A Case Study: The Effect of Hormone Therapy on Vascular Function in a Male-to-Female Transgender Endurance Athlete

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Title

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Abstract

The aim of this case study was to assess vascular function in a 27-year-old male-to-female transgender endurance athlete before hormone therapy and during treatment with gender affirming hormone therapy (GAHT) in an effort to better understand the effects of estrogen therapy and testosterone blockade on male vascular physiology. Testing occurred at 4-8 week intervals for 19 months. At each visit, testing included measurement of blood hormone levels including free testosterone, total testosterone and estradiol, resting heart rate and blood pressure, non-invasive central blood pressure measurements, pulse wave velocity (PWV), ultrasound quantified arterial flow mediated dilation (FMD), and dual-energy x-ray absorptiometry (DEXA) scans. These data were analyzed over time to observe gross trends and then analyzed for correlation. Visceral body fat measured remained unchanged from baseline after 15 months gender affirming hormone therapy. Systolic and diastolic blood pressures increased throughout treatment and systolic pressures were positively correlated with time. PWV showed signs of decreasing arterial stiffness after initiation of GAHT, but returned to baseline by the end of the study. FMD trended downwards initially with GAHT, indicating reduced vascular reactivity, but returned towards baseline following sustained treatment with GAHT. More research is needed to examine the long-term effects of gender affirming hormone therapy on vascular function, blood pressure, and vascular stiffness.

Introduction

Sex has long been considered to be an independent predictor of cardiovascular health outcomes. The incidence of cardiovascular disease in the general population is lower in women than in men up to 75 years. While it was originally hypothesized that sex hormones alone could explain this difference, research suggests that the risk factors for cardiovascular disease are multifactorial. The incidence of cardiovascular disease in males and females can be partially explained by sex differences and gender differences. Biological sex differences include differences is sex hormones and subsequent differences in gene expression in the cardiovascular system and vascular function. Gender differences can include sociocultural practices, such as behavioral or environmental factors, including diet, lifestyle, stress, and attitudes about preventative health practices[1]. While much research has been conducted on cardiovascular disease in biologically male and female individuals, there is still much to understand regarding the specific cardiovascular risk associated with sex and gender differences. In particular, what are the specific cardiovascular risk in transgendered individuals?

Gender affirming hormone therapy (GAHT) is the cornerstone of the medical management of transgendered individuals, yet there is little known about the long-term impacts of cross-sex hormone therapy, including how the cardiovascular system is affected. There are three major summaries for gender affirming hormone therapy (GAHT) – The Endocrine Society Guidelines[2], The World Professional Association for Transgender Health (WPATH) Standards of Care (SOC)[3], and The Center of Excellence for Transgender Health at the University of California, San Francisco[4]. The Endocrine Society Guidelines[2] states that the two major goals of GAHT should be to reduce endogenous sex hormone levels to reduce the secondary sex characteristics of the individual's natal sex and to replace sex hormone to levels consistent with the normal physiologic range for the affirmed gender. There has not yet been any controlled clinical trials on any feminizing/masculinizing hormone regimens, nor has there been any studies conducted to evaluate safety or efficacy in producing physical transition. As a result, there are wide variations in doses and types of hormones that are used for GAHT. Regimens for feminizing GAHT typically include estrogen and anti-androgen medications[3].

Bioidentical estrogen, 17-beta estradiol, is most commonly delivered to transgender women via a transdermal patch, oral or sublingual tablet, or injection of a conjugated ester, estradiol valerate or estradiol cypionate. Spironolactone, a potassium sparing diuretic, is the most commonly used androgen blocker in the United States. Other anti-androgens are used in different countries including Cyproterone acetate, a synthetic progestogen with strong anti-androgen activity, and GnRH agonists[4]. The target range for feminizing GAHT is estradiol less than 200 pg/mL and testosterone 30-100 ng/dL.

The Coronary Drug Project (CDP) was a landmark clinical trial conducted between 1966 and 1975. Its purpose was to assess the effect of lipid influencing therapy on vascular measures in men with a history of myocardial infarction. Estrogen was one of the five drugs that was studied, but it was stopped early in the study due to trends toward worsening cardiovascular disease and adverse effects in participants receiving estrogen therapy[5]. A 2014 review in the European Journal of Endocrinology showed that male-to-female transgendered individuals

treated with estrogens and anti-androgens showed more cardiovascular pathology than female-to-male transgendered participants receiving testosterone[6]. Another study from 2011 assessed mortality in transgendered individuals and observed an increased rate of cardiovascular mortality in male-to-female transgendered individuals compared with the general population[7].

