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Metabolic Effects of Hormone Therapy in Transgender Patients

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Abstract

Objective—Transgender patients may seek hormone therapy to induce physical changes to simulate their expressed or experienced gender. However, many providers are uncomfortable prescribing transgender hormones due to fears over safety. The goal of this study was to determine if transgender hormone therapy with estrogen and spironolactone for male-to-female (MtF) patients or with testosterone for female-to-male (FtM) patients had adverse anthropomorphic or metabolic effects.

Methods—This retrospective chart review study analyzed changes over time for 33 MtF and 19 FtM endocrine clinic patients at an academic endocrine practice with follow up for up to 18 months after hormone initiation.

Results—Compared to baseline labs obtained prior to initiation of hormone therapy statistically significant changes for the MtF cohort included an increase in HDL and decrease in creatinine; however, triglycerides did not show a statistically significant change. In the FtM cohort, there was a statistically significant increase in body mass index, creatinine, hemoglobin, and hematocrit. These changes were minimal for both cohorts.

Conclusion—In our practice, hormone therapy was found to be safe in this retrospective study.

Keywords

transgender; transsexual; hormone therapy

1.0 Introduction

Transgender is an umbrella term for people whose gender identity and/or gender expression differs from their natal sex. According to the Diagnostic and statistical manual of mental disorders (5th ed.) (DSM-5), transgender individuals can be diagnosed with gender dysphoria, a term that describes the distress accompanying a marked difference in the expressed or experienced gender from their natal sex [1]. Recently, there has been a dramatic increase in public awareness of transgender individuals due to mainstream media exposure of trans celebrities such as athlete Caitlyn Jenner and *Orange is the New Black* actress Laverne Cox. The increased visibility may also increase the patient population size through

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educating people about the existence of gender dysphoria and about treatment options. According to one estimate, transgender people comprise approximately 0.3% of the United States population [2]. Therefore, it is vital to continue educating providers about the care and treatment of transgender individuals.

Individuals identifying as transgender often seek hormonal therapy – estrogen, with or without the anti-androgenic effects of spironolactone, prescribed for male-to-female (MtF) patients and testosterone prescribed for female-to-male (FtM) patients. The Endocrine Society published guidelines for the initiation and monitoring of transgender hormone therapy [3]. This therapy is meant to induce physical changes to simulate the patient's desired gender. However, the use of estrogen and testosterone has metabolic side effects, and many providers are uncomfortable with the use of hormone therapy regardless of whether it is used in same gender (cisgender) or transgender populations, especially due to the lack of knowledgeable providers on appropriate treatment options for transgender patients [4]. Risks associated with estrogen use include cancer risks, cardiovascular risks including thrombosis and hypertension, and weight changes, among others. The major risks associated with spironolactone include hyperkalemia and blood pressure effects, particularly if subjects have underlying renal or liver disease. Testosterone risks include cardiovascular disease, hypertension, and polycythemia; liver toxicity is more associated with oral than parenteral administration, but remains a potential concern. Although transgender individuals are increasingly accessing the health care system to seek hormonal therapy, little is known regarding outcomes and prevalence of metabolic perturbations in the trans community. The primary goal of this study was to determine if transgender hormone therapy had any adverse anthropomorphic or metabolic effects in a "real world" cohort.

2.0 Methods

This was a retrospective chart review of subjects attending endocrinology clinics at the University of Kentucky between 1/1/2008 and 2/28/2014. This study was approved by and work was completed in compliance with the Institutional Review Board of the University of Kentucky. Subjects were identified by ICD-9 codes 302.85 (gender identity disorder in adolescents or adults). Only subjects with a baseline and at least one follow up visit in this study window were included. Subjects admitting to use of hormones – whether prescribed or obtained by the patient without a prescription – prior to the baseline visit were excluded; thus, the dataset includes only subjects new to hormone therapy at the baseline visit. Individual providers, per their personal practice, performed medical care, monitoring, and hormone prescriptions; treatment, laboratory screening and patient management were not part of this study. Demographic data collected include age at time of baseline visit, recorded gender (i.e. legally recognized gender; thus, once an individual has legally changed their gender, this was reflected on their medical record), weight, height, body mass index (BMI) and ethnicity. If the medical record listed a primary care provider (PCP) and/or health care insurance, this was noted. However, information as to whether health care insurance covered the treatment of transgender care was not available. Smoking status was ascertained at every visit as "yes" (acknowledged current smoking of any amount) or "no" (subject denies current smoking).

