Metabolic effects of cross-sex hormone therapy in transgender individuals in Taiwan

Yu-Hsien Liu[a], Tsung-Hui Wu[a,b], Chia-Huei Chu[c,d], Yi-Chun Lin[a,b], Liang-Yu Lin[a,b,*]

[a]Division of Endocrinology and Metabolism, Department of Medicine, Taipei. Veterans General Hospital, Taipei, Taiwan, ROC; [b]Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Otorhinolaryngology-Head and Neck Surgery, Mackay Memorial Hospital, Taipei, Taiwan, ROC; [d]Department of Audiology and Speech Language Pathology, Mackay Medical College, New Taipei City, Taiwan, ROC

Abstract

Background: Transgender individuals often require gender-affirming interventions, such as endogenous sex hormone inhibition or gender-affirming hormone therapy (HT), while there is discordance between their body and gender identity. However, a recent study found that the incidence of cardiovascular events is higher in transgender patients receiving cross-sex HT. The aim of this study was to investigate the metabolic effects of an altered sex hormone profile.

Methods: This retrospective study, conducted in a referral center in Northern Taiwan, analyzed metabolic changes over time in 65 trans masculine and 45 trans feminine persons. The transgender individuals were examined at 4 time points: before the gender affirming HT, as well as 3, 6, and 12 months following treatment.

Results: Compared with baseline measurements, the trans masculine patients showed significant increases in body mass index (BMI) (22.6 ± 0.3 vs 23.3 ± 0.4 kg/m^2; $p < 0.001$; t = 3M), low-density lipoprotein cholesterol (124.3 ± 3.7 vs 131.3 ± 3.9 mg/dL; $p = 0.03$; t = 12M), creatinine (0.75 ± 0.01 vs 0.83 ± 0.14 mg/dL; $p < 0.001$; t = 12M), and hemoglobin (13.5 ± 0.7 vs 15.2 ± 0.2 g/dL; $p < 0.001$; t = 12M), as well as decreased high-density lipoprotein cholesterol (57 ± 2.1 vs 51 ± 2.0 mg/dL; $p < 0.001$; t = 12M). The trans feminine patients had reduced low-density lipoprotein cholesterol (104.2 ± 3.2 vs 100.8 ± 3.5 mg/dL; $p = 0.05$; t = 3M), hemoglobin (14.0 ± 0.1 vs 13.5 ± 0.1 g/dL; $p = 0.008$; t = 12M), and creatinine (0.82 ± 0.01 vs 0.79 ± 0.14 mg/dL; $p < 0.001$; t = 3M) compared with baseline data. In addition, most of these metabolic effects persisted during the follow-up period.

Conclusion: This observational, retrospective study revealed that gender-affirming HT increased the relative cardiovascular risk in trans masculine individuals.

Keywords: Gender affirming hormone therapy; Metabolic effect; Transgender

1. INTRODUCTION

The effect of sex on distinct biological mechanisms is an important topic in medical research as there are marked sex-associated differences in the epidemiology, risk, clinical manifestations, course, and treatment of various diseases.[1] Many differences in vascular biology between men and women may be driven by different levels of estrogen and testosterone.[2] Sex differences exist in the regulation of arterial pressure and renal function by the renin–angiotensin system. Early evidence demonstrated that premenopausal woman compared with aged-matched men is protected from hypertension, renal, and cardiovascular disease. Nowadays, awareness of the diverse population of transgender persons and their desire for gender-affirming hormone therapy (HT) is growing rapidly. A meta-regression of population-based probability samples extrapolated that the population of transgender individuals in the United States in 2016 was 390 adults per 100,000, or almost 1 million adults nationally.[3] Therefore, it is crucial to focus on the care and treatment of transgender individuals.