At the time of this study in 2017, little was known about the cardiovascular consequences of female sex hormone exposure on human male physiology. The aim of this case study was to comprehensively assess the vascular function in a single male-to-female transgender endurance athlete before hormone therapy, during estrogen treatment, and during testosterone blockade in an effort to better understand the vascular effects of gender affirming hormone therapy in female transgendered individuals. Our hypothesis was that vascular function would decline with feminizing GAHT.

Methods

Participant:
The participant in this case study was a biologically male, 27-year-old Caucasian distance runner undergoing male-to-female gender transition. The participant was enrolled while undergoing social transition in the March of 2017. Medical transition was initiated in April 2017 under the guidance of the participant's Endocrinologist. The participants GAHT regimen included nine months of self-administered subcutaneous estradiol valerate 10mg every seven days, then an additional four months of oral estriol/estradiol (80:20) taken each day plus oral spironolactone 100mg each day. In this case study, there were no controls, and no other subjects were recruited.

Informed consent and ethics statement:
Detailed explanation of all data collection and procedures were discussed. Additionally, the risks of each procedure were discussed in detail including the low risk of ultrasound procedures[8], the minimal radiation associated with DEXA scans[9], and the possibility of potentially being identified given the single-subject design of this study. After a detailed explanation of all data collection procedures, the participant completed written informed consent before any testing was performed. Included in the written consent was a statement detailing permission for the publication of all collected data. Approval by an independent ethics committee was not deemed necessary for several reasons, including the following: the participant approached the laboratory and requested that the tests be conducted on her and was, therefore, a volunteer with no recruitment process, the participant specifically requested that the results of the tests be published in a peer-reviewed scientific journal because of the general and scientific interest that these results would generate, and the data were collected as an observation, and no intervention, experimental method, or prospective nature was applied.

Methods:
This single case study design utilized repeated measures. Testing occurred at 4-8 week intervals depending on the participant's availability. At each visit, testing included:

- blood hormone levels including free testosterone, total testosterone, and estradiol
- body mass index (BMI) measurements
- dual-energy x-ray absorptiometry (DEXA) scans
- ultrasound quantified brachial artery flow-mediated dilation (FMD)
- non-invasive central aortic systolic/diastolic blood pressures and PWV

Two baseline assessments were made before the initiation of hormone treatment. Six assessments were conducted while the subject was on an estrogen-only treatment regimen, and three assessments were done after the addition of a testosterone blockade.

Body Composition Testing:

Studies have shown that the distribution of body fat is a significant and independent risk factor for cardiovascular disease (CVD) and related mortality. In particular, visceral adipose tissue is associated with metabolic complications that are risk factors for CVD, including insulin resistance, type II diabetes, changes in plasma lipids and lipoproteins, and hypertension[10]. In this case study anthropometric testing and body composition were assessed at each visit.

The participant's weight was measured on a standard scale. Height was assessed on a stadiometer. Body composition was assessed via Dual-energy X-ray Absorptiometry (DEXA) (Lunar iDXA, GE Healthcare, Madison, WI). At each visit, after height and weight were assessed, the participant would lay flat on the Lunar iDXA to equilibrate any fluid shifts. The participant would then be positioned for the scans. The Lunar iDXA scanner, with its CoreScan software, is able calculate bone mineral density, lean tissue mass, visceral adipose tissue, and subcutaneous adipose tissue using computed tomography and densitometry. DEXA was chosen over air displacement plethysmography due to its accuracy and precision in measuring body fat and tracking changes in visceral adiposity. Total body precision for fat and lean mass is 1.0% and 0.5% coefficient of variation (CV) respectively[9].