Metabolic data including fasting labs at each visit was collected when available. Medication dosing is recorded as the average daily dose (for injected medications average daily dose was calculated as injected dose/days between injections). Most providers had patients return for follow up approximately 3 months after initiation of hormones and then again every 3-12 months. However, there was a wide range of timing of follow up visits; thus Visit 1 is classified as 3-6 months and Visit 2 as 6-18 months after hormone therapy was initiated. Patients with multiple visits in this time frame had the data reviewed from the visit closest to 3 months and 12 months. Not all subjects attended each visit or had metabolic data at each visit with available data indicated by "N" within tables 3 and 4. Statistical analyses: Patients transitioning from male-to-female and from female-to-male were analyzed separately. Results were analyzed using paired t-tests compared to baseline visit, with each individual compared to themselves at baseline.

3.0 Results

In calendar years 2008-2011 there was an average of 5 new transgender patients/year; in 2012 this increased to 15 new transgender patients, and to 39 new transgender patients in 2013; 33 MtF and 19 FtM patients met inclusion/exclusion criteria. The two cohort demographics described in Table 1 and Table 2 had an average age of 31 (MtF) and 27 (FtM) at initiation of hormone therapy. In terms of generalizability, it is worth noting that the majority of patients in both cohorts had insurance, had a primary care physician, did not smoke, and self-identified as white, non-Hispanic, reflecting the population of Kentucky.

MtF (Table 3)

Standard practice in the clinic includes assessment of physical and laboratory parameters at baseline and in follow up visits. In the MtF cohort, this includes a fasting lipid panel, liver and renal function tests, and potassium. In most subjects a "comprehensive metabolic panel" is obtained.

The dose and route of administration of estrogen, and the use of spironolactone was recorded at each visit. Per inclusion/exclusion criteria no subjects were using estrogen at the baseline visit. Approximately half the subjects were using oral estrogen at follow up visits with an average daily dose of 1.44 mg/day (visit 1) and 1.71 mg/d (visit 2), with the remaining subjects using transdermal estrogen (22% at visit 1; 14% at visit 2) or intramuscular injections of estrogen (22% at visit 1; 36% at visit 2). The N was too small to compare results between different routes of administration. The majority of subjects were using spironolactone at an average dose of just over 100 mg/day.

In this cohort, there was no change in body weight (not shown) or body mass index (BMI) with hormone therapy. There was a trend toward decreased blood pressure from baseline to Visit 2, but this did not reach statistical significance. HDL was the only lipid parameter that showed a statistically significant increase, with an increase at Visit 1 and a statistically non-significant trend to a further increase at Visit 2. There were non-significant trends toward an increase for both total cholesterol and LDL from baseline to Visit 2. Despite the association of estrogen use and triglyceride elevations, triglycerides did not change from Baseline to Visit 2.

Despite the concern about hyperkalemia with spironolactone use, there were no significant increases in potassium level, although there was a trend toward increased potassium from Baseline to Visit 2. There was a statistically significant decrease in creatinine from Baseline to Visit 1, but this was no longer significant at Visit 2. Neither of the liver enzyme markers ALT and AST had any significant changes with hormone therapy.

FtM (Table 4)

In the FtM cohort treated with testosterone, the standard practice is to measure a fasting lipid panel, liver and renal function tests. Again, in most subjects a “comprehensive metabolic panel” as well as a hemogram was obtained. Although testosterone is available in transdermal and injectable forms, all subjects were using intramuscular injections of testosterone in follow up, with an average daily dose of approximately 11mg/day, calculated as injected dose divided by days between injections. Seventy-five percent of subjects were injecting testosterone every 2 weeks, while 25% were using smaller doses injected every week.

