly after injection administration, with lower concentrations (troughs) between injection administration periods.

The absorption kinetics of various testosterone esters depends on the length of the esterified fatty acid chain, with longer chains resulting in longer elimination half-lives.[68] Usage of longer-acting IM injections may reduce the risk of side effects, such as mood swings and changes in energy levels, compared to short-acting IM injections, but they may be more costly.[65] Short-acting testosterones like testosterone cypionate and ethanoate can be administered intramuscularly every 2-4 weeks or subcutaneously once every 7-10 days.[42,71] In contrast, long-acting testosterone undecanoate (1 g/4mL IM injection) is typically administered every 10-14 weeks or more, depending on patient tolerance and dose of medication.[71] While there is currently no clear target level of total serum testosterone, the Endocrine Society recommends concentrations between 320 and 1000 ng/dL and the 2022 Standards of Care for the Health of Transgender and Gender Diverse People recommends a target level of 400 to 700 ng/dL.[42,58,64] A comparison of various testosterone therapies is shown in Table 2.

Administration of testosterone alone, without using aromatase conversion inhibitors, suppresses endogenous estrogen production and elevates serum male sex hormone concentrations for individuals utilizing MHT.[72] Testosterone enanthate and cypionate are prescribed at 50-100 mg IM/SC weekly and 100-200 mg IM every two weeks, respectively. IM administration of testosterone undecanoate at dosages of 100 mg every 12 weeks or 750 mg every 10 weeks can also be utilized. Interestingly, recent research has suggested that SC administration of testosterone is just as effective as IM administration.[58] Testosterone pellets can also be administered under the skin, lasting several months.[73] Transdermal forms like testosterone patches (2.5-7.5 mg/day) and gels (50-100 mg/day) are popular routes for hormone administration for testosterone

replacement therapy and MHT. Each of these methods has been documented to have comparable results, so the selection of an administrative route is often based on individual preferences. Oral forms of testosterone were not previously used as part of MHT due to concerns with hepatotoxicity. The FDA approved newer oral medications (Jazento® and Kyzatrex®) for treating hypogonadism in men, but these medications have yet to be assessed for their efficacy as a part of MHT and are not outlined in the 2022 Standards or Endocrine Society guidelines.[74-77]

For individuals receiving MHT, laboratory monitoring for sex hormone concentrations of testosterone is recommended every 3 months (with dose changes) during the first year of therapy and once or twice per year thereafter.[58] Monitoring guidelines after initiation of testosterone therapy include obtaining a complete history and physical examination (3 to 6 months following initiation, then annually) and complete blood count (CBC) at baseline, 3 to 6 months following initiation, then annually. For individuals at risk of prostate cancer or osteoporosis, physicians should also monitor prostate specific antigen (PSA) and perform a digital rectal exam (DRE) at baseline, 3 to 6 months following initiation of therapy, and annually thereafter. It is also recommended that these patients receive a bone density assessment 1 to 2 years after initiation.[71]

The recommended sex hormone concentration range for transgender male or transmasculine individuals receiving MHT is 400-700 ng/dL.[58,65] The timing of obtaining serum total testosterone labs after initiation of GAHT is based on the route and type of testosterone prescribed:[42]

1) For testosterone enanthate and cypionate: measure midway between injections
2) For testosterone undecanoate: measure just before next injection

3) For transdermal testosterone: measure no sooner than after 1 week of daily application, at least 2 hours after application of product

2.4 Health Concerns for the Transgender and Gender-Diverse Population

Data collected from the 2021 U.S. Census Bureau's Household Pulse Survey shows an increase in individuals in the U.S. identifying as LGBTQ+; other reports confirm this increase.[78] Currently, LGBTQIA+ individuals represent approximately 7.1-8% of the adult population in the U.S., with one report estimating that nearly 10% of reported non-heterosexual adults identify as transgender.[79,80] While the total number of adults in the U.S. who identify as transgender has remained relatively constant, the number of teens who identify as transgender has doubled. A recent report by The Williams Institute estimates that nearly 1.3 million adults and 300,000 adolescents (ages 13-17) identify as transgender or gender nonconforming, with millennials being "significantly more likely to openly identify as part of the LGBTQIA+ community compared to older generations."[81] Explanations for the age discrepancies in the number of younger individuals identifying as transgender have yet to be elucidated, but some research points towards improvements in awareness of transgender individuals and acceptance of gender diversity in the community.[82] While the number of individuals seeking gender-affirming care continues to rise, transgender individuals, are rarely the subject of research studies, resulting in the continued scarcity of evidence-based guidelines and reference materials for healthcare professionals. In addition, poor visibility and a lack of educational awareness within the healthcare community of the unique needs of transgender individuals have deterred many in this population from seeking needed healthcare for fear of being misgendered, dismissed, and judged.

The transgender population in the U.S. accounts for a relatively small portion of the total population, with approximately 0.3%-0.6% of the adult population identifying as transgender.[58] However, research has demonstrated that this population is "burdened by substantial adverse health indicators" across all income levels.[2] Transgender individuals face healthcare challenges that stem from various political, social, and environmental factors.[83]

First, research designs often do not include methods of delineation between sex and gender, making it challenging to identify and include gender-diverse individuals as study participants. A disproportionate amount of the research is dedicated to only a handful of health topics.[2] While adverse health outcomes like presence of HIV, disordered eating, and substance use have been heavily researched, other health risks like metabolic syndrome, diseases of lipid metabolism, and food insecurity remain relatively unexplored.[28]

Second, difficulties obtaining and maintaining a consistent source of income due to discrimination and social isolation have contributed to increased risks of homelessness, substance abuse, and overall financial instability for transgender persons.[84] Greater financial instability can also affect their ability to pay for needed health services, such as recommended check-ups, annual physicals, and medically necessary prescriptions and surgeries. Additional barriers can also arise from poor familial support, with fewer than 1 in 3 transgender or nonbinary youths reporting to have lived in a gender-affirming home.[85]

Third, legislative opposition and lack of affordable coverage for gender-affirming medical care have severely limited access for transgender persons, especially in states

that enforce punitive restrictions. The 2022 Trevor Project found that 93% of transgender and nonbinary youth were concerned about being denied gender-affirming care due to state or local laws.[85] Fourth, societal stressors have demonstrated a great deal of influence over the dietary patterns of transgender and gender nonconforming individuals, with this community experiencing higher rates of disordered eating than cisgender populations.[86,87]

Negative experiences with individuals and institutions in the U.S. have contributed to the increased risk of anxiety, depression, and suicide, all of which have been attributed to higher disordered eating rates in this population. In addition, the 2015 U.S. Transgender Survey[47] reported that nearly one-third of respondents restricted their intake of food or beverages to reduce the risk of needing to use a public restroom, with 8% of individuals reporting to have developed either a urinary tract infection or kidney infection as a result of restroom avoidance.

2.5 Food Insecurity in the Transgender Population

Data collected by the United States Department of Agriculture (USDA) states that 1 in 10 people in 2021 reported some degree of food insecurity, with 3.8% of food insecure persons demonstrating very low food security.[88] In addition, the 2022 Map the Meal Gap Report on County Food Insecurity (2020 data) reported that 8 out of 10 high food insecurity counties are located in the South, with an estimated 1 in 5 counties having high food insecurity (17.1% or greater).[89,90] Food insecurity has been correlated with higher rates of overweight and obesity in individuals of all ages, with discrepancies between genders, age groups, and inclusion in the LGBTQIA+ community.[16-21] While the relationship between body mass index (BMI) and food insecurity may appear paradoxical in nature, it is important to note that the presence of food insecurity does not inherently

indicate the presence of extreme hunger or lack of food in its entirety. Rather, food insecurity can be present when individuals cannot obtain nutritionally adequate or safe foods for consumption, or the inability to acquire appropriate or needed foods.[91-93] Regions that are unable to provide sufficient nutrition in an affordable manner often feature high incidences of low-income households, inadequate access to transportation, and limited availability of nutritionally substantive foods.[25,94,95]

Food insecurity in Georgia affects approximately 11% of the population, and current research suggests that federal and local food programs like food banks and food pantries can play a major role in mitigating food insecurity and poor fruit and vegetable intake among the food insecure.[96,97] A recent 2022 descriptive analysis of food pantries in 12 states (AL, GA, IL, IN, KS, KY, LA, MI, MS, OH, TN, WV) estimated that Georgia has 240 urban and 86 rural food pantries.[98] However, only 53.5% of counties were found to have a minimum of one food pantry in their county area, forcing many individuals to travel to an adjacent county to receive food assistance. Additionally, of the 326 food pantries identified in Georgia, 62.9% were faith-based, which could create additional stress for TGD persons needing help.[98] TGD individuals are sometimes asked to provide government identification that contains their deadname (the name that a TGD person was given at birth and no longer uses) or incorrect pronouns/gender identity, placing them at risk of experiencing additional stress related to being misgendered, mistreated, or turned away from institutions, further deterring this population from seeing needed aid.[99] This is further corroborated by statistics from the 2015 U.S. Transgender Survey (USTS), which reported that 73% of respondents in Georgia did not have identification that contained the name and gender they preferred.[47] Of the 614 Georgia respondents, over one-third of

individuals (35%) who have shown identification that contained a name or gender that "did not match their gender presentation were verbally harassed, denied benefits or service, asked to leave, or assaulted."[47] Another study that looked at food insecurity in the Southeast U.S. (n=166) found that 80% of TGD participants reported food insecurity, and participants reported feeling "unwelcome at local food pantries due to their transgender and gender non-conforming (TGNC) status."[99,100] Participants stated that some faith-based organizations required pantry goers to attend church services and listen to anti-homosexuality seminars, creating reportedly "uncomfortable" situations for TGD persons.[99]

The current sociopolitical environment does not explicitly protect transgender individuals from discrimination. As such, institutions and individuals have been allowed to purposefully misgender and deny services to TGD persons under the guise of free speech and religious freedom.[101] Denial of services, including health care, can result in decreased desire to seek other beneficial resources, such as food pantries, and simultaneously increases stress and reduces access to support infrastructures. The unique influence of biological, social, and environmental factors on the overall well-being of the TGD population demonstrates the importance of considering sex and gender as independent but synergistically impactful components of health. Incorporating more inclusive research study designs would provide key knowledge on the specific sex and gender-dependent pathways that influence the development, progression, and treatment of chronic diseases.

2.6 Metabolic Syndrome in the Transgender and Gender-Diverse Population

Approximately 1 in 3 adults in the U.S. has metabolic syndrome, with recent increases matching similar trends seen in obesity rates.[102] Metabolic syndrome is defined as the combination of several disorders that can increase the risk of developing cardiovascular disease, diabetes mellitus, and stroke. Metabolic syndrome is diagnosed based on the presence of three out of five of the following risk factors: 1) waist circumference more than 40 inches in men and 35 inches in women, 2) triglyceride levels equal to or greater than 150 mg/dL, 3) reduced HDL cholesterol (less than 40 mg/dL in men or less than 50 mg/dL in women), 4) fasting blood glucose greater or equal to 100 mg/dL, and/or 5) blood pressure values equal to or greater than 130 mmHg and/or 85 mmHg for systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively.[103] Atherogenic dyslipidemia, elevated blood glucose, and elevated blood pressure are the primary risk factors of metabolic syndrome and contribute to developing a hypercoagulable and proinflammatory state.[104] While abdominal obesity and insulin resistance are considered the two predominant risk factors for the development of metabolic syndrome, other underlying factors like inadequate physical activity, chronological aging, genetic predisposition, certain chronic diseases, and hormonal imbalance have also been linked to its clinical manifestation.

Transgender individuals are at increased risk of experiencing financial instability, mental health issues (anxiety, depression, disordered eating), and poor social support, all of which have been associated with increased cardiovascular risk. In a recent 2020 study on cardiovascular disease (CVD) and social support, healthy (cisgender) geriatric individuals who experienced social isolation experienced a 66% increased risk of incident cardiovascular disease.[105] The presence of poor mental health and poor social support are

significant risk factors for "poor prognosis in cardiac patients, and some evidence supports their independence in predicting adverse outcomes."[106] Variations in cardiovascular risk between transgender and gender-diverse population have also been identified, with one study reporting that transgender women and gender non-conforming individuals have 2.66 and 2.21 times higher odds of CVD compared to cisgender women and cisgender individuals as a whole, respectively, there was no significant difference identified in risk of CVD between transgender men and cisgender men.[107] The American Heart Association (AHA) identified eight key risk factors for the development of CVD: 1) tobacco use, 2) physical activity, 3) diet/nutrition, 4) weight management, 5) lipid profile, 6) glycemic status, 7) blood pressure, and 8) sleep.[108] Current research suggests that TGD may be at greater risk of inadequate physical activity, unsafe weight management behaviors (i.e., fasting, diet pill use, laxative abuse), disordered eating, and overweight/obesity.[107,109] Additional risk factors include HIV infection, vascular dysfunction, inadequate sleep duration/poor sleep quality, and alcohol usage. Rates of CVD are significantly higher in the presence of HIV infection compared to uninfected individuals, with TGD people having higher rates of HIV.[107,110] Current research indicates that individuals living in the South and areas within or neighboring Atlanta are disproportionately impacted by HIV, placing TGD individuals in Georgia at even greater risk of developing CVD and metabolic syndrome.[111,112]

CHAPTER III

METHODS

3.1 Study Design

This study is a retrospective chart review. A retrospective review is relatively quick to conduct, inexpensive, and can examine multiple outcomes within the target population. This study design is suited for estimating disease prevalence (overweight/obesity and metabolic syndrome risk factors) in the target population. Consequently, this type of study cannot provide information regarding causality and might not capture potential latent diseases at the time of data collection. Approval for this prevalence study will be submitted to the institutional review board (IRB) at Georgia State University and the Research Oversight Committee of the hospital gender clinic.