Transgender individuals may need gender-affirming interventions, such as endogenous sex hormone inhibition or cross-hormone replenishment, to induce physical changes to stimulate their expressed or experienced gender. In Taiwan, transgender therapy for adults, in other words, testosterone for trans masculine patients and estrogen and antiandrogen for trans feminine patient are frequently prescribed. These therapies are intended to induce physical changes to align with the patient's gender identity. However, the use of testosterone and estrogen might have metabolic side effects on lipid profiles and hemogram results,[4] which may be concerning for many transgender individuals. Hormone replacement therapy in transgender individuals has enabled, to some extent, investigation of the physiological role of sex steroids.

Due to the increased number of transgender individuals seeking gender-affirming HT, the outcome and prevalence of metabolic perturbations in transgender individuals become a more important problem. Moreover, recent studies found that the incidence of cardiovascular events is higher in trans feminine receiving gender-affirming HT.[5,6] The primary aim of this study was to investigate the metabolic effects of an altered sex hormone profile in transgender therapy.

*Address correspondence. Dr Liang-Yu Lin, Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: linly@vghtpe.gov.tw (L.-Y. Lin).

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2. METHODS

2.1. Patients

We performed a retrospective review of the electronic medical records of transgender patients receiving cross-sex HT at the Taipei Veterans General Hospital, a referral medical center in Northern Taiwan, from January 2011 to April 2019. The Institution Review Board of Taipei Veterans General Hospital approved the research, which was conducted in accordance with the Declaration of Helsinki. All study subjects were diagnosed with the ICD-10 code F64.9 (gender identity disorder unspecified including gender dysphoria) and had been approved to undergo gender-affirming medical intervention. Only individuals with a baseline (V0) and at least one follow-up visit in the study period were included. Exclusion criteria included a history of dyslipidemia, prior hormone treatment, and incomplete data on body weight or laboratory testing at baseline. Trans masculine patients who had taken oral contraceptives to stop their menstrual cycle 6 months before the beginning of the therapy were not included. Most patients were examined every 3 months after the start of HT and received blood sampling for biochemical examination in fasting. However, timing of examinations varied, so we used the following definitions: visit 1 (V1) occurred at 3–6 months, visit 2 (V2) occurred at 7–12 months, and visit 3 (V3) occurred at 13–24 months after the initiation of hormone replacement therapy. Gender-affirming HT with testosterone cypionate was administered intramuscularly every 2 weeks to the trans masculine group. Conjugated estrogen was prescribed twice daily, in addition to cyproterone acetate once daily if indicated, to the trans feminine group. We adjusted the dosage of hormone replacement therapy during each visit based on previous levels of estradiol, according to recent gender dysphoria guidelines.[7]

2.2. Clinical data

Demographic data collected included age at the time of the baseline visit, BMI calculated as the weight (kg) divided by the square of height (m), smoking status, and history of any systemic disease. Electrochemiluminescence immunoassays were utilized to measure testosterone, estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Routine measurements including total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides, fasting glucose, and insulin level were collected. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance, using the following equation: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405. Medication dosing was recorded as the average 2 weeks dosage.

2.3. Statistical analysis

Statistical analysis was carried out with SPSS software, version 24.0 (IBM Corporation, Armonk, NY). An independent analysis of variance was conducted to explore continuous variable differences, which were expressed as means ± SD. Categorical variables, expressed as numbers and percentages, were compared using Pearson's chi-squared test. To evaluate the metabolic effects of hormone replacement therapy on outcome variables, the paired t test was used to identify changes in metabolic parameters over time in the 2 groups.

3. RESULTS

3.1. Baseline characteristics

A total of 110 individuals were enrolled in the present analysis, including 65 trans masculine and 45 trans feminine patients, from January 2011 to April 2019. The mean age was 27.2 ± 0.6 years. Two (1.8%) patients had a history of diabetes mellitus and 7 (6.3%) subjects had a habit of smoking. Other baseline characteristics and the duration of follow-up are listed in Table 1. The number of participants of each of the following time period was 65 on visit 1, 45 on visit 2, and 47 on visit 3 in the trans masculine group; 45 on visit 1, 29 on visit 2, and 26 on visit 3 in the trans feminine group.