This cohort showed a statistically significant increase in BMI from Baseline to Visit 1, but this effect was lost by Visit 2. There were no significant changes in either systolic or diastolic blood pressure. Several trends were observed from the lipid profile with a tendency towards a decrease in HDL, increase in LDL, and decrease in triglycerides; however, none of these changes reached statistical significance. Creatinine showed a statistically significant increase from Baseline at Visits 1 and 2. There was no change in serum calcium. ALT and AST both trended downward, but neither had changes that were statistically significant. However, as expected, there was a statistically significant increase in hemoglobin, hematocrit, and red blood cell count from Baseline to Visit 1 and Visit 2.

4.0 Discussion

This retrospective chart review of transgender individuals seeking hormone therapy at an endocrinology clinic demonstrates that there are minimal metabolic or health changes associated with initiation of transgender hormones. In this study, there was no significant change in blood pressure for either the MtF or FtM cohort. However, there was an increase in BMI for the FtM patients. The only significant change observed from the lipid profile was an increase in HDL in the MtF cohort, with no significant negative changes – including no significant change in triglycerides – in either cohort. For the metabolic markers, the MtF cohort had a decrease in creatinine while the FtM cohort had an increase in creatinine. No change in potassium was noted in the MtF cohort despite the majority of patients being prescribed spironolactone. Finally, the FtM cohort had a statistically significant increase in all the recorded hematological markers, including hemoglobin, hematocrit, and red blood cell count. This is a well known side effect of testosterone therapy, and thus not surprising.

Estrogen therapy in postmenopausal cisgender women produces a decrease in total cholesterol and LDL without significantly changing the HDL profile [5]. However, the literature on lipid profile changes after estrogen treatment for transgender women has some discrepancies. One retrospective study compared transgender and cisgender lipid profiles. While there was a statistically significant difference between cisgender men and cisgender

women, transgender women HDL levels were found to lie intermediate to the cisgender averages, not significantly deviating from either [6]. Two papers suggest that there is no change in either total cholesterol or HDL after hormone therapy for transgender women [7], [8]. Additionally, two papers note a significant increase in triglycerides for transgender women [6], [8], while other studies reported no change in triglycerides [7]. This study found a significant increase ($p < 0.01$) in HDL at Visit 1, as would be expected if the lipid profile of the trans women were shifting to resemble that of average cisgender women. Additionally, and importantly, no change in triglycerides was observed for the MtF cohort. Estrogen therapy in postmenopausal cisgender women does not affect blood pressure or BMI [5]. A previous study did not find an effect of estrogen therapy on BMI in MtF patients [9], and our results confirm this. As a potassium-sparing diuretic, spironolactone can cause hyperkalemia. However, our MtF cohort did not show a statistically significant change in potassium after initiation of hormone therapy. This may be due to the limited doses used, but is a reassuring finding. MtF creatinine levels may more closely resemble the cisgender male creatinine range than the cisgender female creatinine range [6]. This study found a decrease in creatinine for the MtF cohort at Visit 1, but no significant changes at Visit 2; lack of statistical significance is likely due to the smaller number of subjects with data at Visit 2.

In cisgender patients, testosterone therapy in testosterone deficient men results in a reduction in systolic and diastolic blood pressures and a significant decrease in BMI [10]. However, this is different to transgender testosterone therapy in which patients are not deficient in testosterone, but rather receiving supplementation to raise levels to that seen in biological males. Only one study, performed in 1986, has followed blood pressure change over time after initiation of hormone therapy in MtF and FtM transgender patients [7]. Neither our study nor *Meyer, et al.* 1986 found a statistically significant change in blood pressure over a short period of time after initiation of hormone therapy in either MtF or FtM cohorts. While a 2012 cross-sectional study did show that a significant proportion (22.5%) of an MtF cohort with an average of 10 years of hormone use had an elevated blood pressure, this cohort was also proportionately overweight (24%) and/or obese (14%) [11].