3.2 Setting

The study team did not interact with participants. All data was extracted or calculated from existing information available in the patient's electronic health record (EHR). De-identified data was entered into a separate Microsoft Excel data spreadsheet. Each eligible participant was assigned a unique identification number (study ID) to protect patient privacy. No paper source documents were maintained for this study, and there was no recruitment period or follow-up period.

3.3 Participants

The target population for this study includes adult TGD individuals between 18 and 65 years of age. The current practice guidelines for adolescent hormone therapy advise against initiating endocrine therapy for individuals under the age of 16. In addition, while the effective timeline for developing the desired physical and structural alterations of hormone therapy varies from person to person, the generally accepted time frame in which patients achieve the full effects is between 1-2 years of therapy. In addition, the patient population for the included healthcare facility consists predominantly of adults. As such, a minimum age of 18 years was deemed appropriate for this study. To determine the upper limit for age inclusion in this study, the effective start and stop dates of heavily studied hormone replacement therapies in cisgender populations were assessed. The approximate age for testosterone replacement therapy (TRT) in cisgender men varies, with most studies demonstrating initiation around the age of 65.[113-115] Initiation of menopausal hormone therapy for cisgender women experiencing menopause symptoms is recommended within 10 years of onset, typically between 45 and 55 years of age. Menopausal hormone treatment is associated with increased risks for heart disease, stroke, venous thrombocytosis, and breast cancer in women over 60, so hormone therapy after age 65 is not recommended. Thus, included participants will be between the ages of 18 and 65 at the time of data collection. In addition, obtaining a baseline measurement of hormone levels for study participants will be necessary to trend data over the course of hormone therapy. As such, for the purposes of this study, included participants will be TGD individuals who started gender-affirming hormone therapy, either masculinizing or feminizing hormone therapy, at the clinic.

Exclusion criteria include participants outside the designated age range of 18 to 65, beginning hormone therapy outside the designated facility, and cisgender gender identity.

3.4 Method of Sampling

Participants for this study were selected through convenience sampling from the clinic provider schedule based on the inclusion and exclusion criteria. The estimated number of patients visiting the clinic was approximately 250. As a pilot study, it was determined that a minimum of 20 participants would be a reasonable sample size.

3.5 Variables

The exposure for this study is the initiation of GAHT. The outcome of this study is the prevalence of overweight/obesity and markers of metabolic syndrome. Potential predictors of increased metabolic syndrome risk include age, gender, and race/ethnicity.[116,117] Deidentified demographic data was collected for included participants. Characteristics included sex at birth, gender identity, preferred pronouns, current anatomy and transition history, ethnicity/race, and age (years). Anthropometric and other physical data include blood pressure (mmHg), height (inches), weight (pounds), calculated body mass index (BMI). Low levels of HDL cholesterol and hypertension (blood pressure) are well documented risk factors for metabolic syndrome, so these data points were included in the study.[104] Data collected from laboratory tests that assess the quantity of health-related biomarkers, such as lipid profiles including high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), triglycerides (mg/dL), and total calculated cholesterol (mg/dL), CBC and/or CBD, and complete metabolic panels (CMPs) or basic metabolic panels (BMPs) were

collected. Diagnosis of metabolic syndrome was determined using the risk factor assessment method and risk level (Tables 3 and 4). Additional laboratory test values for estradiol, testosterone, iron panels, and vitamin D were collected from patient charts for individuals utilizing FHT or MHT, including prolactin for individuals receiving FHT. Information regarding participant medications that are utilized during the course of GAHT was also documented. Current literature indicates that the presence of certain chronic conditions like obstructive sleep apnea, chronic kidney disease, nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), lipodystrophies, cholesterol gallstones, and HIV may independently contribute towards the development of metabolic syndrome, so evidence of these conditions (ICD-10 codes) were included as possible confounding variables when feasible[104]

3.6 Ethical Considerations

Incorporating transgender individuals in research studies will provide additional healthcare data to improve current medical protocols and increase inclusivity in research studies. Individuals within the transgender community face unique health issues related to minority stress, characterized by negative social attitudes toward transgender people, discrimination, and internalized stigma. These conditions are "linked to transgender people seeking out less preventative care than that of cisgender people of similar ages."[118] Unfortunately, such limitations can hinder efforts to assess and provide necessary healthcare to TGD individuals properly. As such, it is essential that all information collected in this study remain protected and that the structure and design of the study can properly incorporate the preferred gender of the participant.

3.7 Data Management Plan and Statistical Analysis

All data was extracted or calculated from information available in the participants' EHR. Each participant was assigned a study ID, which appears on the Microsoft Excel data collection spreadsheet. A separate, password-protected list of participant names and their associated study ID were maintained by the student principal investigator (PI) and stored on a secure hospital server. The study key was accessible only to the Student PI. Remote access to the study key or EHR data was not available, so all data extraction occurred on-site. Once the participant was assigned a study ID, associated data from the participant's EHR was manually extracted by the Student PI and entered into a separate, password-protected Microsoft Excel data spreadsheet. The Student PI was responsible for selecting, coding, and extracting participant data. The study key and all data extracted for the study will be permanently deleted after the study is completed.

Frequency analysis was conducted to determine the prevalence of overweight/obesity and other risk factors for metabolic syndrome in the TGD population. Normality statistics were conducted to determine if the continuous variable laboratory data are normally distributed or skewed. The Analysis of Variance (ANOVA) for normally distributed data or Kruskal-Wallis test for skewed data were used to assess differences between metabolic syndrome risk factor and gender-specific hormone laboratory values by specified gender identity (woman, man, gender nonconforming). The Student's t-test for normally distributed data or Mann-Whitney U test for skewed data were used to assess differences between metabolic syndrome risk factors and gender-specific hormone laboratory values by therapy type (utilization of feminizing or

masculinizing hormone therapy). The Chi-square test of independence was used to determine if the prevalence of metabolic syndrome differs by specified gender identity or by therapy type. Chi-square was not able to be performed by confounding variable status due to the small sample size. The statistical analysis was conducted using Statistical Program of Social Sciences (SPSS) version 27.0 database (SPSS, Inc., an IBM Company, Chicago, IL.). A p-value of <0.05 was considered statistically significant.

3.8 Bias

Information collected for this study was based on previously documented patient data and all information was de-identified prior to analysis. Additionally, the research team did not interact directly with participants.

CHAPTER IV

RESULTS

Data from 28 adults (median age 30.5 years [Interquartile range [IQR]; 25.5, 37.5], 68% Black or African American, 4% Hispanic) were included in the analysis. Most participants (75%) received therapy for three or more years, with FHT (57%) accounting for the majority of the population. A full description of the demographic characteristics of the population is shown in Table 2.

A summary of the MetS risk scores by variable and therapy period is shown in Table 3. Of the MetS risk factor levels examined (BMI, systolic and diastolic blood pressure, glucose, hemoglobin A1c, triglyceride, and high-density lipoprotein [HDL] cholesterol), no significant difference was found between therapy types during either the pre- or post-therapy periods (Table 4). However, trends in both the pre-therapy and post-therapy periods were found. In the pre-therapy period, individuals who received masculinizing hormone therapy had higher initial BMI, diastolic blood pressure, glucose, hemoglobin A1c, and HDL levels, in addition to lower systolic blood pressure and triglyceride levels than those in the feminizing therapy group. In contrast, in the post therapy period, individuals who received masculinizing hormone therapy had lower BMI, glucose, and HDL levels than the feminizing therapy group, in addition to higher triglyceride levels.

A significant difference was found between the masculinizing and feminizing therapy groups for estradiol level (126 [IQR; 75.6, 299.5] vs. 30.0 [IQR; 20.0. 41.8] in the pre-therapy period (Table 5). Testosterone levels remained significantly different between the masculinizing and feminizing therapy groups for the pre-therapy (57.3 [IQR; 46.9, 73.7] vs. 387.0 [IQR; 322.4, 457.5]), two years post-therapy (588.3 [IQR; 460, 660] vs. 142.1 [IQR; 23.5, 193.8]), and five years post-therapy periods (554.1 [IQR; 358.5, 629.1] vs. 155.5 [IQR; 36.7, 226.7]), respectively. These shifts in hormone levels between the pre-therapy and post-therapy groups were expected. During the pre-therapy period, the masculinizing therapy group had higher estradiol and lower testosterone levels than the FHT group. In contrast, the feminizing hormone therapy group had higher post-therapy estradiol levels and lower testosterone levels than the masculinizing therapy group. Interestingly, the MHT group had higher prolactin levels during the pre-therapy, two years post-therapy, and five years post-therapy periods.

Significant differences were observed between pre-therapy and post-therapy levels of triglycerides (60.0 ± 7.8 vs. 92.4 ± 7.8, respectively; P=0.003) and HDL cholesterol (54.8 ± 2.1 vs. 44.8 ± 2.5, respectively; P=0.012) for participants in the MHT group (Table 6). Participants in the FHT group were found to have significant differences in systolic blood pressure (129.8 ± 3.1 vs. 123.9 ± 3.0, respectively; P=0.028) between the pre-therapy and post-therapy periods. BMI, SBP, DBP, and TG were higher in the post-therapy period compared to the pre-therapy period for the masculinizing therapy group. BMI, and HDL levels were higher in the post-therapy period compared to the pre-therapy period for the FHT group. However, these differences were not statistically significant.

Non-significant increases in BMI were noted within the FHT and MHT groups between the pre-therapy and post-therapy periods. Bivariate analysis revealed that only the MHT group demonstrated a significant correlation between estrogen levels and average post-therapy BMI (0.617, P=0.033, N=12) and testosterone levels and BMI (0.588, P=0.044, N=12) at 5-year post-therapy.

In the MHT group, significant differences were observed in hormone levels between the pre- and post-therapy periods in testosterone levels (57.3 [IQR; 46.9, 73.7] vs. 588.3 [IQR; 470.4, 660.9] vs. 544.1 [IQR; 358, 629], respectively; P<0.001) for the MHT group (Table 7). Significant differences were observed between the pre-therapy, 2-year post-therapy, and 5-year post-therapy periods for prolactin (7.3 [IQR; 5.5, 12.3] vs. 16.7 [IQR; 8.6, 21.3] vs. 15.1 [IQR; 8.6, 21.3], respectively; P<0.001), estradiol (30.0 [IQR; 20.0, 41.8] vs. 142.5 [IQR; 40.4, 341.7] vs. 147 [IQR; 43.9, 313.4], respectively; P<0.001), and testosterone (IQR; 387.0 [332.4, 457.5] vs. 142.1 [IQR; 23.5, 193.8] vs. 155 [IQR; 36.7, 226.7], respectively; P<0.001) in the FHT group.

Chi-square analysis showed an association between HDL cholesterol risk score (determined based on sex assigned at birth) and therapy type in participants post-treatment (Table 13). The majority of individuals receiving masculinizing therapy (86%) are categorized as high risk after therapy, while the majority of individuals receiving FHT (92%) are at low risk (P=0.002). Metabolic Syndrome risk score did not differ statistically by therapy type pre- or post-therapy for other risk factors.

CHAPTER V

DISCUSSION

Gender-affirming hormone therapy (GAHT) is considered safe when it is monitored by medical professionals.[58] However, there are long-term consequences that warrant regular monitoring of patient hormone levels and tolerance of prescribed treatments. The objective of this study was to describe MetS risk status before and after feminizing or masculinizing therapy.

No significant differences were found between group analyses (masculinizing vs. feminizing) during the pre-therapy or the post-therapy time periods, but significant differences were identified for some MetS risk factors for the within group analysis. During the pre-therapy period, participants in the MHT group had an average BMI, diastolic blood pressure, glucose, hemoglobin A1c, and HDL level greater than the FHT group. During the post-therapy period, participants in the MHT group only had an average diastolic blood pressure, hemoglobin A1c, and triglyceride level greater than the FHT group.