3.2. Trans masculine patients

The longitudinal data of the trans masculine group are shown in Table 2. The average dosage per 2 weeks of testosterone was approximately 166.6 mg. There was a significant increase in BMI compared to baseline at every visit (V1: 23.3 ± 0.4 vs 22.6 ± 0.3 kg/m^2, $p < 0.001$; V2: 23.2 ± 0.3 vs 22.6 ± 0.3 kg/m^2, $p < 0.001$; V3: 22.8 ± 0.3 vs 22.6 ± 0.3 kg/m^2, $p = 0.004$; Fig. 1A). We also observed a statistically significant increase in LDL-c (V3: 131.3 ± 3.9 vs 124.3 ± 3.7 mg/dL, $p = 0.030$; Fig. 1B) and a decrease in HDL-c (V1: 52.8 ± 1.9 vs 57.9 ± 2.1 mg/dL, $p < 0.001$; V2: 52.7 ± 2.2 vs 57.9 ± 2.1 mg/dL, $p < 0.001$; V3: 51.2 ± 2.0 vs 57.9 ± 2.1 mg/dL, $p < 0.001$; Fig. 1C).

We observed a trend of decreased insulin (V3: 5.7 ± 0.4 vs 8.2 ± 1.0 μU/mL; $p = 0.004$) and HOMA-IR (V3: 1.31 ± 0.12 vs 1.75 ± 0.20 μU/mol, $p = 0.022$). However, there were no changes in fasting glucose or HbA1c. Serum creatinine was significantly higher compared with baseline at all visits (V1: 0.77 ± 0.00 vs 0.75 ± 0.01 mg/dL, $p < 0.001$; V2: 0.80 ± 0.01 vs 0.75 ± 0.01 mg/dL, $p < 0.001$; V3: 0.83 ± 0.01 vs 0.75 ± 0.01 mg/dL, $p < 0.001$; Fig. 1D). As expected, statistically significant increases were observed compared with baseline in hemoglobin (V1: 13.9 ± 0.1 vs 13.5 ± 0.7 g/dL, $p < 0.001$; V2: 14.5 ± 0.2 vs 13.5 ± 0.7 g/dL, $p < 0.001$; V3: 15.2 ± 0.2 vs 13.5 ± 0.7 g/dL, $p < 0.001$; Fig. 1E) and hematocrit (V1: 42.5 ± 0.5 vs 40.7 ± 0.5%, $p < 0.001$; V2: 44.8 ± 0.5 vs 40.7 ± 0.5%, $p < 0.001$; V3: 45.9 ± 0.6 vs 40.7 ± 0.5%, $p < 0.001$).

3.3. Trans feminine patients

The longitudinal data of the trans feminine group are shown in Table 3. In this cohort, no obvious changes in body weight, BMI, or blood pressure were found between the baseline and subsequent visits. In the lipid profile, there were trends toward increased HDL-c (V1: 64.4 ± 2.3 vs 63.9 ± 2.6 mg/dL, $p = 0.699$; V2: 64.0 ± 2.8 vs 63.9 ± 2.6 mg/dL, $p = 0.728$; V3: 65.0 ± 3.0 vs 63.9 ± 2.6 mg/dL, $p = 1.000$) and decreased LDL-c (V1: 100.8 ± 3.5 vs 104.2 ± 3.2 mg/dL, $p = 0.050$; V2: 99.3 ± 5.8 vs 104.2 ± 3.2 mg/dL, $p = 0.369$; V3: 100.4 ± 6.3 vs 104.2 ± 3.2 mg/dL,