SphygmoCor Assessment of Central Aortic Blood Pressures and Pulse-Wave Velocity (PWV):

Arterial stiffness is an independent predictive factor for cardiovascular events[11]. Much of the research on arterial stiffness in cardiovascular disease has been through non-invasive analysis of the pulse wave velocity (PWV) through the large arteries[12]. PWV is a measure of large artery stiffness and proportional to arterial stiffness. Slower PWV is associated with better heart health. Similarly, the augmentation index (AIx) is a composite measure that is an independent predictor of cardiovascular disease and may be particularly sensitive in younger individuals[11]. The SphygmoCor Cardiovascular Management Suite (CvMS; AtCor Medical, Sydney, NSW, Australia) is capable of non-invasive PWV and aortic pressure waveform assessment and shows excellent agreement with invasive aortic blood pressure[13]. This device uses applanation tonometry for acquisition of the radial, carotid, and femoral blood pressure waveforms, and has shown to have a 0.2 m/s difference from invasively measured aortic PWV[12]. The average PWV for a male <30 years old is 6.6 ± 0.8 m/s[14].

At each visit, the participant laid down in a dimly lit room and had resting blood pressure measured using an automated blood pressure machine at 0, 10, and 15 minutes after initially laying down to ensure that hemodynamic stability was achieved. After that, an appropriately

sized blood pressure cuff was placed on the left arm, and central and peripheral blood pressures were assessed using the non-invasive SphygmoCor system. The brachial waveform was then analyzed by the SphygmoCor system to provide a central aortic waveform and central blood pressure measurements. Three measurements were taken with the SphygmoCor device, and the two closest values were averaged to obtain peripheral and central blood pressures. After that, the patient's carotid-femoral pulse wave velocity was assessed (cf-PWV) using the same device. A blood pressure cuff was placed around the participant's thigh and inflated to sub-systolic pressure (<150 mmHg) to capture the femoral artery waveform. A tonometer pressure sensor was used to capture the Carotid waveform. The pulse transit time, which is the time that the pulse takes to travel from the carotid artery to the femoral artery, was recorded. The distance between the Carotid and femoral arteries was measured, and the pulse wave velocity was determined by dividing the distance by the pulse transit time. Three measurements were taken with the SphygmoCor device, and the two closest values were averaged to obtain the pulse wave velocity.

Brachial Artery Flow Mediated Dilation:

Flow Mediated Dilation (FMD) is a non-invasive assessment of endothelial function. Brachial artery FMD assess the brachial artery's ability to dilate in response to an increase in blood flow and is assessed using ultrasound. Flow mediated dilation is proportional to endothelial function and in particular, brachial artery FMD has been shown to be inversely associated with cardiovascular events[15].

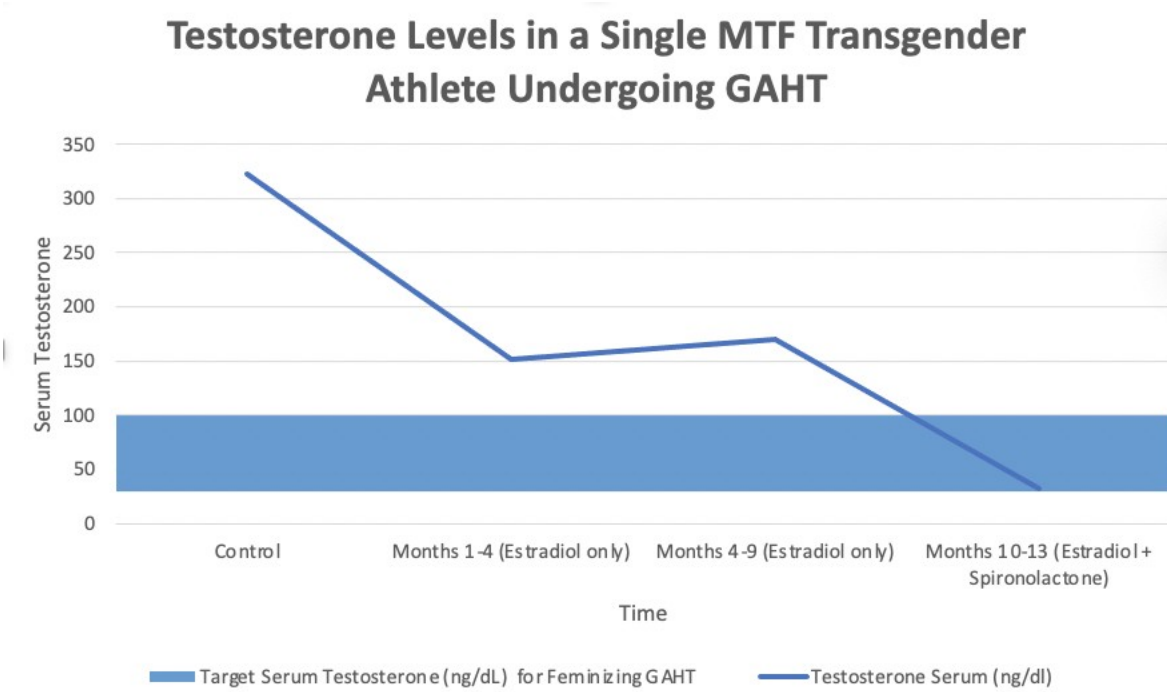
This procedure was performed using the Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force[16]. At each assessment, the participant was instructed to lie supine on a padded ultrasound table. All measurements were made on the participant's non-dominant arm. A blood pressure cuff was positioned on the participant's forearm. After recording baseline ultrasound measures on the upper arm, the blood pressure cuff was inflated to 250mmHg for 5 minutes. The cuff was then deflated rapidly, and brachial artery blood flow and arterial diameter are measured continuously for 5 minutes using the ultrasound probe[16].