BMI was not significantly associated with estradiol levels or testosterone levels for the feminizing therapy group. Previous studies indicated that individuals receiving MHT or FHT, and this weight gain is predicted to stabilize after 3-6 years of treatment.[119,120] BMI

results in this study support these findings, with less than significant changes being reported.

Significant differences in systolic blood pressure (SBP) were noted within the feminizing therapy group between the pre- and post-therapy periods. The FHT group experienced a decrease in SBP, while the MHT group demonstrated an increase in systolic blood pressure. Diastolic blood pressure was not significant for either group. Trends in diastolic blood pressure were similar to those for systolic blood pressure, with the FHT group showing a decrease over time and the MHT group demonstrating an increase over time. Results from this study are consistent with those found in the literature for systolic blood pressure. One observational study found that transgender women (n=247) experienced an average decrease in systolic blood pressure (4.0 mm Hg) while transgender men (n=223) experienced an increase (2.6 mm Hg).[121]

Significant differences in triglyceride levels were also identified in the MHT group for triglycerides and HDL between the pre-therapy and post-therapy periods. While endogenous levels of testosterone in cis-men are associated with antiatherogenic lipid profiles (higher HDL-C and lower triglycerides), testosterone replacement therapy or exogenous testosterone is also associated with increased risk of cardiovascular events.[122] In contrast with the FHT group, which demonstrated an average decrease in triglyceride levels and an increase in HDL-C, the MHT group experienced the opposite effect. The specific relationship between testosterone and lipid profile levels has yet to be elucidated, but several studies on lipid profiles in adult and adolescent transgender populations have demonstrated similar alterations in HDL-C and triglyceride levels.[123,124] Based on these

findings and those in other studies, it is highly advised that individuals receiving MHT are monitored for potentially harmful alterations in lipid profile levels to prevent the progression and/or development of various cardiovascular conditions.

This research highlights the importance of assessing risk factors for MetS by the type of hormone therapy (feminizing or masculinizing), and the individual goals and health concerns of the patient. It is also important to consider medication adherence to address potential undesirable changes in hormone panels. While the FHT group demonstrated decreased SBP and increased HDL cholesterol levels, this population is still at risk of developing metabolic syndrome. HIV is associated with a variety of metabolic complications, including dyslipidemia and insulin resistance, placing patients who are living with HIV at increased risk of developing MetS.[125,126] Reports on HIV prevalence demonstrate the disparate health burden placed on Black/African American transgender individuals. The U.S. Department of Health & Human Services reports that Black/African Americans accounted for 42.1% of HIV infection cases in 2019.[127] In addition, prevalence of HIV amongst the transgender population is estimated between 25-58%, with 84% identifying as transgender women. HIV and the use of antiretroviral therapy (ART) is associated with metabolic alterations, such as insulin resistance and dyslipidemias, and concerns with adherence to ART could exacerbate metabolic and hormonal dysregulation.[125,126,128,129] In addition, transgender men are at increased risk of metabolic syndrome due to alterations in lipid levels, namely triglycerides and HDL cholesterol, and increased blood pressure. The gender-specific presentation of metabolic syndrome risk factors in participants utilizing GAHT may be difficult to assess due to

limitations in large, longitudinal studies to evaluate metabolic syndrome development in this population.

There was a significant difference in estradiol and testosterone levels in the pre-therapy period with subsequent changes over time as expected based on therapy type. Serum testosterone and estradiol increased in the MHT and FHT groups over the course of treatment, respectively, and these changes parallel results found in the literature.[58,130] The target level of serum testosterone for individuals receiving MHT is 400-700 ng/dL, while the target level of estradiol for individuals receiving FHT is 100-200 pg/mL, with serum testosterone levels less than 50 ng/dL.[58] The average 2-year post-therapy and 5-year post-therapy hormone levels for participants were slightly above the recommended limits for testosterone in the feminizing therapy group. GAHT may still be considered effective even if total testosterone levels in individuals receiving feminizing hormone therapy are above 50 ng/dl, so it is important for providers to assess the patient's perceptions of the therapeutic effects.[131]

Deviation from recommended laboratory ranges in the FHT group could be the result of altered adherence to recommended hormone therapy. Unlike masculinizing therapy, in which exogenous testosterone alone is capable of reducing endogenous estrogen production,[72] estrogen monotherapy is "insufficient to adequately suppress endogenous testosterone production in most transgender women", warranting the addition of anti-androgenic agents.[131] Limited adherence to hormone therapy (estrogen and anti-androgenic agents), which may result from lapses in healthcare coverage, limited access to care, poor social support/harassment regarding transition, negative experiences with healthcare providers, and financial limitations may have contributed to the higher than

expected testosterone levels in the feminizing therapy group. This may also be impacted by the higher prevalence of participants living with HIV (44%) that were identified in the feminizing therapy group. Androgen deficiency is a common side effect associated with HIV in both cis-men and cis-women.[132,133] In contrast, ART was also associated with increased levels of testosterone in cisgender men living with HIV, but indications for transwomen are limited.[128] Drug-drug interactions between ART and FHT have not demonstrated elevated testosterone levels in transgender women, but concerns for medication adherence for this population may contribute to less effective hormone therapy management.[134]

Cardiovascular disease is the leading cause of death in women, and there is a prominent difference in disease risk after menopause.[135] In addition, CVD typically develops several years later in men. Since several known risk factors, such as polycystic ovary syndrome, gestational diabetes, and age of first period and menopause, related to the development of CVD in women may not apply to transgender women, so providers have to rely on other factors to determine disease risk. CVD is also the leading cause of death for men, but disease symptoms may present differently between men and women; men are more likely to report chest pain, while women are likely to have symptoms like chest discomfort, shortness of breath, nausea, and extreme fatigue. Being able to adequately assess risk of CVD in TGD persons is imperative to reduce morbidity and mortality and improve life expectancy and overall quality of life for these patients.

One study reported that significant differences in contributors for MetS between women and men existed for low HDL cholesterol (25% vs. 34%; $P < 0.0001$), increased waist circumference (63% vs. 42%; $P < 0.0001$), and hyperglycemia (42% vs. 25%; $P <$

0.0001).[136] Another study on a relatively large, homogenous aging Asian population (N=446,813) found significant differences in MetS risk factor presentation between men and women for all five components of MetS (abdominal adiposity, low HDL cholesterol, high blood pressure, hypertriglyceridemia, elevated blood sugar), with the primary gender differences being the higher prevalence of abdominal obesity (males: 54.4%, females: 60.8%; $p<0.0001$) and low HDL cholesterol (males: 31.3%, female: 59.9%; $p<0.001$) in women and higher prevalence of elevated TG level (males: 83.5%, females: 79.3%; $p<0.0001$), high BP (males: 83.1%, females: 78.5%; $p<0.0001$), and elevated blood sugar (males:87.5%, females: 78.6%; $p<0.0001$) in men.[137] The gender-specific differences in adiposity and TG levels were compounded by increased age, which was associated with increased visceral abdominal fat in aging women. Women in this population were also found to have decreased physical activity levels, another contributing factor to disease development.[138]

Long-Term Implications and Future Studies

The impact of gender on the development of MetS presents significant problems for the TGD community. First, lifestyle habits such as inactivity, poor sleep quality, inadequate diet quality, disordered eating, smoking, and substance abuse, are exacerbated by additional external factors that do not impact cisgender individuals to the same extent as TGD persons.[139-141] It is widely accepted that lifestyle interventions, specifically exercise and nutrition, can significantly reduce the risk of developing MetS.[142] However, TGD individuals face unique barriers to incorporating adequate physical activity as a health supporting behavior. [143] Compared to cisgender populations, TGD persons have demonstrated lower levels of physical activity, with many also reporting negative

experiences when engaging in competitive sports and sport-related physical activity.[144-146] TGD individuals receiving GAHT engaged in more physical activity than TGD participants who were not receiving GAHT. Access to safe, inclusive fitness centers, social inclusion/support, age of engagement in sport activities, and methods of gender-affirming care (e.g., inclusion of GAHT) can all affect physical activity levels and potential risks of inactivity in the TGD community.

While current literature has provided mechanisms to improve cultural sensitivity training and develop TGD safe spaces in healthcare, there is a noticeable absence of nutritional guidelines to support this population.[28] Without appropriate screening and assessment tools, medical professionals are unable to provide evidence-based nutrition recommendations. The Endocrine Society Clinical Practice Guideline on the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM) in patients at metabolic risk recommends that identified at-risk patients undergo "10-year global risk assessment for ASCVD or coronary heart disease," but gender is also included in this risk estimator.[147] It is also important to note that gender identity should not be used as the sole indicator of increased predisposition towards negatively perceived lifestyle habits (e.g., substance use, HIV, mental health concerns). Understanding how external factors like social isolation, institutional discrimination, and threat of harm/violence can influence patient behavior is imperative to address the unique health needs of TGD individuals.

Strengths

The primary strength of this study is that at least two years of data after initiation of therapy were available for the majority of participants (89%). Another strength is that

patient laboratory values were available prior to the initiation of hormone therapy to determine the change from baseline to the end of the study period. To ensure that anthropometric data, specifically weight, systolic blood pressure, and diastolic blood pressure values, were not influenced by acute illness, participant data was included for medical visits that did not involve hospitalization (e.g., office visits). In addition, accuracy and consistency of hormone therapy initiation periods were achieved by comparing prescription and lab order dates, to reviewing participant chart notes for key phrases (e.g., initiation of hormone therapy) and provider documentation of start dates.

Limitations

One of the primary limitations of this study was the inability to assess body composition or waist circumference. A recent statement from the American Medical Association reports that BMI is an imperfect measure of assessing health because it does not directly assess body fat.[148] Since waist circumference data was not available, weight fluctuations calculated as BMI were included to assess potential changes in patient body composition, with the assumption that increases in BMI were associated with increased fat mass. Incorporating dual-energy X-ray absorptiometry (DEXA), the "gold standard" of body composition testing, or the addition of waist circumference measurements would improve the assessment capabilities of healthcare professionals for determining the risk of metabolic syndrome in this population. Another limitation of this study is the relatively small sample size (n=28). As a pilot study, this was deemed an appropriate study size, but additional research is necessary to increase the generalizability of this report. This study focused on reporting prevalence of risk factors for MetS and did not account for

participant medications that were used to manage present health conditions, such as hypertensions and dyslipidemias.

Conclusions

The development of MetS risk factors places individuals at high risk for numerous chronic health conditions. This study demonstrates the health effects that may result from GAHT, a vital therapeutic practice for this population. MetS risk was similar between treatment types during the pre-therapy and post-therapy periods. However, within group analysis demonstrated significant shifts in TG and HDL levels (masculinizing) and systolic blood pressure (feminizing) over the course of treatment. A portion of the participants (25%) are living with HIV, which increases the risk of developing MetS. Lifestyle factors such as smoking, physical inactivity, alcohol consumption, stress, and increased adiposity increase the risk of MetS, and subsequently cardiovascular disease. The increased risk of developing MetS in this population may warrant earlier and more thorough lifestyle and dietary interventions to adequately prevent and manage disease progression.

REFERENCES

1. Moran C. LGBTQ population health policy advocacy. Position Paper. January 1, 2021 2021;34(1):19-21. doi:10.4103/efh.EfH_243_18
2. Reisner SL, Poteat T, Keatley J, et al. Global health burden and needs of transgender populations: a review. *Lancet*. Jul 23 2016;388(10042):412-436. doi:10.1016/s0140-6736(16)00684-x
3. Lambda Legal. Creating Equal Access to Quality Health Care for Transgender Patients; Transgender Affirming Hospital Policies, 2016. ed. ed. 2016. https://www.lambdalegal.org/sites/default/files/publications/downloads/fs_20160525_transgender-affirming-hospital-policies.pdf
4. Zanetos JM, Skipper AW. The Effects of Health Care Policies: LGBTQ Aging Adults. *J Gerontol Nurs*. Mar 1 2020;46(3):9-13. doi:10.3928/00989134-20200203-02
5. Linsenmeyer W, Garwood S, Waters J. An Examination of the Sex-Specific Nature of Nutrition Assessment within the Nutrition Care Process: Considerations for Nutrition and Dietetics Practitioners Working with Transgender and Gender Diverse Clients. *Journal of the Academy of Nutrition and Dietetics*. 2022;122(6):1081-1085. doi:10.1016/j.jand.2022.02.014
6. Ogden C, Lamb M, Carroll M, Flegal K. Obesity and socioeconomic status in adults: United States 1988-1994 and 2005-2008. NCHS data brief no 50. ed. ed.