Several studies note an increase in BMI for FtM patients after initiation of hormone therapy [9], [12], [13], [14]. Similarly, our study also saw an increase in BMI at Visit 1 in the FtM cohort, possibly due to increased muscle mass. A lack of change in BMI for Visit 2 may be due to the smaller N or due to a stabilization of weight and BMI. Additionally, the FtM cohort showed an increase in creatinine at both Visit 1 and Visit 2; this would be an expected change if the FtM cohort had an average increase in muscle mass and thus muscle break-down products – a possibility given the observed increase in BMI. Testosterone use in hormone therapy for transgender men is associated with an increase in hemoglobin and hematocrit [11], [12], [13] [14], [15]. Our study also observed an increase in the hemogram parameters for the FtM cohort at Visit 1 and Visit 2. While these changes reflect a shift toward the average cisgender male hemogram parameters, these changes are still within normal human range. However, most providers decreased testosterone dose if patients had elevations in hemoglobin or hematocrit beyond the normal male range. Our numbers are too small to assess if weekly administration of lower doses had different effects than biweekly administration of higher testosterone doses.

There are several limitations of our study. As this was a retrospective chart review, data is limited to what was available, which varied by patient and provider. The study does not have sufficient power to compare the incidence of adverse effects to the general population. The population in our study is relatively young, and the risks may different in older subjects on hormone therapy. The timing of follow up visits after hormone initiation varied, with some patients having closer follow up whereas others had long intervals between visits; additionally, subjects who were lost to follow up were not included. In addition, plasma levels of testosterone and estradiol are available on very few subjects; recent guidelines recommend attaining plasma levels in the normal range for the desired gender. Interpretation of the efficacy of the doses used is not available due to lack of hormone measurements, and the doses used in this study may be lower than those in other studies. Finally, the number of subjects having data at visit 2 is less than visit 1; while this may be due in part to subject drop out (lack of follow up), the majority of this is due to the increase in new patients toward the end of the study. There was a sharp increase in the number of new patients initiating care between 2008 and 2014; many of these individuals continue to obtain their care at our clinic, but their follow up dates were beyond the approved study date (2/28/2014). However, despite these limitations this data adds to the literature indicating the safety of transgender hormone use.

5.0 Conclusion

In this real world cohort of transgender individuals obtaining care at a single academic endocrinology clinic, the use of cross gender hormone therapy is safe. We agree with guidelines recommending that these individuals should be monitored for changes in lipid parameters as estrogen is well known to induce hypertriglyceridemia in some individuals. However, in our population the observed lipid change was an increase in HDL, which could be anticipated to be beneficial. Female-to-male patients should be monitored for changes in BMI and hemogram parameters, as increased levels are expected. Our experience indicates that metabolic changes are minimal and transgender hormone therapy appears to be safe.

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Abbreviations

MtF	male-to-female
FtM	female-to-male

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Table 1

Study Male to Female Cohort Demographics

N	33
Average Age	31 (range: 16-56)
Ethnicity	64%
White, non-Hispanic	6%
Hispanic	6%
Black/African American	24%
Not specified	
Have insurance	75%
yes	25%
no	
Have PCP	63%
yes	37%
no	
Currently smokes	9%
yes	91%
no	
Listed Gender	30%
Female	70%
Male	

N = total number of patients in the study; PCP = primary care physician; Listed Gender = the gender currently on the electronic medical record, entry in concordance with state-assigned/legal gender. Data shown is average ± SEM or percent, as indicated

Table 2

Study Female to Male Cohort Demographics

N	19
Average Age	27 (range: 19-47)
Ethnicity	89%
White, non-Hispanic	0%
Hispanic	0%
Black/African American	11%
Not specified	
Have insurance	88%
yes	12%
no	
Have PCP	33%
yes	67%
no	
Currently smokes	35%
yes	65%
no	
Listed Gender	26%
Male	74%
Female	

N = total number of patients in the study; PCP = primary care physician; Listed Gender = the gender currently on the electronic medical record, entry in concordance with state-assigned/legal gender.

Data shown is average ± SEM or percent, as indicated.

Table 3

Metabolic data over time for the Male-to-Female patient population.