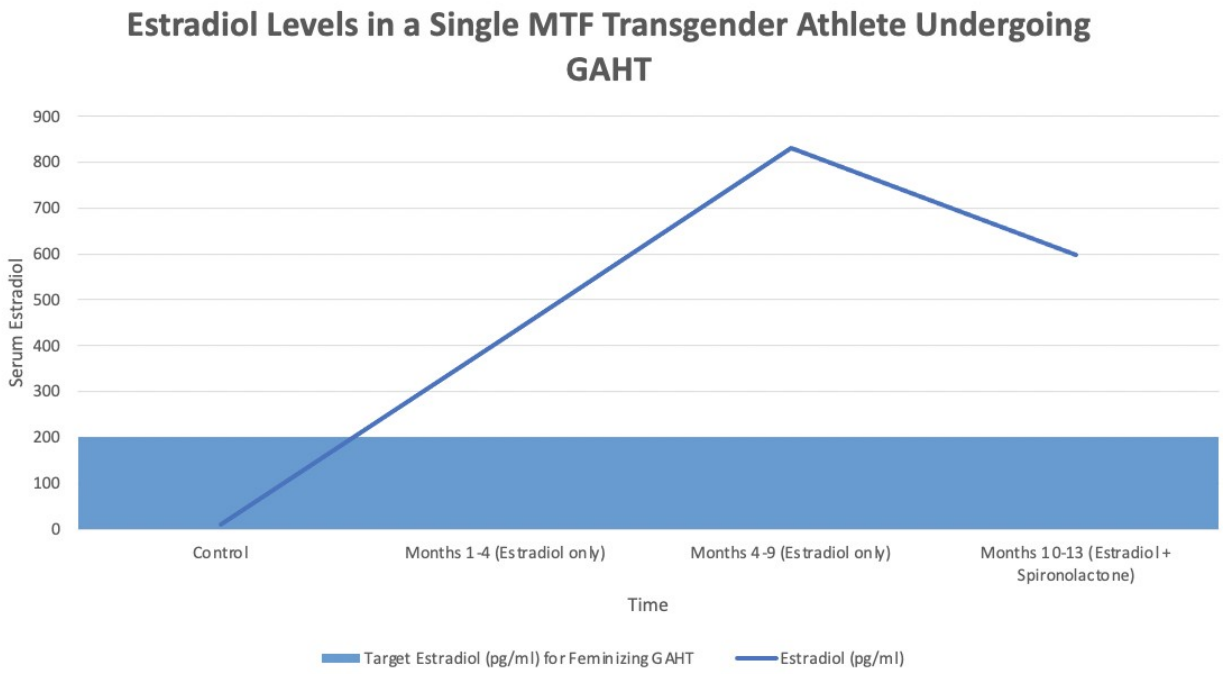
Numerous factors are known to affect flow-mediated vascular reactivity, including the time of day, temperature, food, drugs, sympathetic stimuli, and menstruation[16]. Therefore, the participant was instructed to arrive at the laboratory at the same time for every session, fast for at least 6 hours prior to testing, and abstain from caffeine and exercise for at least 24 hours, alcohol for a minimum of 48 hours, smoking for at least 12 hours, and any medications for a minimum of four half-lives prior to testing. Prior to testing, the participant was instructed to lay down supine with legs fully extended on a padded ultrasound table, in a quiet, dimly lit room, with no distractions, and temperature-controlled for a minimum of 20 minutes. The participant was instructed to refrain from the use of cell phone, music, or TV during this period to avoid any sympathetic stimulation.