Table 1

Baseline characteristic of trans masculine and trans feminine subjects

		All (n = 110)	Trans masculine (n = 65)	Trans feminine (n = 45)
Age, y		27.2 ± 0.6	27.9 ± 0.7	26.0 ± 1.1
Following time, mo		14.1 ± 0.8	14.7 ± 1.2	13.3 ± 0.9
SRS number, n (%)	Total	48 (43.6%)	42 (64.6%)	6 (13.3%)
	Before hormone therapy	15 (13.6%)	13 (20%)	2 (4.4%)
	After hormone therapy	33 (30%)	29 (44.6%)	4 (8.9%)
DM, n (%)		2 (1.8%)	2 (3.0%)	0
Smoking, n (%)	Yes	7 (6.3%)	5 (7.6%)	2 (4.4%)
	Quit	5 (4.5%)	5 (7.6%)	0
TSH (μIU/mL)		1.59 ± 0.10	1.54 ± 0.10	1.66 ± 0.10
fT4 (ng/dL)		1.04 ± 0.02	1.01 ± 0.02	1.09 ± 0.02
Prolactin (ng/mL)		17.1 ± 2.0	17.6 ± 3.2	16.5 ± 1.8

Data are presented as numbers and percentages in noncontinuous variables and mean ± SD in continuous variables.

DM = diabetes mellitus; fT4 = free thyroxine; SRS = sex reassignment surgery; TSH = thyroid stimulating hormone.

Table 2

Longitudinal metabolic data for trans masculine subjects

	V0 (baseline) n = 65	V1 (3–6M) n = 65	*p*	V2 (6–12M) n = 45	*p*	V3 (12–24M) n = 47	*p*
BW (kg)	59.3 ± 1.0	60.8 ± 1.0	<0.001	60.8 ± 1.1	<0.001	60.2 ± 1.0	0.003
BMI (kg/m^2)	22.6 ± 0.3	23.3 ± 0.4	<0.001	23.2 ± 0.3	<0.001	22.8 ± 0.3	0.004
sBP (mmHg)	119.9 ± 1.9	120.2 ± 1.9	0.879	117.8 ± 1.9	0.520	114.8 ± 2.0	0.158
dBP (mmHg)	70.2 ± 1.1	70.1 ± 1.1	0.965	69.5 ± 1.2	0.664	71.1 ± 1.5	0.522
TC (mg/dL)	183.4 ± 3.8	178.2 ± 4.0	0.032	181.1 ± 4.0	0.229	184.1 ± 4.7	0.935
HDL-c (mg/dL)	57.9 ± 2.1	52.8 ± 1.9	<0.001	52.7 ± 2.2	<0.001	51.2 ± 2.0	<0.001
LDL-c (mg/dL)	124.3 ± 3.7	124.2 ± 3.6	0.898	131.1 ± 3.6	0.131	131.3 ± 3.9	0.030
TG (mg/dL)	76.7 ± 4.7	73.5 ± 4.2	0.333	73.9 ± 4.7	0.921	77.3 ± 4.1	0.855
Glucose (mg/dL)	93.0 ± 2.8	90.7 ± 1.2	0.317	91.7 ± 1.4	0.669	93.5 ± 3.2	0.962
Insulin (μU/mL)	8.2 ± 1.0	7.4 ± 1.1	0.265	7.0 ± 0.9	0.859	5.7 ± 0.4	0.004
HbA1c (%)	5.4 ± 0.0	5.3 ± 0.0	0.069	5.3 ± 0.0	0.593	5.5 ± 0.1	0.608
HOMA-IR	1.75 ± 0.20	1.43 ± 0.13	0.129	1.68 ± 0.27	0.836	1.31 ± 0.12	0.022
WBC (10^3/μL)	7056 ± 176	6946 ± 197	0.546	7278 ± 269	0.222	7452 ± 307	0.063
Hgb (g/dL)	13.5 ± 0.7	13.9 ± 0.1	<0.001	14.5 ± 0.2	<0.001	15.2 ± 0.2	<0.001
Hct (%)	40.7 ± 0.5	42.5 ± 0.5	<0.001	44.8 ± 0.5	<0.001	45.9 ± 0.6	<0.001
ALT (U/L)	16.7 ± 1.3	16.0 ± 1.1	0.491	16.4 ± 1.2	0.867	18.4 ± 1.4	0.258
Creat. (mg/dL)	0.75 ± 0.01	0.77 ± 0.00	<0.001	0.80 ± 0.01	<0.001	0.83 ± 0.01	<0.001
eGFR (mL/min/1.73 m2)	97.6 ± 2.0	93.0 ± 1.7	<0.001	89.9 ± 1.8	<0.001	88.0 ± 2.1	<0.001