National Center for Health Statistics; 2010. Accessed October 20, 2022. https://www.cdc.gov/nchs/products/databriefs/db50.htm

7. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. *Comput Biol Med*. Sep 2021;136:104754. doi:10.1016/j.compbiomed.2021.104754

8. Scott KM, McGee MA, Wells JE, Oakley Browne MA. Obesity and mental disorders in the adult general population. *J Psychosom Res*. Jan 2008;64(1):97-105. doi:10.1016/j.jpsychores.2007.09.006

9. Cao Q, Yu S, Xiong W, et al. Waist-hip ratio as a predictor of myocardial infarction risk: A systematic review and meta-analysis. *Medicine*. 2018;97(30):e11639-e11639. doi:10.1097/MD.0000000000011639

10. Krueger PM, Reither EN. Mind the Gap: Race/Ethnic and Socioeconomic Disparities in Obesity. *Current Diabetes Reports*. 2015/09/16 2015;15(11):95. doi:10.1007/s11892-015-0666-6

11. Anekwe CV, Jarrell AR, Townsend MJ, Gaudier GI, Hiserodt JM, Stanford FC. Socioeconomics of Obesity. *Curr Obes Rep*. Sep 2020;9(3):272-279. doi:10.1007/s13679-020-00398-7

12. Hales C, Carroll M, Fryar C, Ogden C. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief, no 360. ed. ed. National Center for Health Statistics; 2020. Accessed October 20, 2022. https://www.cdc.gov/nchs/data/databriefs/db360-h.pdf

13. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. *South Med J*. Jan 2015;108(1):29-36. doi:10.14423/smj.0000000000000214

14. Kapoor N, Arora S, Kalra S. Gender Disparities in People Living with Obesity - An Unchartered Territory. *J Midlife Health*. Apr-Jun 2021;12(2):103-107. doi:10.4103/jmh.jmh_48_21

15. Audureau E, Pouchot J, Coste J. Gender-Related Differential Effects of Obesity on Health-Related Quality of Life via Obesity-Related Comorbidities. 2016;9(3):246-256. doi:doi:10.1161/CIRCOUTCOMES.115.002127

16. Holben DH, Marshall MB. Position of the Academy of Nutrition and Dietetics: Food Insecurity in the United States. *Journal of the Academy of Nutrition and Dietetics*. 2017;117(12):1991-2002. doi:10.1016/j.jand.2017.09.027

17. Jilcott SB, Wall-Bassett ED, Burke SC, Moore JB. Associations between Food Insecurity, Supplemental Nutrition Assistance Program (SNAP) Benefits, and Body Mass Index among Adult Females. *Journal of the American Dietetic Association*. 2011;111(11):1741-1745. doi:10.1016/j.jada.2011.08.004

18. Parnarouskis L, Gearhardt AN, Mason AE, et al. Association of Food Insecurity and Food Addiction Symptoms: A Secondary Analysis of Two Samples of Low-Income Female Adults. *Journal of the Academy of Nutrition and Dietetics*. 2022;122(10):1885-1892. doi:10.1016/j.jand.2022.04.015

19. Jia J, Fung V, Meigs JB, Thorndike AN. Food Insecurity, Dietary Quality, and Health Care Utilization in Lower-Income Adults: A Cross-Sectional Study.

Journal of the Academy of Nutrition and Dietetics. 2021;121(11):2177-2186.e3. doi:10.1016/j.jand.2021.06.001

20. McGough SMA, Kurzynske JS. Understanding Food Insecurity in a Southern State. *Journal of the American Dietetic Association*. 1999;99(9):A61. doi:10.1016/S0002-8223(99)00617-3

21. Bruening M, Brennhofer S, van Woerden I, Todd M, Laska M. Factors Related to the High Rates of Food Insecurity among Diverse, Urban College Freshmen. *Journal of the Academy of Nutrition and Dietetics*. 2016;116(9):1450-1457. doi:10.1016/j.jand.2016.04.004

22. Ballering AV, Bonvanie IJ, Olde Hartman TC, Monden R, Rosmalen JGM. Gender and sex independently associate with common somatic symptoms and lifetime prevalence of chronic disease. *Social Science & Medicine*. 2020/05/01/ 2020;253:112968. doi:https://doi.org/10.1016/j.socscimed.2020.112968

23. Hernandez DC, Reesor LM, Murillo R. Food insecurity and adult overweight/obesity: Gender and race/ethnic disparities. *Appetite*. Oct 1 2017;117:373-378. doi:10.1016/j.appet.2017.07.010

24. Myers CA, Beyl RA, Martin CK, Broyles ST, Katzmarzyk PT. Psychological mechanisms associated with food security status and BMI in adults: a mixed methods study. *Public Health Nutr*. Oct 2020;23(14):2501-2511. doi:10.1017/s1368980020000889

25. Cooksey-Stowers K, Schwartz MB, Brownell KD. Food Swamps Predict Obesity Rates Better Than Food Deserts in the United States. *Int J Environ Res Public Health*. Nov 14 2017;14(11)doi:10.3390/ijerph14111366

26. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes*. Oct 2017;7(5):273-289. doi:10.1111/cob.12203

27. Opio J, Croker E, Odongo GS, Attia J, Wynne K, McEvoy M. Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: A systematic review and meta-analysis of prospective cohort studies. *Obes Rev*. Dec 2020;21(12):e13127. doi:10.1111/obr.13127

28. Rozga M, Linsenmeyer W, Cantwell Wood J, Darst V, Gradwell EK. Hormone therapy, health outcomes and the role of nutrition in transgender individuals: A scoping review. *Clin Nutr ESPEN*. Dec 2020;40:42-56. doi:10.1016/j.clnesp.2020.08.011

29. Yun Y, Kim D, Lee ES. Effect of Cross-Sex Hormones on Body Composition, Bone Mineral Density, and Muscle Strength in Trans Women. *J Bone Metab*. Feb 2021;28(1):59-66. doi:10.11005/jbm.2021.28.1.59

30. Van Caenegem E, Wierckx K, Taes Y, et al. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case–controlled study (ENIGI). *European Journal of Endocrinology*. 01 Feb. 2015 2015;172(2):163-171. doi:10.1530/EJE-14-0586

31. Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *European Journal of Endocrinology*. 01 Feb. 2018 2018;178(2):163-171. doi:10.1530/EJE-17-0496

32. Linsenmeyer W, Waters J. Sex and gender differences in nutrition research: considerations with the transgender and gender nonconforming population. *Nutrition Journal*. 2021/01/15 2021;20(1):6. doi:10.1186/s12937-021-00662-z

33. Fergusson P, Greenspan N, Maitland L, Huberdeau R. Towards Providing Culturally Aware Nutritional Care for Transgender People: Key Issues and Considerations. *Can J Diet Pract Res*. Jun 1 2018;79(2):74-79. doi:10.3148/cjdpr-2018-001

34. Linsenmeyer W, Drallmeier T, Thomure M. Towards gender-affirming nutrition assessment: a case series of adult transgender men with distinct nutrition considerations. *Nutrition Journal*. 2020/07/16 2020;19(1):74. doi:10.1186/s12937-020-00590-4

35. Kirby SR, Linde JA. Understanding the Nutritional Needs of Transgender and Gender-Nonconforming Students at a Large Public Midwestern University. *Transgender health*. 2020;5(1):33-41. doi:10.1089/trgh.2019.0071

36. Rokach A, Patel K. Sexual orientation. In: Rokach Ami, Patel Karishma, eds. *Human Sexuality*. Academic Press; 2021:165-193.

37. Kliegman RM, St Geme J, Blum NJ, Shah SS, Tasker RC, Wilson KM. Gender and Sexual Identity. In: Bockting Walter O, ed. *Nelson Textbook of Pediatrics*. 21st ed. Elsevier; 2020:4328-4343:chap 133.

38. The Center of Excellence on LGBTQ+ Behavioral Health Equity (CoE LGBTQ+ BHE). Sexual Orientation, Gender Identity & Expression Glossary of Terms. Institute for Innovation and Implementation, University of Maryland's School of

Social Work. https://lgbtqequity.org/wp-content/uploads/2021/04/SOGIE-Glossary.pdf

39. Gharekhanloo F. The ultrasound identification of fetal gender at the gestational age of 11-12 weeks. *J Family Med Prim Care*. Jan-Feb 2018;7(1):210-212. doi:10.4103/jfmpc.jfmpc_180_17

40. Manzanares S, Benítez A, Naveiro-Fuentes M, López-Criado MS, Sánchez-Gila M. Accuracy of fetal sex determination on ultrasound examination in the first trimester of pregnancy. 2016;44(5):272-277. doi:https://doi.org/10.1002/jcu.22320

41. Division of Adolescent and School Health NCfHA, Viral Hepatitis, STD, and TB Prevention,. Health Disparities: Health Considerations for LGBTQ Youth, Terminology. Centers for Disease Control and Prevention. https://www.cdc.gov/healthyyouth/terminology/sexual-and-gender-identity-terms.htm#:~:text=Questioning%3A%20For%20some%2C%20the%20process,such%20as%20anatomy%20and%20chromosomes.

42. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. Nov 1 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658

43. Klein DA, Paradise SL, Goodwin ET. Caring for Transgender and Gender-Diverse Persons: What Clinicians Should Know. *Am Fam Physician*. Dec 1 2018;98(11):645-653.

44. Grant JM, Mottet LA, Tanis J, HArrison J, HErman JL, Keisling M. *Injustice at every turn: a report of the National Transgender Discrimination Survey*. 2011. Accessed September 10, 2022. https://transequality.org/sites/default/files/docs/resources/NTDS_Report.pdf

45. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2022. https://archive.org/details/diagnosticstatis0005unse

46. Hamidi O, Davidge-Pitts CJ. Transfeminine Hormone Therapy. *Endocrinol Metab Clin North Am*. Jun 2019;48(2):341-355. doi:10.1016/j.ecl.2019.02.001

47. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anafi M. The Report of the 2015 U.S. Transgender Survey. National Center for Transgender Equality. https://transequality.org/sites/default/files/docs/usts/USTS-Executive-Summary-Dec17.pdf

48. Digitale E. Better Mental Health Found Among Transgender People Who Started Hormones as Teens. Stanford Medicine. Updated January 12. Accessed October 1, 2022. https://med.stanford.edu/news/all-news/2022/01/mental-health-hormone-treatment-transgender-people.html

49. Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *Journal of Adolescent Health*. 2022;70(4):643-649. doi:10.1016/j.jadohealth.2021.10.036

50. Radix A, Deutsch MB. Bone health and osteoporosis. UCSF Transgender Care. Updated June 17. https://transcare.ucsf.edu/guidelines/bone-health-and-

osteoporosis#:~:text=In%20one%20study%2C%20researchers%20found,lower%20levels%20of%20vitamin%20D.

51. Pinzone MR, Di Rosa M, Malaguarnera M, et al. Vitamin D deficiency in HIV infection: an underestimated and undertreated epidemic. *Eur Rev Med Pharmacol Sci*. May 2013;17(9):1218-32.

52. Shuhart CR, Yeap SS, Anderson PA, et al. Executive Summary of the 2019 ISCD Position Development Conference on Monitoring Treatment, DXA Cross-calibration and Least Significant Change, Spinal Cord Injury, Peri-prosthetic and Orthopedic Bone Health, Transgender Medicine, and Pediatrics. *J Clin Densitom*. Oct-Dec 2019;22(4):453-471. doi:10.1016/j.jocd.2019.07.001

53. Akhavan AA, Sandhu S, Ndem I, Ogunleye AA. A review of gender affirmation surgery: What we know, and what we need to know. *Surgery*. 2021/07/01/ 2021;170(1):336-340. doi:https://doi.org/10.1016/j.surg.2021.02.013

54. Moisés da Silva GV, Lobato MIR, Silva DC, et al. Male-to-Female Gender-Affirming Surgery: 20-Year Review of Technique and Surgical Results. Original Research. *Frontiers in Surgery*. 2021;8

55. Frey JD, Poudrier G, Thomson JE, Hazen A. A Historical Review of Gender-Affirming Medicine: Focus on Genital Reconstruction Surgery. *J Sex Med*. Aug 2017;14(8):991-1002. doi:10.1016/j.jsxm.2017.06.007

56. Cleveland Clinic Medical Professional. Feminizing Genitoplasty. Cleveland Clinic. Updated May 31. Accessed October 1, 2022. https://my.clevelandclinic.org/health/treatments/16202-feminizing-genitoplasty

57. UCSF Gender Affirming Health Program, Department of Family and Community Medicine, University of California San Francisco. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. 2nd ed. Deutsch MB, ed. 2016. Accessed November 10, 2022. transcare.ucsf.edu/guidelines.

58. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*. 2022/08/19 2022;23(sup1):S1-S259. doi:10.1080/26895269.2022.2100644

59. National Center for Biotechnology Information. PubChem Compound Summary for CID 13791, Estradiol valerate. Accessed November 17, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Estradiol-valerate

60. Oliver-Williams C, Glisic M, Shahzad S, et al. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: a systematic review. *Hum Reprod Update*. Mar 1 2019;25(2):257-271. doi:10.1093/humupd/dmy039

61. U.S. Food & Drug Administration. Menopause: Medicines to Help You. Updated August 22. Accessed November 12, 2022. https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you

62. Kim S-M, Kim SE, Lee D-Y, Choi D. Serum estradiol level according to dose and formulation of oral estrogens in postmenopausal women. *Scientific Reports*. 2021/02/11 2021;11(1):3585. doi:10.1038/s41598-021-81201-y

63. Nolan BJ, Cheung AS. Estradiol Therapy in the Perioperative Period: Implications for Transgender People Undergoing Feminizing Hormone Therapy. *Yale J Biol Med*. Sep 2020;93(4):539-548.

64. Wilkes J. Gender-Dysphoric/Gender-Incongruent Persons: Treatment Recommendations from the Endocrine Society. *Am Fam Physician*. May 1 2018;97(9):608-609.

65. Jayasena CN, Anderson RA, Llahana S, et al. Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. 2022;96(2):200-219. doi:https://doi.org/10.1111/cen.14633

66. Arver S, Stief C, de la Rosette J, Jones TH, Neijber A, Carrara D. A new 2% testosterone gel formulation: a comparison with currently available topical preparations. 2018;6(3):396-407. doi:https://doi.org/10.1111/andr.12487

67. McCullough A. A Review of Testosterone Pellets in the Treatment of Hypogonadism. *Curr Sex Health Rep*. 2014;6(4):265-269. doi:10.1007/s11930-014-0033-7

68. Nieschlag E, Behre HM, Nieschlag S. *Testosterone : Action, Deficiency, Substitution*. Cambridge University Press; 2012.

69. Shoskes JJ, Wilson MK, Spinner ML. Pharmacology of testosterone replacement therapy preparations. *Transl Androl Urol*. Dec 2016;5(6):834-843. doi:10.21037/tau.2016.07.10

70. Westfield G, Kaiser UB, Lamb DJ, Ramasamy R. Short-Acting Testosterone: More Physiologic? *Front Endocrinol (Lausanne)*. 2020;11:572465. doi:10.3389/fendo.2020.572465

71. Petering RC, Brooks NA. Testosterone Therapy: Review of Clinical Applications. *Am Fam Physician*. Oct 1 2017;96(7):441-449.

72. Chan KJ, Jolly D, Liang JJ, Weinand JD, Safer JD. ESTROGEN LEVELS DO NOT RISE WITH TESTOSTERONE TREATMENT FOR TRANSGENDER MEN. *Endocr Pract*. Apr 2018;24(4):329-333. doi:10.4158/ep-2017-0203

73. Unger CA. Hormone therapy for transgender patients. *Transl Androl Urol*. Dec 2016;5(6):877-884. doi:10.21037/tau.2016.09.04

74. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet*. Aug 6 1977;2(8032):262-3.

75. Swerdloff RS, Dudley RE. A new oral testosterone undecanoate therapy comes of age for the treatment of hypogonadal men. *Ther Adv Urol*. Jan-Dec 2020;12:1756287220937232. doi:10.1177/1756287220937232

76. Swerdloff RS, Wang C, White WB, et al. A New Oral Testosterone Undecanoate Formulation Restores Testosterone to Normal Concentrations in Hypogonadal Men. *J Clin Endocrinol Metab*. Aug 1 2020;105(8):2515-31. doi:10.1210/clinem/dgaa238

77. Kyzatrex. Package insert. Marius Pharmaceuticals. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213953s000lbl.pdf

78. We are here: Understanding the size of the LGBTQ+ community. ed. ed. Human Rights Campaign Foundation; 2022. 10/9/2021. Accessed October 28, 2022. https://hrc-prod-requests.s3-us-west-2.amazonaws.com/We-Are-Here-120821.pdf

79. Jones JM. LGBT Identification in the U.S. Ticks Up to 7.1%. Updated February 22. Accessed October 28, 2022. https://news.gallup.com/poll/389792/lgbt-identification-ticks-up.aspx

80. U.S Census Bureau. Vintage 2021 Population Estimates. ed. ed. 2022. Accessed October 28, 2022. https://www.census.gov/newsroom/press-releases/2021/2021-population-estimates.html

81. Herman JL, Flores AR, O'Neill KK. How many adults and youth identify as transgender in the United States? ed. ed. The Williams Institute; 2022. Accessed October 28, 2022. https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-Pop-Update-Jun-2022.pdf

82. Pang KC, de Graaf NM, Chew D, et al. Association of Media Coverage of Transgender and Gender Diverse Issues With Rates of Referral of Transgender Children and Adolescents to Specialist Gender Clinics in the UK and Australia. *JAMA Network Open*. 2020;3(7):e2011161-e2011161. doi:10.1001/jamanetworkopen.2020.11161 %J JAMA Network Open

83. Rahman R, Linsenmeyer WR. Caring for Transgender Patients and Clients: Nutrition-Related Clinical and Psychosocial Considerations. *J Acad Nutr Diet*. May 2019;119(5):727-732. doi:10.1016/j.jand.2018.03.006

84. Centers for Disease Control and Prevention. Patient-Centered Care for Transgender People: Recommended Practices for Health Care Settings. Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. Updated February 18, 2022. Accessed August 20, 2022.

https://www.cdc.gov/hiv/clinicians/transforming-health/health-care-providers/affirmative-care.html#understanding

85. Project TT. 2022 National Survey on LGBTQ Youth Mental Health. ed. ed. 2022. Accessed October 5, 2022. https://www.thetrevorproject.org/

86. Linsenmeyer WR, Katz IM, Reed JL, Giedinghagen AM, Lewis CB, Garwood SK. Disordered Eating, Food Insecurity, and Weight Status Among Transgender and Gender Nonbinary Youth and Young Adults: A Cross-Sectional Study Using a Nutrition Screening Protocol. *LGBT Health*. Jul 2021;8(5):359-366. doi:10.1089/lgbt.2020.0308

87. Romito M, Salk R, Roberts S, Thoma B, Levine M, Choukas-Bradley S. Exploring transgender adolescents' body image concerns and disordered eating: Semi-structured interviews with nine gender minority youth. *Body Image*. 06/01 2021;37:50-62. doi:10.1016/j.bodyim.2021.01.008

88. United States Department of Agriculture. Food Security and Nutrition Assistance. Updated October 18. Accessed 2022, November 20. https://www.ers.usda.gov/data-products/ag-and-food-statistics-charting-the-essentials/food-security-and-nutrition-assistance/#:~:text=In%202021%2C%2089.8%20percent%20of,from%2010.5%20percent%20in%202020.

89. Hake M, Engelhard E, Dewey A. Map the meal gap 2022: An analysis of county and congressional district food insecurity and county food cost in the United States in 2020. Feeding America. ed. ed. 2022. Accessed November 21, 2022.

https://www.feedingamerica.org/sites/default/files/2022-09/Map%20the%20Meal%20Gap%202022%20Report_0.pdf

90. America F. Food Insecurity among All Ages in Georgia. Accessed November 21, 2022. https://map.feedingamerica.org/county/2020/overall/georgia

91. Dhurandhar EJ. The food-insecurity obesity paradox: A resource scarcity hypothesis. *Physiol Behav*. Aug 1 2016;162:88-92. doi:10.1016/j.physbeh.2016.04.025

92. Dinour LM, Bergen D, Yeh M-C. The Food Insecurity-Obesity Paradox: A Review of the Literature and the Role Food Stamps May Play. *Journal of the American Dietetic Association*. 2007;107(11):1952-1961. doi:10.1016/j.jada.2007.08.006

93. Hernandez DC, Reesor L, Murillo R. Gender Disparities in the Food Insecurity-Overweight and Food Insecurity-Obesity Paradox among Low-Income Older Adults. *Journal of the Academy of Nutrition and Dietetics*. 2017;117(7):1087-1096. doi:10.1016/j.jand.2017.01.014

94. Gripper AB, Nethery R, Cowger TL, White M, Kawachi I, Adamkiewicz G. Community solutions to food apartheid: A spatial analysis of community food-growing spaces and neighborhood demographics in Philadelphia. *Social Science & Medicine*. 2022/10/01/ 2022;310:115221. doi:https://doi.org/10.1016/j.socscimed.2022.115221

95. Kim TJ, von dem Knesebeck O. Income and obesity: what is the direction of the relationship? A systematic review and meta-analysis. *BMJ Open*. Jan 5 2018;8(1):e019862. doi:10.1136/bmjopen-2017-019862

96. Bertmann F, Rogomentich K, Belarmino EH, Niles MT. The Food Bank and Food Pantries Help Food Insecure Participants Maintain Fruit and Vegetable Intake During COVID-19. *Front Nutr*. 2021;8:673158. doi:10.3389/fnut.2021.673158

97. Eicher-Miller HA. A review of the food security, diet and health outcomes of food pantry clients and the potential for their improvement through food pantry interventions in the United States. *Physiol Behav*. Jun 1 2020;220:112871. doi:10.1016/j.physbeh.2020.112871

98. Riediger ND, Dahl L, Biradar RA, Mudryj AN, Torabi M. A descriptive analysis of food pantries in twelve American states: hours of operation, faith-based affiliation, and location. *BMC Public Health*. Mar 17 2022;22(1):525. doi:10.1186/s12889-022-12847-0

99. Russomanno J, Jabson Tree JM. Food insecurity and food pantry use among transgender and gender non-conforming people in the Southeast United States. *BMC Public Health*. Apr 29 2020;20(1):590. doi:10.1186/s12889-020-08684-8

100. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol*. Dec 2015;70(9):832-64. doi:10.1037/a0039906

101. Franklin J. A university pays $400K to professor who refused to use a student's pronouns. Updated April 20. Accessed November 20, 2022. https://www.npr.org/2022/04/20/1093601721/shawnee-state-university-lawsuit-pronouns

102. National Heart L, and Blood Institute. What is Metabolic Syndrome? National Institute of Health. Updated May 18. Accessed November 8, 2022. https://www.nhlbi.nih.gov/health/metabolic-

syndrome#:~:text=Metabolic%20syndrome%20is%20common%20in,3%20adults%20have%20metabolic%20syndrome.

103. Swarup S, Goyal A, Girigorova Y, Zeltser R. Metabolic Syndrome. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK459248

104. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and Management of the Metabolic Syndrome. *Circulation*. 2005/10/25 2005;112(17):2735-2752. doi:10.1161/CIRCULATIONAHA.105.169404

105. Freak-Poli R, Ryan J, Neumann JT, et al. Social isolation, social support and loneliness as predictors of cardiovascular disease incidence and mortality. *BMC Geriatrics*. 2021/12/13 2021;21(1):711. doi:10.1186/s12877-021-02602-2

106. Compare A, Zarbo C, Manzoni GM, et al. Social support, depression, and heart disease: a ten year literature review. *Front Psychol*. 2013;4:384. doi:10.3389/fpsyg.2013.00384

107. Howerton I, Harris JK. Transgender Identity and Cardiovascular Disease. *Transgender Health*. 2022/10/01 2021;7(5):407-415. doi:10.1089/trgh.2020.0188

108. American Heart Association. Life's Essential 8. Accessed November 10, 2022. https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

109. Meyer IH, Brown TN, Herman JL, Reisner SL, Bockting WO. Demographic Characteristics and Health Status of Transgender Adults in Select US Regions: Behavioral Risk Factor Surveillance System, 2014. *Am J Public Health*. Apr 2017;107(4):582-589. doi:10.2105/ajph.2016.303648

110. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific

Statement From the American Heart Association. 2019;140(2):e98-e124. doi:doi:10.1161/CIR.0000000000000695

111. Sullivan PS, Satcher Johnson A, Pembleton ES, et al. Epidemiology of HIV in the USA: epidemic burden, inequities, contexts, and responses. *Lancet*. Mar 20 2021;397(10279):1095-1106. doi:10.1016/s0140-6736(21)00395-0

112. Hixson BA, Omer SB, del Rio C, Frew PM. Spatial clustering of HIV prevalence in Atlanta, Georgia and population characteristics associated with case concentrations. *J Urban Health*. Feb 2011;88(1):129-41. doi:10.1007/s11524-010-9510-0

113. Qaseem A, Horwitch CA, Vijan S, Etxeandia-Ikobaltzeta I, Kansagara D. Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. *Annals of Internal Medicine*. 2020/01/21 2020;172(2):126-133. doi:10.7326/M19-0882