Statistical Analysis:
Data from each visit was plotted over time to observe gross trends and Pearson correlation coefficients were assessed using the IBM SPSS software (IBM Coorperation, Australia).

Results

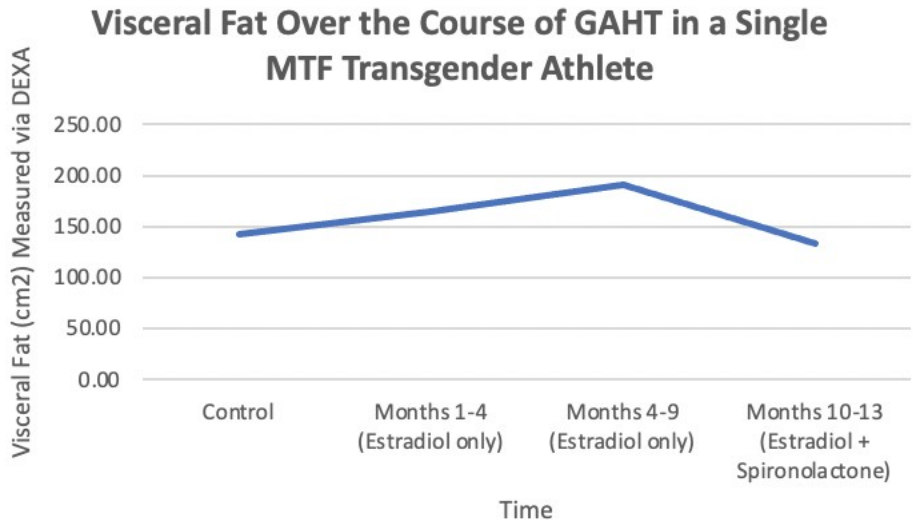
Hormone Levels Over Time
Prior to initiating GAHT, the participant, a male assigned at birth, had hormonal levels within reference range for a male[17], including total serum testosterone 323.00 ng/dL, free testosterone 43.35 pg/mL and Estradiol 9 pg/mL. Over nine months of estradiol only treatment, our participant was supratherapeutic for estradiol levels in GAHT. Estradiol rose to over 800 pg/mL when the target range for feminizing GAHT is estradiol less than 200 pg/mL. The participant was kept supratherapeutic under the guidance of her endocrinologist. The participant's testosterone levels fell through the course of GAHT to therapeutic levels of less than 55 ng/dL total testosterone[2]. Over the course of 13 months of GAHT, the participant did not reach target estrogen levels, but testosterone levels were withing range for a female by month 10 with the addition of the testosterone blocker Spironolactone.





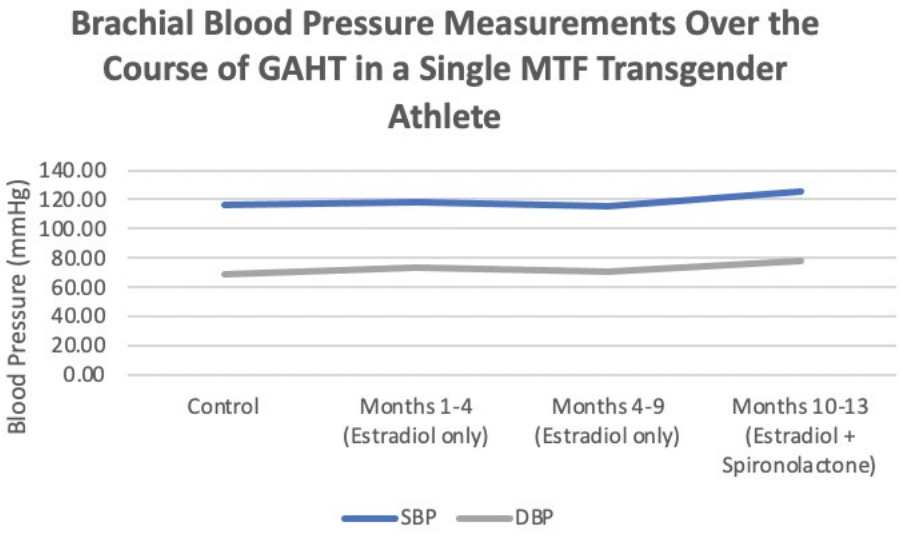
<u>Effects of Feminizing GAHT on Visceral Adipose Tissue:</u>