Data are expressed as numbers and percentage for noncontinuous variables and mean ± SD for continuous variables.

p value using paired t test comparing to baseline visiting data.

ALT = alanine transaminase; BMI = body mass index; Creat. = creatinine; dBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; Hct = hematocrit; HDL-c = high-density lipoprotein cholesterol; Hgb = hemoglobin; HOMA-IR = homeostasis model assessment insulin resistance index; LDL-c = low-density lipoprotein cholesterol; sBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; WBC = white blood count.

$p = 0.638$). Despite the known association between the use of estrogen and elevated triglycerides, there were no significant trends toward elevated triglycerides (V3: 89.0 ± 7.4 vs 85.4 ± 7.7 mg/dL, $p = 0.598$). Furthermore, there were no changes in fasting glucose, insulin, or HOMA-IR. There was a statistically significant decrease in creatinine (V1: 0.79 ± 0.14 vs 0.82 ± 0.01 mg/dL, $p < 0.001$; V2: 0.78 ± 0.01 vs 0.82 ± 0.01 mg/dL, $p < 0.001$; V3: 0.79 ± 0.01 vs 0.82 ± 0.01 mg/dL, $p < 0.001$). Additionally, downward trends in hemoglobin (V1: 13.7 ± 0.1 vs 14.0 ± 0.1 g/dL, $p = 0.143$; V2: 13.5 ± 0.1 vs 14.0 ± 0.1 g/dL, $p = 0.008$; V3: 13.5 ± 0.1 vs 14.0 ± 0.1 g/dL, $p = 0.024$) and hematocrit (V1: 41.2 ± 0.4 vs 41.5 ± 0.4%, $p = 0.355$; V2: 40.3 ± 0.3 vs 41.5 ± 0.4%, $p = 0.040$; V3: 40.7 ± 0.5 vs 41.5 ± 0.4%; $p = 0.142$) were identified compared with baseline data.

Sex hormone levels in transgender subjects receiving cross-sex HT are presented in Table 4. There was a significant decrease in LH levels in both trans masculine patients (V1: 7.5 ± 1.7 vs 11.0 ± 2.3 mIU/mL, $p = 0.017$) and trans feminine groups (V1: 2.0 ± 0.5 vs 4.1 ± 1.0 mIU/mL, $p = 0.006$) that persisted at all subsequent examinations. However, FSH decreased in the trans feminine individuals (V2: 1.6 ± 0.8 vs 5.4 ± 1.6 mIU/mL, $p = 0.005$) in the first 12 months, but did not in the trans masculine population. As expected, serum estradiol increased in the trans feminine individuals (V1: 54.9 ± 6.3 vs 37.7 ± 5.1 pg/mL, $p = 0.006$) and decreased in the trans masculine patients (V2: 66.3 ± 9.9 vs 95.6 ± 14.4 pg/mL, $p = 0.025$). In contrast, testosterone decreased in trans feminine patients (V1: 1.5 ± 0.4 vs 4.3 ± 0.6 ng/mL, $p < 0.001$) but increased in trans masculine patients (V1: 8.9 ± 0.9 vs 0.4 ± 0.0 ng/mL, $p < 0.001$).