114. Borst SE, Mulligan T. Testosterone replacement therapy for older men. *Clin Interv Aging*. 2007;2(4):561-6. doi:10.2147/cia.s1609

115. Malik RD, Wang CE, Lapin B, Lakeman JC, Helfand BT. Characteristics of Men Undergoing Testosterone Replacement Therapy and Adherence to Follow-up Recommendations in Metropolitan Multicenter Health Care System. *Urology*. Jun 2015;85(6):1382-8. doi:10.1016/j.urology.2015.01.027

116. Hirode G, Wong RJ. Trends in the Prevalence of Metabolic Syndrome in the United States, 2011-2016. *JAMA*. 2020;323(24):2526-2528. doi:10.1001/jama.2020.4501 %J JAMA

117. Auer MK, Ebert T, Pietzner M, et al. Effects of Sex Hormone Treatment on the Metabolic Syndrome in Transgender Individuals: Focus on Metabolic Cytokines. *The Journal of Clinical Endocrinology & Metabolism*. 2017;103(2):790-802. doi:10.1210/jc.2017-01559 %J The Journal of Clinical Endocrinology & Metabolism

118. Mayo Clinic. Health Concerns for Transgender People. Updated 2021. Accessed October 30, 2021. https://www.mayoclinic.org/healthy-lifestyle/adult-health/in-depth/transgender-health/art-20154721

119. Suppakitjanusant P, Ji Y, Stevenson MO, et al. Effects of gender affirming hormone therapy on body mass index in transgender individuals: A longitudinal cohort study. *Journal of Clinical & Translational Endocrinology*. 2020/09/01/ 2020;21:100230. doi:https://doi.org/10.1016/j.jcte.2020.100230

120. Kyinn M, Banks K, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Weight gain and obesity rates in transgender and gender-diverse adults before and during hormone therapy. *International Journal of Obesity*. 2021/12/01 2021;45(12):2562-2569. doi:10.1038/s41366-021-00935-x

121. Banks K, Kyinn M, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults. 2021;77(6):2066-2074. doi:doi:10.1161/HYPERTENSIONAHA.120.16839

122. Thirumalai A, Rubinow KB, Page ST. An update on testosterone, HDL and cardiovascular risk in men. *Clin Lipidol*. 2015;10(3):251-258. doi:10.2217/clp.15.10

123. Millington K, Finlayson C, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan Y-M. Association of High-Density Lipoprotein Cholesterol With Sex Steroid Treatment in Transgender and Gender-Diverse Youth. *JAMA Pediatrics*. 2021;175(5):520-521. doi:10.1001/jamapediatrics.2020.5620 %J JAMA Pediatrics

124. Defreyne J, Van de Bruaene LDL, Rietzschel E, Van Schuylenbergh J, T'Sjoen GGR. Effects of Gender-Affirming Hormones on Lipid, Metabolic, and Cardiac Surrogate Blood Markers in Transgender Persons. *Clinical Chemistry*. 2019;65(1):119-134. doi:10.1373/clinchem.2018.288241 %J Clinical Chemistry

125. Pedro MN, Rocha GZ, Guadagnini D, et al. Insulin Resistance in HIV-Patients: Causes and Consequences. *Front Endocrinol (Lausanne)*. 2018;9:514. doi:10.3389/fendo.2018.00514

126. Sarker S, Brown TT. Lipid Disorders in People with HiV. MDText.com. Updated January 21, 2023. Accessed June 16, 2023. https://www.ncbi.nlm.nih.gov/books/NBK567198/#:~:text=HISTORY%20OF%20LIPID%20DISORDERS%20IN,Table%202)%20(12).

127. Prevention. CfDCa. HIV/AIDS and African Americans. U.S. Department of Health & Human Services. Updated February 17, 2023. Accessed June 2014, 2023.

128. Collazos J, Martinez E, Mayo J, Ibarra S. Sexual hormones in HIV-infected patients: the influence of antiretroviral therapy. *Aids*. Apr 12 2002;16(6):934-7. doi:10.1097/00002030-200204120-00018

129. Karim R, Mack WJ, Kono N, et al. Gonadotropin and sex steroid levels in HIV-infected premenopausal women and their association with subclinical atherosclerosis in HIV-infected and -uninfected women in the women's interagency HIV study (WIHS). *J Clin Endocrinol Metab*. Apr 2013;98(4):E610-8. doi:10.1210/jc.2012-3195

130. Chantrapanichkul P, Stevenson MO, Suppakitjanusant P, Goodman M, Tangpricha V. SERUM HORMONE CONCENTRATIONS IN TRANSGENDER INDIVIDUALS RECEIVING GENDER-AFFIRMING HORMONE THERAPY: A LONGITUDINAL RETROSPECTIVE COHORT STUDY. *Endocr Pract*. Jan 2021;27(1):27-33. doi:10.4158/ep-2020-0414

131. Badowski ME, Britt N, Huesgen EC, et al. Pharmacotherapy considerations in transgender individuals living with human immunodeficiency virus. *Pharmacotherapy*. Mar 2021;41(3):299-314. doi:10.1002/phar.2499

132. Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. *Clin Infect Dis*. Sep 15 2001;33(6):857-64. doi:10.1086/322695

133. Dobs AS. Androgen therapy in AIDS wasting. *Baillieres Clin Endocrinol Metab*. Oct 1998;12(3):379-90. doi:10.1016/s0950-351x(98)80096-7

134. Sevelius JM, Carrico A, Johnson MO. Antiretroviral therapy adherence among transgender women living with HIV. *J Assoc Nurses AIDS Care*. May-Jun 2010;21(3):256-64. doi:10.1016/j.jana.2010.01.005

135. Khoudary SRE, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A

Scientific Statement From the American Heart Association. 2020;142(25):e506-e532. doi:doi:10.1161/CIR.0000000000000912

136. Beigh SH, Jain S. Prevalence of metabolic syndrome and gender differences. *Bioinformation*. 2012;8(13):613-6. doi:10.6026/97320630008613

137. Lee S, Ko Y, Kwak C, Yim E-s. Gender differences in metabolic syndrome components among the Korean 66-year-old population with metabolic syndrome. *BMC Geriatrics*. 2016/01/23 2016;16(1):27. doi:10.1186/s12877-016-0202-9

138. Kodoth V, Scaccia S, Aggarwal B. Adverse Changes in Body Composition During the Menopausal Transition and Relation to Cardiovascular Risk: A Contemporary Review. *Womens Health Rep (New Rochelle)*. 2022;3(1):573-581. doi:10.1089/whr.2021.0119

139. National Heart L, and Blood Institute. Metabolic Syndrome: Causes and Risk Factors. Updated May 18, 2022. Accessed June 1, 2023. https://www.nhlbi.nih.gov/health/metabolic-syndrome/causes

140. Virmani A, Binienda ZK, Ali SF, Gaetani F. Metabolic Syndrome in Drug Abuse. https://doi.org/10.1196/annals.1403.004. *Annals of the New York Academy of Sciences*. 2007/12/01 2007;1122(1):50-68. doi:https://doi.org/10.1196/annals.1403.004

141. Hudson JI, Lalonde JK, Coit CE, et al. Longitudinal study of the diagnosis of components of the metabolic syndrome in individuals with binge-eating disorder. *Am J Clin Nutr*. Jun 2010;91(6):1568-73. doi:10.3945/ajcn.2010.29203

142. Myers J, Kokkinos P, Nyelin E. Physical Activity, Cardiorespiratory Fitness, and the Metabolic Syndrome. *Nutrients*. Jul 19 2019;11(7)doi:10.3390/nu11071652

143. Holder J, Morris J, Spreckley M. Barriers and Facilitators for Participation in Physical Activity in the Transgender Population: A Systematic Review. *Physical Activity and Health*. 2022;doi:10.5334/paah.190

144. Jones BA, Arcelus J, Bouman WP, Haycraft E. Sport and Transgender People: A Systematic Review of the Literature Relating to Sport Participation and Competitive Sport Policies. *Sports Med*. Apr 2017;47(4):701-716. doi:10.1007/s40279-016-0621-y

145. Teti M, Bauerband LA, Rolbiecki A, Young C. Physical activity and body image: Intertwined health priorities identified by transmasculine young people in a non-metropolitan area. *Int J Transgend Health*. 2020;21(2):209-219. doi:10.1080/26895269.2020.1719950

146. Jones BA, Haycraft E, Bouman WP, Arcelus J. The Levels and Predictors of Physical Activity Engagement Within the Treatment-Seeking Transgender Population: A Matched Control Study. *J Phys Act Health*. Feb 1 2018;15(2):99-107. doi:10.1123/jpah.2017-0298

147. Rosenzweig JL, Bakris GL, Berglund LF, et al. Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2019;104(9):3939-3985. doi:10.1210/jc.2019-01338 %J The Journal of Clinical Endocrinology & Metabolism

148. Berg S. AMA: Use of BMI alone is an imperfect clinical measure. June 14, 2023. Accessed June 14, 2023. https://www.ama-assn.org/delivering-care/public-health/ama-use-bmi-alone-imperfect-clinical-measure

APPENDICES

Table 1. Risk Assessment for Metabolic Syndrome

Associated Risk Factor	Assessment Method		Risk Level		
			Low Risk	Moderate Risk	High Risk
Adiposity	BMI		Underweight or Normal	Overweight	Obese
Insulin Resistance	A1C %		< 5.7%	5.7-6.4%	≥ 6.5%
	Blood Glucose		70 - 99 mg/dL	100 - 125 mg/dL	≥ 126 mg/dL
	Diagnosis			Diagnosis of prediabetes	Diagnosis of diabetes
	Medication				Prescribed medication to manage blood glucose
Abnormal TG Metabolism	Triglycerides		< 150 mg/dL		≥ 150 mg/dL
	Diagnosis				Diagnosis of dyslipidemias related to TG
	Medication				Prescribed medication to manage TGs
Abnormal Cholesterol Metabolism	HDL-C	Under age 20 years	> 45 mg/dL		< 45 mg/dL
		Male (20+)	≥ 40 mg/dL		< 40 mg/dL
		Female (20+)	≥ 50 mg/dL		< 50 mg/dL
	Diagnosis				Diagnosis of dyslipidemias related to HDL-C
	Medication				Prescribed medication to manage HDL-C
Hypertension (HTN)	Blood Pressure		< 120/80 mmHg	120 - 129 and < 80 mmHg	≥ 130 mmHg systolic or 80 mmHg diastolic
	Diagnosis				Diagnosis of hypertension
	Medication				Prescribed medication to manage HTN

Explanation for Risk Criteria:
While abdominal obesity, measured by waist circumference or waist to hip ratio, is the strongest risk factor for developing MetS, excess adipose tissues is also linked to disruptions in metabolic function. In addition, while fasting blood glucose levels are currently used as part of the diagnostic criteria for identifying MetS, recent research indicates that elevated random blood glucose levels are capable of detecting risk for diabetes and abnormalities in glucose metabolism. An assumption is being made that participants included in this study do not have non-normative lean body mass or skeletal muscle mass.