The patient's visceral fat was estimated as a predictor of cardiovascular risk during GAHT. Throughout estradiol only treatment, the participant's visceral fat increased from 143 cm^2 to 190.5 cm^2. After treatment with spironolactone, the participant's visceral fat fell below the baseline control value of 133.25 cm^2.



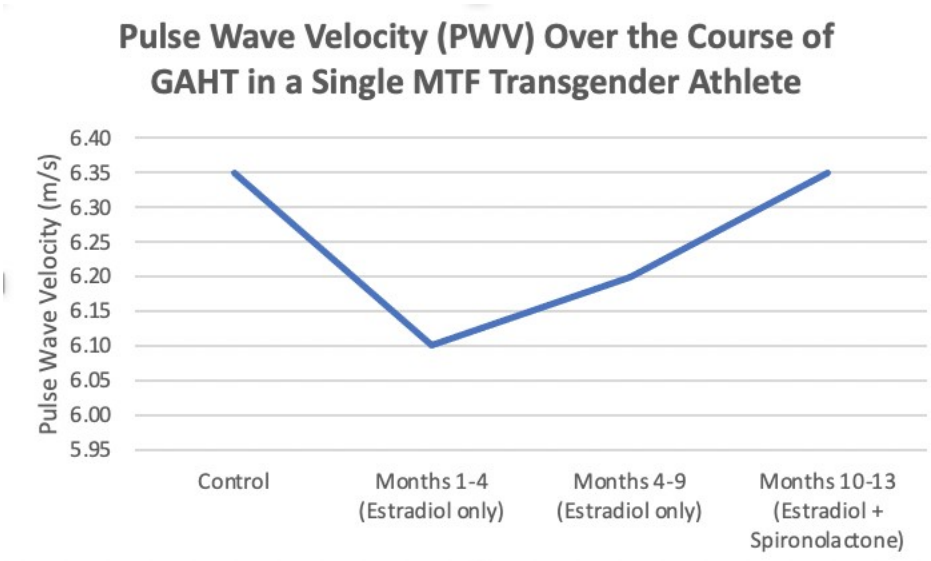
Effects of Feminizing GAHT on Blood Pressure:

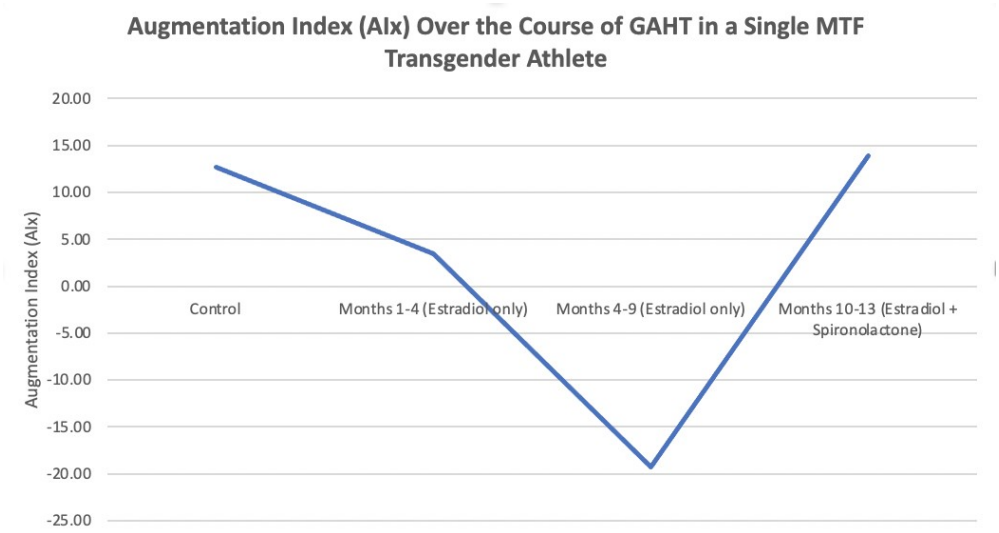
Over the course of GAHT, brachial blood pressure measurements increased only slightly. A Spearman Correlation relative to time was assessed, and peripheral systolic blood pressure (SBP) and central systolic blood pressure (cSBP) were significantly positively correlated with time in this study (Pearson Correlation Coefficient r=0.667, p=0.049 and Pearson Correlation Coefficientr= 0.678, p=0.045 respectively).