4. DISCUSSION

In this study, cross-sex HT resulted in the reversal of sexual dimorphism in body mass. Significant increases in BMI were noted in every follow-up visit compared with baseline in trans masculine individuals. This finding is in accordance with earlier studies in the trans masculine population,[4] and is supported by the fact that testosterone can directly increase the amount of muscle in both women and men.[8] A previous study did not report differences in BMI and blood pressure in postmenopausal cisgender individuals under estrogen therapy.[9] Other study did not identify effects of estrogen therapy on BMI and blood pressure in the trans feminine population,[10] similar to our findings. Testosterone therapy in the testosterone-deficient cisgender population reduced blood pressure in a recent study.[11] Some studies in transgender patients have detected modest increases or clinically irrelevant blood pressure changes with testosterone therapy.[4] A recent study in 2018 revealed that changes in systolic blood pressure could be explained by changes in resistin levels in trans masculine individuals.[12] However, a study in 2008 did not identify effects of estrogen therapy on BMI or blood pressure in the trans feminine population.[10] No statistically significant changes in blood pressure over a short period of time after initiating treatment in both the trans masculine and trans feminine populations were observed.

Estrogen therapy in cisgender postmenopausal patients decreases total cholesterol and LDL-c.[9,13] The Women's Health Initiative HT trials also mentioned postmenopausal patients who received estrogen therapy would also restore their cardiovascular protection.[14] However, whether the fasting lipid profile changes after cross-sex HT in transgender women is still ambiguous.[15] In our trans masculine individuals, HDL-c decreased at all time periods, although it remained stable in the trans feminine population. The serum levels of LDL-c increased in the trans masculine population 7–12 months after therapy, yet remained stable in the trans feminine population. Substantial alterations in lipid parameters were observed in both sexes during treatment in our study. The total cholesterol levels remained stable in trans masculine patients, primarily due to reduced HDL-c and increased LDL-c in this study. All of these findings are in accordance with previous studies and the gender dimorphism of lipoproteins in the general population.[16,17] The clinical effects of the observed changes in LDL-c and HDL-c levels in the trans masculine population remain uncertain. To date, data regarding cardiovascular outcomes in trans masculine transgender individuals are insufficient.[18] Levels of serum triglycerides remained