References:

1. Otieno FC, Ng'ang'a L, Kariuki M. Validity of random blood glucose as a predictor of the quality of glycaemic control by glycated haemoglobin in out-

2. patient diabetic patients at Kenyatta National Hospital. *East Afr Med J*. Sep 2002;79(9):491-5. doi:10.4314/eamj.v79i9.9122

3. Rhee MK, Ho Y-L, Raghavan S, et al. Random plasma glucose predicts the diagnosis of diabetes. *PLOS ONE*. 2019;14(7):e0219964. doi:10.1371/journal.pone.0219964

4. Bowen ME, Xuan L, Lingvay I, Halm EA. Random Blood Glucose: A Robust Risk Factor For Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(4):1503-1510. doi:10.1210/jc.2014-4116 %J The Journal of Clinical Endocrinology & Metabolism

Table 2. Demographic Characteristics of Gender Clinic Adults Who Received Gender Affirming Hormone Therapy

Variables	Frequency n (%)		Duration of Therapy n (%)				
Age, years							
18-29	13	(46.4)	***1 Year***	***2 Years***	***3 Years***	***4 Years***	***5+ Year)***
30-64	15	(53.6)					
Ethnicity							
Not Hispanic or Latino	27	(96.4)	3 (100)	4 (100)	6 (85.7)	7 (100)	7 (100)
Hispanic	1	(3.6)	-	-	1 (14.3)	-	
Race							
American Indian/Alaska Native	1	(3.6)	-	-	1 (14.3)	-	-
Black or African American	19	(67.9)	3 (100)	3 (75.0)	4 (57.1)	5 (71.4)	4 (57.1)
White	6	(21.4)	-	1 (25.0)	2 (28.6)	1 (14.3)	2 (28.6)
More Than One Race	2	(7.1)	-	-	-	1 (14.3)	1 (14.3)
Gender Identity							
Female	4	(14.3)	-	1 (25.0)	-	1 (14.3)	2 (28.6)
Male	4	(14.3)	1 (33.3)	-	-	1 (14.3)	2 (28.6)
Transgender Female (MTF)	12	(42.9)	2 (66.7)	2 (50.0)	4 (57.1)	4 (57.1)	-
Transgender Male (FTM)	7	(25.0)	-	1 (25.0)	3 (42.9)	-	3 (42.9)
Labels not preferred or used	1	(3.6)	-		-	1 (14.3)	-
Sex Assigned at Birth							
Female	12	(42.9)	1 (33.3)	1 (25.0)	3 (42.9)	2 (28.6)	5 (71.4)
Male	16	(57.1)	2 (66.7)	3 (75.0)	4 (57.1)	5 (71.4)	2 (28.6)
Pronouns							
She/Her/Hers	15	(53.6)	2 (66.7)	2 (50.0)	4 (57.1)	5 (71.4)	2 (28.6)
He/Him/His	10	(35.7)	1 (33.3)	-	3 (42.9)	1 (14.3)	5 (71.4)
They/Them/Theirs	3	(10.7)	-	2 (50.0)	-	1 (14.3)	-
Treatment Type							
Feminizing	16	(57.1)	2 (66.7)	3 (75.0)	4 (57.1)	5 (71.4)	2 (28.6)
Masculinizing	12	(42.9)	1 (33.3)	1 (25.0)	3 (42.9)	2 (28.6)	5 (71.4)

Table 3. Metabolic Syndrome Risk Factor Scores for Gender Clinic Adults Who Received Gender Affirming Hormone Therapy

Variable	Risk Score	Pre-Treatment n (%)	Post-Treatment n (%)
BMI	***0***	13 (46.4)	12 (42.9)
	1	6 (21.4)	6 (21.4)
	2	9 (32.1)	10 (35.7)
	Total	28	28
BP	***0***	8 (28.6)	10 (37.0)
	1	5 (17.9)	5 (18.5)
	2	15 (53.6)	12 (44.4)
	Total	28	27
Glucose	***0***	18 (75.0)	25 (89.3)
	1	5 (20.8)	3 (10.7)
	2	1 (3.6)	- -
	Total	24	28
A1C	***0***	7 (58.3)	7 (63.6)
	1	4 (33.3)	4 (36.4)
	2	1 (8.3)	-
	Total	12	11
TG	***0***	15 (83.3)	17 (89.5)
	2	3 (16.7)	2 (10.5)
	Total	18	19
HDL, by sex assigned at birth	***0***	12 (75.0)	12 (63.2)
	2	4 (25.0)	7 (36.8)
	Total	16	19
HDL, by treatment type	***0***	10 (62.5)	15 (75.0)
	2	6 (37.5)	5 (25.0)
	Total	16	20

BMI – body mass index, BP – blood pressure, TG – triglyceride, HDL – high density lipoprotein

Low Risk – 0, Moderate Risk – 1, High Risk – 2

Table 4. Difference in Metabolic Syndrome Risk Factor Levels between Adults Receiving Masculinizing and Feminizing Therapy (Pre- and Post-Therapy)

Variable	Pre-Therapy			Post-Therapy		
	Masculinizing	Feminizing	P-value	Masculinizing	Feminizing	P-value
BMI (kg/m2)* (n)	26.1 (23.2, 40.7) (12)	25.0 (21.5, 32.7) (16)	0.478	26.1 (23.3, 36.4) (12)	26.6 (20.6, 35.0) (16)	0.767
SBP (mm Hg)* (n)	121.0 (112.3, 127.3) (12)	127.0 (121.5, 141.2) (16)	0.090	123.7 (114.2, 137.8) (12)	124.2 (114.9, 128.9) (16)	0.732
DBP (mm Hg)** (n)	80.0 ± 11.9 (12)	79.3.0 ± 8.5 (16)	0.854	80.6 ± 12.4 (12)	77.5 ± 6.1 (16)	0.443
Glucose (mg/dL)* (n)	92.3 (85.3, 96.5) (9)	92.0 (83.0, 104.0) (15)	1.000	85.9.2 (78.2, 94.2) (12)	92.9 (88.8, 98.6) (16)	0.053
A1c (%)** (n)	5.6 ± 0.4 (5)	5.4 ± 0.6 (7)	0.476	5.5 ± 0.6 (5)	5.4 ± 0.6 (6)	0.834
TG (mg/dL)* (n)	70.0 (52.8, 105.0) (8)	101.8 (91.6, 148.3) (10)	0.083	97.0 (64.0, 106.0) (7)	88.3 (78.7, 131.3) (12)	0.536
HDL (mg/dL)** (n)	52.2 ± 9.9 (8)	48.1 ± 17.4 (8)	0.575	45.6 ± 7.2 (7)	53.9 ± 11.7 (12)	0.109

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, A1c – hemoglobin A1c, TG – triglyceride, HDL – high density lipoprotein

*Median (interquartile range; 25%, 75%)
**Mean ± standard deviation

Table 5. Difference in Hormone Levels Between Adults Receiving Masculinizing and Feminizing Therapy (Pre-Therapy, 2-Year Post-Therapy, 5-Year Post-Therapy)

Variable	Pre-Therapy			Post-Therapy, 2 Years			Post-Therapy, 5 Years		
	Masculinizing	Feminizing	P-value	Masculinizing	Feminizing	P-value	Masculinizing	Feminizing	P-value
Prolactin (ng/mL)* (n)	42.1 (14.1, --) (2)	7.3 (5.5, 12.3) (11)	0.103	55.3 (55.3, 55.3) (1)	16.7 (8.7, 19.8) (13)	0.286	45.8 (45.8, 45.8) (1)	15.1 (8.7, 19.8) (15)	0.250
Estradiol (pg/mL)* (n)	126 (75.6, 299.5) (10)	30.0 (20.0, 41.8) (16)	0.002	71.5 (51.5, 107.1) (11)	142.5 (40.4, 341.7) (15)	0.305	66.2 (43.5, 88.9) (12)	147.1 (43.9, 313.4) (16)	0.090
Testosterone (ng/mL)* (n)	57.3 (46.9, 73.7) (10)	387.0 (322.4, 457.5) (15)	<0.001	588.3 (460, 660) (12)	142.1 (23.5, 193.8) (15)	<0.001	554.1 (358.5, 629.1) (12)	155.5 (36.7, 226.7) (16)	<0.001

*Median (interquartile range; 25%, 75%)

Table 6. Difference in Metabolic Syndrome Risk Factor Levels (Pre- and Post-Therapy) by Treatment Type

Variable	Masculinizing				Feminizing			
	n	Pre-therapy	Post-therapy	P-value	n	Pre-therapy	Post-therapy	P-value
BMI (kg/m^2)**	12	30.4 ± 10.1	30.7 ± 3.2	0.681	16	29.0 ± 2.8	30.0 ± 3.0	0.061
SBP (mm Hg)**	12	122.3 ± 4.5	127.5 ± 4.7	0.066	16	129.8 ± 3.1	123.9 ± 2.7	0.028
DBP (mm Hg)*	12	79.0 (74.1, 85.9)	81.4 (69.0, 88.6)	0.433	16	78.1 (72.8, 87.7)	77.5 (71.9, 82.0)	0.179
Glucose (mg/dL)**	9	92.1 ± 3.1	89.6 ± 3.0	0.198	15	99.6 ± 8.0	93.0 ± 2.3	0.330
A1c (%)**	3	5.9 ± 0.2	5.7 ± 0.4	0.579	5	5.5 ± 0.2	5.5 ± 0.7	0.832
TG (mg/dL)**	5	60.0 ± 7.8	92.4 ± 7.8	0.003	9	167.8 ± 59.9	106.9 ± 11.9	0.290
HDL (mg/dL)**	5	54.8 ± 2.1	44.8 ± 2.5	0.012	8	48.1 ± 6.2	54.6 ± 4.5	0.135

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, A1c – hemoglobin A1c, TG – triglyceride, HDL – high density lipoprotein

*Median (interquartile range; 25%, 75%)
**Mean ± standard deviation

Table 7. Difference in Hormone Levels (Pre-Therapy, 2-Years Post-Therapy, 5 Years Post-Therapy) by Treatment Type

Variable	Masculinizing					Feminizing				
	n	Pre-therapy	2 years post-therapy	5 years post-therapy	P-value	n	Pre-therapy	2 years post-therapy	5 years post therapy	P-value
Prolactin (ng/mL)*	1	-	-	-	-	9	7.3 (5.5, 12.3)	16.7 (8.6, 21.3)	15.1 (8.6, 21.3)	<0.001
Estradiol (pg/mL)*	10	126.0 (75.6, 299.5)	71.5 (51.5, 107.1)	66.2 (43.5, 88.9)	0.169	15	30.0 (20.0, 41.8)	142.5 (40.4, 341.7)	147.1 (43.9, 313.4)	<0.001
Testosterone (ng/mL)*	10	57.3 (46.9, 73.7)	588.3 (470.4, 660.9)	544.1 (358, 629)	<0.001	14	387.0 (322.4, 457.5)	142.1 (23.5, 193.8)	155 (36.7, 226.7)	<0.001

*Median (interquartile range; 25%, 75%)

Table 8. Body Mass Index Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	13	5 (38.5)	8 (61.5)	12	5 (41.7)	7 (58.3)
Medium	6	3 (50.0)	3 (50.0)	6	3 (50)	3 (50)
High	9	4 (44.4)	5 (55.6)	10	4 (40.0)	6 (60.0)

Low – BMI less than 24.9 kg/m^2
Moderate – BMI between 24.9 and 29 kg/m^2
High – BMI greater than 30 kg/m^2

Table 9. Blood Pressure Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	8	5 (62.5)	3 (37.5)	10	4 (40)	6 (60)
Medium	5	1 (20)	4 (80)	5	1 (20.0)	4 (80.0)
High	15	6 (40)	9 (60)	12	7 (58.3)	5 (41.7)

Low – SBP <120 and DBP < 80
Moderate – SBP of 120 to 129 and DBP <80
High – SBP $\geq$ 130 and/or DBP $\geq$ 80

Table 10. Glucose Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	18	8 (44.4)	10 (55.6)	25	11 (44.0)	14 (56.0)
Medium	5	1 (20)	4 (80)	3	1 (33.3)	2 (66.7)
High	1	0	1 (100)	0	0	0

Low – Less than 100 mg/dL
Moderate – 100 to 125 mg/dL
High – Greater than 125 mg/dL

Table 11. Hemoglobin A1C Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	7	3 (42.9)	4 (57.1)	7	3 (42.9)	4 (57.1)
Medium	4	2 (50)	2 (50)	4	2 (50)	2 (50)
High	1	1 (100)	0	0	0	0

Low – Less than 5.7%

Moderate – 5.7% to 6.4%
High – Greater than 6.4%

Table 12. Triglyceride Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	15	7 (46.7)	8 (53.3)	17	7 (41.2)	10 (58.8)
High	3	1 (33.3)	2 (66.7)	2	0	2 (100)

Low – Less than 150 mg/dL
High – Greater than or equal to 150 mg/dL

Table 13. High Density Lipoprotein (based on Sex Assigned at Birth) Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	12	6 (50)	6 (50)	12	1 (8.3)	11 (91.7)
High	4	2 (50)	2 (50)	7	6 (85.7)	1 (14.3)

*P = 0.002 (Fisher's Exact Test)
Low – male: ≥40 mg/dL; female: ≥50 mg/dL
High – male: <40 mg/dL; female: <50 mg/dL

Table 14. High Density Lipoprotein (based on Treatment Type) Risk Score by Therapy Type

Risk Score	Pre-Therapy			Post-Therapy		
	N	Masculinizing (%)	Feminizing (%)	N	Masculinizing (%)	Feminizing (%)
Low	10	7 (70)	3 (30)	15	6 (40)	9 (60)
High	6	1 (16.7)	5 (83.3)	5	2 (40)	3 (60)

Low – male: ≥40 mg/dL; female: ≥50 mg/dL
High – male: <40 mg/dL; female: <50 mg/dL

Table 15. Number of Participants with Variable Risk Scores of 2, by HDL Variable Used

Includes HDL Score based on Sex Assigned at Birth			Includes HDL Score based on Therapy Type		
# of High-Risk Variables	Therapy Period		# of High-Risk Variables	Therapy Period	
	Pre-Therapy (n=33)	Post-Therapy (n=31)		Pre-Therapy (n=35)	Post-Therapy (n=29)
1 Variable	10	10	1 Variable	10	10
2 Variables	7	3	2 Variables	5	5
3 Variables	3	5	3 Variables	5	3