Effects of feminizing GAHT on Vascular Stiffness:

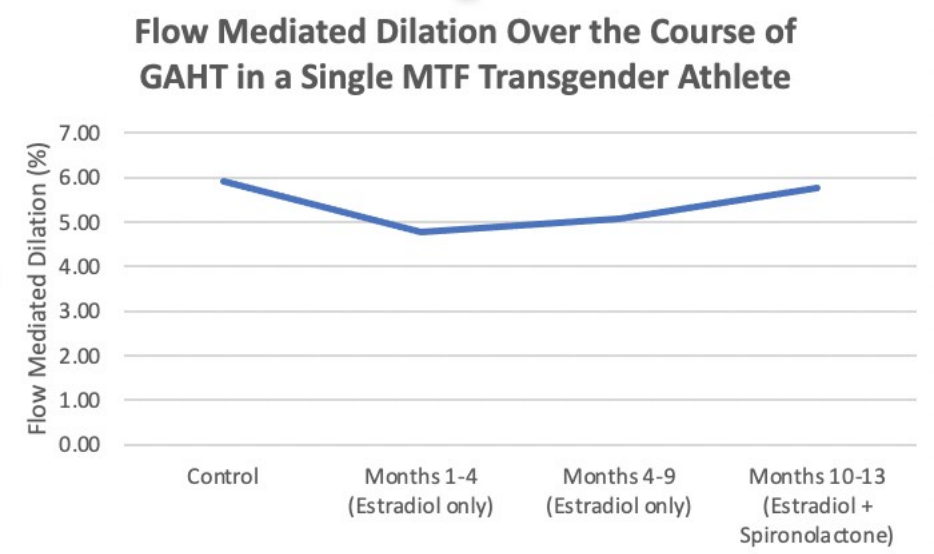
Pulse wave velocity and Augmentation Index showed similar trends, decreasing initially with estrogen therapy but then returning to baseline within the timeframe of the study. The AIx was significantly correlated with cSBP, SBP, and visceral fat (Pearson Correlation Coefficient r=0.624, p=0.030, Pearson Correlation Coefficient r=0.676, p=0.016, and Pearson Correlation Coefficient r=-0.729, p=0.017 respectively).

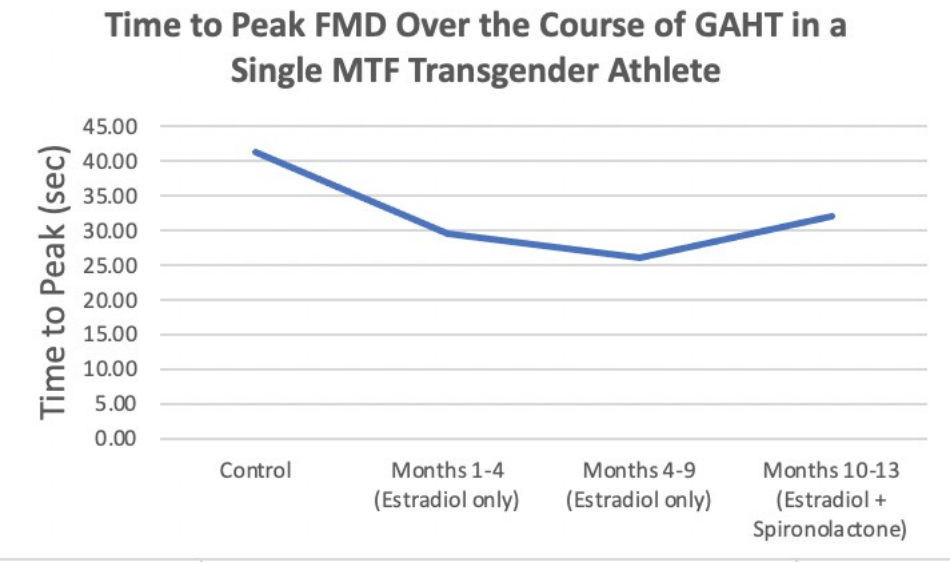




Effects of Feminizing GAHT on Vascular Reactivity:

Flow mediated dilation and time to peak FMD showed similar U shaped trends, decreasing after the initiation of GAHT but then returning towards baseline. FMD was not correlated with other measures in this study. Time to peak was negatively associated with time, but the correlation was not statistically significant (Pearson Correlation Coefficient r=-0.617, p=0.077).