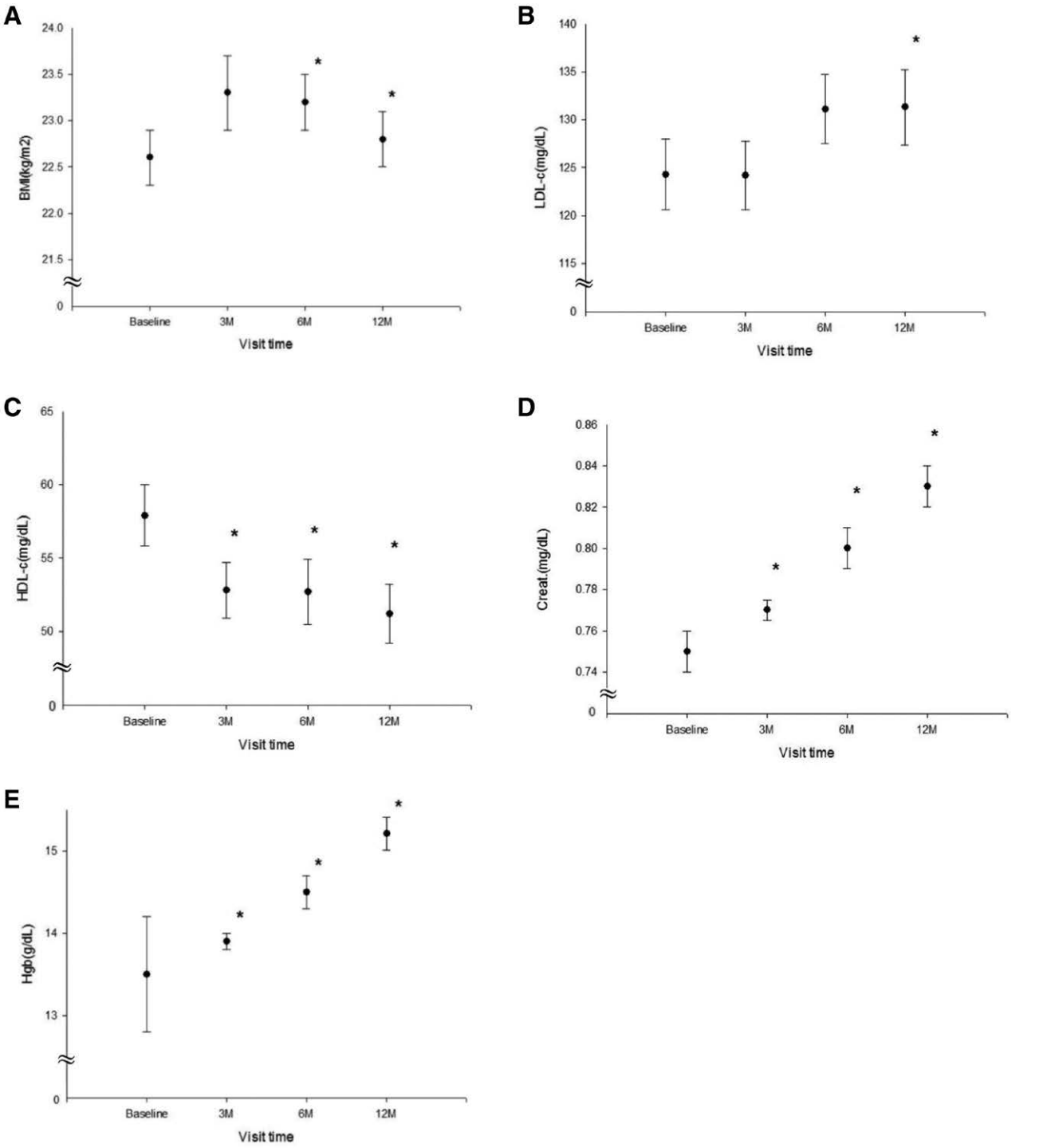

Fig. 1 Error bar showing the means and standard error of (A) body mass index (BMI), (B) low-density lipoprotein cholesterol (LDL-c), (C) high-density lipoprotein cholesterol (HDL-c), (D) creatinine (Creat.), (E) hemoglobin (Hgb) in female-to-male subjects at baseline, 3M (3–6M), 6M (7–12M), and 12M (13–24M). *$p < 0.05$ using paired t test comparing to baseline visiting data.

stable in both the trans masculine and trans feminine populations in our study. However, most studies have shown increased triglyceride levels in both trans masculine and trans feminine individuals.[16,19]

Trans masculine patients treated with testosterone therapy develop the physical characteristics to align with the patients' gender identity, including a masculine body fat distribution and declined renal function. Changes in body fat distribution may also alter lipid profile and metabolism.[20,21] Long-term testosterone therapy for trans men increases visceral adipose tissue while reducing subcutaneous fat mass.[22] Due to the hyperlipolytic properties of the visceral adipose tissue, it releases large amount of free fatty acids to the liver.[23] The influx of free fatty acids to the liver leads to very low-density lipoprotein-triglyceride (VLDL-TG) secretion. Hypertriglyceridemia is associated with higher LDL-c and lower HDL-c concentrations due to the