Table 16. Diagnostic criteria for metabolic syndrome

DIAGNOSIS OF METABOLIC SYNDROME: 3 OR MORE OF THE FOLLOWING	
RISK FACTOR	**Criteria**
Abdominal Adiposity*	
MALE	waist circumference > 40 inches
FEMALE	waist circumference > 35 inches
High Blood Pressure	BP > 130/85 mmHg or taking BP medications
Elevated Triglycerides	TG > 150 mg/dL
Fasting Blood Glucose	GB > 100 mg/dL or taking glucose lowering medications
Low HDL-Cholesterol	
MALE	HDL < 40 mg/dL or taking medications for low HDL
FEMALE	HDL < 50 mg/dL or taking medications for low HDL

*Increased waist circumference is the form of obesity most strongly correlated with metabolic syndrome[102]

References

1. National Heart L, and Blood Institute. What is Metabolic Syndrome? National Institute of Health. Updated May 18. Accessed November 8, 2022. https://www.nhlbi.nih.gov/health/metabolic-syndrome#:~:text=Metabolic%20syndrome%20is%20common%20in,3%20adults%20have%20metabolic%20syndrome
2. Auer MK, Ebert T, Pietzner M, et al. Effects of Sex Hormone Treatment on the Metabolic Syndrome in Transgender Individuals: Focus on Metabolic Cytokines. *The Journal of Clinical Endocrinology & Metabolism*. 2017;103(2):790-802. doi:10.1210/jc.2017-01559 %J The Journal of Clinical Endocrinology & Metabolism

Table 17. American Board of Internal Medicine Laboratory Test Reference Ranges

Laboratory Test	Sex Assigned at Birth	Reference Range
Estradiol, serum	Female, follicular Mid-cycle peak Luteal Postmenopausal	10-180 pg/mL 100-300 pg/mL 40-200 pg/mL <10 pg/mL
Testosterone, serum	Male Female	291-1100 ng/dL 18-54 ng/mL

Table 18. Comparison of Various Estrogen Therapies Currently Available

Therapy	Route/Delivery System	Estrogen Type	Brands	Dosage
Estrogen Replacement Therapy (ERT)	Oral	Conjugated Estrogen*	PREMARIN®, ENJUVIA®, generic	0.3 mg, 0.625 mg, 0.9 mg, and 1.25 mg tablets, daily
		Esterified Estrogens*	MENEST®, generic	0.3 mg, 0.625mg, 1.25mg, 2.5 daily
		Estradiol*	ESTRACE®, generic	0.5 mg, 1.0 mg, and 2.0 mg, daily
	Vaginal Ring	Estradiol*	ESTRING®	2 mg released at 7.5 mcg per day over three months
			FEMRING®	0.5 mg, 0.10 mg, every 90 days
	Parenteral (IM)	Estradiol Valerate*	DELESTROGEN®, generic	10 mg per mL, 20 mg per mL, and 40 mg per mL Injected monthly
		Estradiol Cypionate*	DEPO-ESTRADIOL®, generic	1 to 5 mg injected every 3 to 4 weeks OR 1.5 to 2 mg injected monthly
	Transdermal – gel	Estradiol* hydroalcoholic	DIVIGEL® 0.10%, generic ELESTRIN® 0.06%, generic ESTROGEL® 0.06%, generic	0.25 mg/g; 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg daily 0.52 mg/0.87 g gel, 1-2 pumps daily 0.75 mg/1.25 g gel, one pump daily
	Transdermal – Cream	Conjugated Estrogen*	PREMARIN®	0.5-2 g cream applied 1-3 times weekly (0.625 mg CEE per 1 g cream)
		Estradiol*	ESTRACE® 0.01%, generic	2-4 g applied one to three times per week (1 mg/g)
	Transdermal – Spray	Estradiol* alcohol and osctisalate solution	EVAMIST® 1.7%	1.53 mg per actuation (90 mcL/spray; typical dose is 1-3 actuations/day)
	Transdermal – Vaginal Tablet	Estradiol* hemihydrate	VAGIFEM®, IMVEXXY®, YUVAFEM®, generic	10 mcg tablet, daily for 2 weeks then twice weekly
	Transdermal patch	Estradiol* reservoir	CLIMARA®, MINIVELLE®, generics	0.025, 0.0375, 0.05, 0.06, 0.075, or 0.1 mg/d (0.41, 0.62, 0.83, 1.24, 1.65 mg total estrogen/patch) CLIMARA® is one patch weekly MINIVELLE® is twice weekly
		Estradiol	CLIMARA PRO®	4.4 mg/patch (0.045 mg/d), one patch weekly

Table Continued

Therapy	Route/Delivery System	Estrogen Type	Brands	Dosage
Contraception**	Vaginal Ring	Ethinyl Estradiol	NUVARING®, generic	Each ring releases ~0.015 mg/d 2.7 mg/ring, 3-week use
	Pills	Ethinyl Estradiol	Most Pills	0.02-0.05 mg, daily
		Estradiol Valerate	NATAZIA®, generic	1-3 mg tablets; four phasic pill packet, one pill daily
	Transdermal Patch	Ethinyl Estradiol	ORTHO EVRA®, generic	0.75 mg per patch, weekly
Gender Affirming Estrogen Therapy	**Oral or Sublingual[8]**	Estradiol*	Estradiol PO/SL (micronized, Estrace)	2.0-6.0 mg/day
	Intramuscular (IM)	Estradiol valerate*	DELESTROGEN®, generic	2-10 mg IM every week OR 5-30 mg IM every 2 weeks
		Estradiol cypionate*	DEPO-ESTRADIOL®, generic	2-10 mg IM every week OR 5-30 mg IM every 2 weeks
	Transdermal – Patch	Estradiol* reservoir	CLIMARA®, MINIVELLE®, generic	0.025-0.2 mg/day
	Transdermal – Gel[10]	Estradiol* hydroalcoholic	DIVIGEL® 0.10%, generic ELESTRIN® 0.06%, generic ESTROGEL® 0.06%, generic	Dosing ranges have not been fully established, 0.75-3 mg/day[10]

*Indicates that there is solely one hormone present in the specified therapy
**All forms of contraception that include estrogen are combination therapies

References:

1. Hill DA, Crider M, Hill SR. Hormone Therapy and Other Treatments for Symptoms of Menopause. *Am Fam Physician*. Dec 1 2016;94(11):884-889.
2. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. Nov 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236
3. U.S. Food & Drug Administration. Menopause: Medicines to Help You. Updated August 22. Accessed November 12, 2022. https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you
4. Oliver-Williams C, Glisic M, Shahzad S, et al. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: a systematic review. *Hum Reprod Update*. Mar 1 2019;25(2):257-271. doi:10.1093/humupd/dmy039
5. Cobin RH, Goodman NF. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause - 2017 update. *Endocr Pract*. Jul 2017;23(7):869-880. doi:10.4158/ep171828.Ps
6. U.S. Food & Drug Administration. Birth Control Guide. Accessed November 10, 2022. https://www.fda.gov/media/150299/download

7. American Society for Health-System Pharmacists I. Estrogen and progestin (oral contraceptives). National Library of Medicine. Accessed November 26, 2022. https://medlineplus.gov/druginfo/meds/a601050.html
8. Doll EE, Gunsolus I, Lamberton N, Tangpricha V, Sarvaideo JL. SUN-LB9 Pharmacokinetics of Sublingual Versus Oral Estradiol in Transgender Women. *J Endocr Soc*. May 8 2020;4(Suppl 1)
9. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*. 2022/08/19 2022;23(sup1):S1-S259. doi:10.1080/26895269.2022.2100644
10. Glintborg D, T'Sjoen G, Ravn P, Andersen MS. MANAGEMENT OF ENDOCRINE DISEASE: Optimal feminizing hormone treatment in transgender people. Eur J Endocrinol. 2021;185(2):R49-R63. Published 2021 Jun 28. doi:10.1530/EJE-21-0059

Table 19. Comparison of Various Testosterone Therapies Currently Available

Therapy	Route	Delivery System	Testosterone Type		Brands	Dosage and Frequency
Testosterone Replacement Therapy (TRT)	Transmucosal	Buccal bioadhesive T tablet	STRIANT® (discontinued)			30 mg controlled-release, twice daily
	Oral	Capsules	Testosterone undecanoate		JATENZO®, KYZATREX®	40 mg capsule, 1-3 capsules 2-3 times daily
	Subcutaneous Implants	Pellets[6]	Crystalline testosterone		TESTOPEL®	100 or 200 mg to a total of 600-1200 mg per dose (3-6 pellets every 4-6 months)
	Transdermal	Gel[7,8]	Hydroalcoholic testosterone		1% TESTIM®, ANDROGEL®, VOGELXO®, generics (50 mg/5mg gel)	50-100 mg, daily
					1.62% ANDROGEL®	20.25-81 mg, daily
					2% FORTESA®	40-70 mg, daily
			Nasal Spray, non-alcoholic gel testosterone		NATESTO® 5.5 mg/pump[11]	1 actuation per nostril, 3 times daily (33 mg total daily)
		Axillary solution[9]	Alcohol and octisalate based testosterone solution		AXIRON®, generic	60 mg, daily
		Patch[12]	Reservoir of testosterone		ANDRODERM®, generic	2 or 4 mg patch, 2-6 mg daily
	Parenteral	Injection	Longer-acting T esters	Undecanoate	AVEED®	750 mg/3 mL OR 1000 mg/4 mL IM, every 10-14 weeks
			Shorter-acting T esters	Enanthate	DELATESTRYL®, XYOSTED®, generic	150-200 mg IM every 2 weeks OR 75-100 mg IM weekly
				Cypionate	DEPO-TESTOSTERONE®, generic	
Masculinizing Hormone Therapy	**Transdermal**	Gel	Hydroalcoholic testosterone		1% TESTIM, ANDROGEL, VOGELXO, generics (50 mg/5mg gel)	50-100 mg/day
		Patch	Reservoir of testosterone		ANDRODERM, generic	2.5-7.5 mg/day

	Parenteral	Injection	Longer-acting T esters	Undecanoate	AVEED	1000 mg/IM every 12 weeks OR 750 mg/IM every 10 weeks
			shorter-acting T esters	Enanthate	DELATESTRYL®, XYOSTED®, generic	50-100 IM or SC weekly OR 100-200 IM, every 2 weeks
				Cypionate	DEPO-TESTOSTERONE®, generic	

*UK only, not available in the U.S

References:

1. Jayasena CN, Anderson RA, Llahana S, et al. Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. 2022;96(2):200-219. doi:https://doi.org/10.1111/cen.14633
2. Qaseem A, Horwitch CA, Vijan S, Etxeandia-Ikobaltzeta I, Kansagara D. Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. *Annals of Internal Medicine*. 2020/01/21 2020;172(2):126-133. doi:10.7326/M19-0882
3. Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. 2020;172(2):126-133. doi:10.7326/m19-0882 %m 31905405
4. Petering RC, Brooks NA. Testosterone Therapy: Review of Clinical Applications. *Am Fam Physician*. Oct 1 2017;96(7):441-449.
5. Borst SE, Mulligan T. Testosterone replacement therapy for older men. *Clin Interv Aging*. 2007;2(4):561-6. doi:10.2147/cia.s1609
6. McCullough A. A Review of Testosterone Pellets in the Treatment of Hypogonadism. *Curr Sex Health Rep*. 2014;6(4):265-269. doi:10.1007/s11930-014-0033-7
7. Arver S, Stief C, de la Rosette J, Jones TH, Neijber A, Carrara D. A new 2% testosterone gel formulation: a comparison with currently available topical preparations. 2018;6(3):396-407. doi:https://doi.org/10.1111/andr.12487
8. Besins Healthcare (UK) Ltd. Testogel 16.2 mg/g gel. Datapharm. Updated May 23. Accessed December 1, 2022. https://www.medicines.org.uk/emc/product/8919/smpc Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*. 2022/08/19 2022;23(sup1):S1-S259. doi:10.1080/26895269.2022.2100644
9. Eli Lilly and Company. AXIRON (testosterone) topical solution. U.S. Food and Drug Administration. Accessed December 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022504s016lbl.pdf
10. Shoskes JJ, Wilson MK, Spinner ML. Pharmacology of testosterone replacement therapy preparations. *Transl Androl Urol*. Dec 2016;5(6):834-843. doi:10.21037/tau.2016.07.10
11. Natesto (testosterone) nasal gel CIII. Trimel BioPharma SRL. Accessed December 1, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205488s000lbl.pdf
12. Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. *Drug Des Devel Ther*. 2014;8:101-12. doi:10.2147/dddt.S43475