Discussion

This case study assessed markers of vascular function in a single male-to-female transgender endurance athlete before and during gender affirming hormone therapy in an effort to better understand the vascular effects of gender affirming hormone therapy. While it was predicted that the participant's vascular function would decline with GAHT based on the current evidence that suggests that transgendered females have an increased risk of cardiovascular pathology[6], the data was inconclusive.

Visceral body fat measures remained unchanged from baseline after 15 months GAHT. While the distribution of body fat, particularly visceral body fat, is an independent risk factor for cardiovascular disease (CVD) and related morbidity and mortality[10]. Body fat and its distribution may not be significantly impacted by feminizing GAHT alone, at least not during this short study

period. It is important to note that visceral fat may also be impacted by other factors that were not controlled for in this study, including diet and exercise.

Results in this case study reflected numerous studies that have suggested increased incidence of hypertension in transgendered populations[18]. The participant in this case study showed increasing systolic and diastolic brachial blood pressures throughout treatment with GAHT and both peripheral and central systolic blood pressures were positively correlated with time in this case study. Because high blood pressure is one of the most significant risk factors for vascular disease[19], this trend needs to be explored in further longitudinal studies.

Arterial stiffness, measured by PWV, similarly is an independent predictor of cardiovascular disease and is sexually dimorphic. Premenopausal females have less arterial stiffness than age-matched males[20] but there is little evidence regarding how GAHT impacts arterial stiffness in transgendered individuals. In this study, results showed signs of decreasing arterial stiffness with estradiol therapy in the study participant, but PWV returned to baseline by the end of the study. Pulse wave velocity and Augmentation Index showed similar trends, decreasing initially with estrogen therapy but then returning to baseline indicating that estrogen may have temporarily decreased arterial stiffness. More long term studies are needed to determine if arterial stiffness would continue to increase, out plateau at baseline.

An original study from 1999 reported that FMD improved in transgendered females taking estrogen long term, an average of 61 months, compared with cisgender individuals[18]. In this case study, FMD trended downwards, indicating reduced reactivity, with the addition of estradiol but returned towards baseline at the end of the study period. Similar to PWV, more studies are needed to determine if arterial reactivity would continue to increase with longer term estrogen therapy.

Overall, the results of this case study did not convincingly support the hypothesis that gender affirming hormone therapy in a male-to-female transgender athlete acutely worsens vascular function, yet it does show evidence that GAHT might have an impact on vascular function. Previous works have demonstrated that transgender females have increased morbidity and mortality from cardiovascular diseases compared with non-transgender males[21]. Evidence published in 2019, from The Behavioral Risk Factor Surveillance System, suggested that transgendered men and women have a greater than 2-fold increase in the rates of myocardial infarction compared to their age-matched, cis-gendered peers, even after adjusting for cardiovascular risk factors[5]. This was the first large-scale analysis demonstrating an association between transgendered individuals and cardiovascular disease in a United States population[22]. This evidence calls for more research dedicated to understanding the pathophysiology of cardiovascular risk in transgendered individuals, particularly in male-to-female transgendered individuals.

While transgendered individuals may choose any combination of social and medical transition, GAHT has shown to improve mental health and quality of life in transgendered individuals[23]. A cohort study of nearly 200 transgendered individuals showed lower prevalence of social distress, anxiety, and depression in individuals who had initiated GAHT than in those without GAHT[24]. Because GAHT is integral to the medical management of transgendered individuals, it is imperative that we explore the long-term cardiovascular effects of GAHT to understand the benefits as well as the risks of this treatment. Future studies are needed to further assess the impact of GAHT in male-to-female transgendered individuals.

Limitations

This case study was limited by its short duration and sample size of one. More participants and a longer study time are needed to more comprehensively study the impact of GAHT on vascular physiology.

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Conflicts of Interest

No financial conflicts to report.

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