Parameter	Baseline	Visit 1 (3-6months)	Visit 2 (6-18 months)
N	33	30	15
BMI (kg/m^2)	28.8 ± 1.4	29.4 ± 1.5	27.7 ± 1.9
sBP (mmHg)	131 ± 3	129 ± 2	125 ± 4
dBP (mm Hg)	82 ± 2	80 ± 2	77 ± 3
TC (mg/dL)	171 ± 7	176 ± 9	194 ± 10
HDL (mg/dL)	41 ± 2	47 ± 2 **	52 ± 5
LDL (mg/dL)	103 ± 6	106 ± 8	116 ± 12
TG (mg/dL)	130 ± 13	115 ± 11	134 ± 21
K (mmol/L)	4.09 ± 0.06	4.12 ± 0.07	4.22 ± 0.08
Creat (mg/dL)	0.90 ± 0.03	0.85 ± 0.03 *	0.83 ± 0.03
Ca (mg/dL)	9.5 ± 0.1	9.5 ± 0.1	9.6 ± 0.1
ALT (U/L)	27 ± 3	28 ± 3	24 ± 4
AST (U/L)	23 ± 1	22 ± 2	23 ± 3
Estrogen use by po (N; avg daily dose)	0	18 (56%); 1.44 mg/day	7 (50%); 1.71 mg/day
Estrogen use by patch (N; avg daily dose	0	7 (22%); 0.1 mg/day	2 (14%); 0.1 mg/day
Estrogen use by injection (N; avg daily dose)	0	7 (22%); 1.21 mg/day	5 (36%); 1.18 mg/day
Spironolactone use (N; avg daily dose)	0	23; 104 mg/day	14; 114 mg/day

N = sample size; BMI = body mass index; sBP = systolic blood pressure; dBP = diastolic blood pressure; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; K = potassium; Creat = creatinine; Ca = calcium; ALT = alanine transaminase; and AST = aspartate transaminase. Data shown is average ± SEM

* signifies $p < 0.05$, using a paired t-test compared to baseline visit.

** signifies $p < 0.01$ using a paired t-test compared to baseline visit.

Table 4

Metabolic data over time for the Female-to-Male patient population.

Parameter	Baseline	Visit 1 (3-6 months)	Visit 2 (6-18 months)
N	19	16	10
BMI (kg/m^2)	28.1 ± 2.1	30.1 ± 2.3*	25.2 ± 2.1
sBP (mmHg)	124 ± 4	133 ± 6	122 ± 5
dBP (mmHg)	76 ± 2	77 ± 2	75 ± 4
TC (mg/dL)	162 ± 6	160 ± 8	168 ± 19
HDL (mg/dL)	54 ± 4	48 ± 3	48 ± 8
LDL (mg/dL)	89 ± 6	94 ± 7	102 ± 15
TG (mg/dL)	96 ± 16	87 ± 11	83 ± 17
Creat (mg/dL)	0.73 ± 0.03	0.87 ± 0.04*	0.82 ± 0.04**
Ca (mg/dL)	9.3 ± 0.1	9.3 ± 0.1	9.6 ± 0.2
ALT (U/L)	23 ± 3	19 ± 2	16 ± 1
AST (U/L)	29 ± 9	23 ± 3	22 ± 3
Hgb (g/dL)	13.4 ± 0.3	14.2 ± 0.4*	15.2 ± 0.4**
Hct (%)	39.8 ± 0.8	43.4 ± 1.1**	45.9 ± 1.2**
RBC (1x10^{12}/L)	4.51 ± 0.10	4.89 ± 0.12*	5.12 ± 0.17*
Average Daily Testosterone dose	0	10.71 mg/day	11.36 mg/day

N = sample size; BMI = body mass index; sBP = systolic blood pressure; dBP = diastolic blood pressure; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; K = potassium; Creat = creatinine; Ca = calcium; ALT = alanine transaminase; and AST = aspartate transaminase. Hgb = hemoglobin; Hct = hematocrit; and RBC = red blood cell count. Data shown is average ± SEM

* signifies $p < 0.05$, using a paired t-test compared to baseline visit.

** signifies $p < 0.01$ using a paired t-test compared to baseline visit.