Table 3

Longitudinal metabolic data for trans feminine subjects

	V0 (baseline) n = 45	V1 (3–6M) n = 45	*p*	V2 (6–12M) n = 29	*p*	V3 (12–24M) n = 26	*p*
BW (kg)	59.4 ± 1.4	60.1 ± 1.8	0.373	61.9 ± 2.0	0.163	59.8 ± 1.7	0.519
BMI (kg/m^2)	20.6 ± 0.4	20.6 ± 0.5	0.985	21.7 ± 0.6	0.191	21.0 ± 0.5	0.339
sBP (mmHg)	122.5 ± 2.7	123.2 ± 2.4	0.675	123.0 ± 2.1	0.852	118.8 ± 2.0	0.328
dBP (mmHg)	74.1 ± 1.7	74.3 ± 1.6	1.000	73.9 ± 1.7	0.922	71.6 ± 1.2	0.178
TC (mg/dL)	165.1 ± 4.8	163.6 ± 4.3	0.348	163.6 ± 6.3	0.620	166.3 ± 6.9	0.752
HDL-c (mg/dL)	63.9 ± 2.6	64.4 ± 2.3	0.699	64.0 ± 2.8	0.728	65.0 ± 3.0	1.000
LDL-c (mg/dL)	104.2 ± 3.2	100.8 ± 3.5	0.050	99.3 ± 5.8	0.369	100.4 ± 6.3	0.638
TG (mg/dL)	85.4 ± 7.7	87.5 ± 6.7	0.736	90.1 ± 8.5	0.358	89.0 ± 7.4	0.598
Glucose (mg/dL)	91.6 ± 1.2	91.0 ± 1.1	0.531	91.6 ± 1.5	0.928	91.9 ± 1.5	0.593
Insulin (μU/mL)	6.6 ± 0.8	6.5 ± 0.6	0.808	6.1 ± 0.5	0.802	5.9 ± 0.8	0.920
HbA1c (%)	5.2 ± 0.0	5.4 ± 0.0	0.017	5.2 ± 0.0	0.720	5.2 ± 0.0	1.000
HOMA-IR	1.55 ± 0.19	1.47 ± 0.14	0.650	1.30 ± 0.11	0.670	1.36 ± 0.12	0.883
WBC (10^3/μL)	6940 ± 254	7091 ± 288	0.303	6904 ± 373	0.482	7095 ± 390	0.429
Hgb (g/dL)	14.0 ± 0.1	13.7 ± 0.1	0.143	13.5 ± 0.1	0.008	13.5 ± 0.1	0.024
Hct (%)	41.5 ± 0.4	41.2 ± 0.4	0.355	40.3 ± 0.3	0.040	40.7 ± 0.5	0.142
ALT (U/L)	21 ± 4	21 ± 4	0.750	21 ± 5	0.440	21 ± 5	0.310
Creat. (mg/dL)	0.82 ± 0.01	0.79 ± 0.14	<0.001	0.78 ± 0.01	0.001	0.79 ± 0.01	0.016
eGFR (mL/min/1.73 m^2)	115.0 ± 2.6	117.8 ± 2.2	0.064	118.4 ± 2.9	0.040	116.3 ± 3.4	0.248

Data are expressed as numbers and percentage for noncontinuous variables and mean ± SD for continuous variables.

p value using paired t test comparing to baseline visiting data.

ALT = alanine transaminase; BMI = body mass index; Creat. = creatinine; dBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; Hct = hematocrit; HDL-c = high density lipoprotein cholesterol; Hgb = hemoglobin; HOMA-IR = homeostasis model assessment insulin resistance index; LDL-c = low density lipoprotein cholesterol; sBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; WBC = white blood count.

Table 4

Sex hormone levels in transgender subjects receiving cross-sex hormone therapy

	Baseline	V1 (3–6M)	*p*	V2 (6–12M)	*P*	V3 (12–24M)	*p*
Trans masculine							
Testosterone (ng/mL)	0.4 ± 0.0	8.9 ± 0.9	<0.001	7.9 ± 0.6	<0.001	8.0 ± 0.6	<0.001
E2 (pg/mL)	95.6 ± 14.4	66.3 ± 9.9	0.025	55.4 ± 5.0	0.009	49.5 ± 6.6	0.005
FSH (mIU/mL)	15.4 ± 4.8	11.1 ± 3.2	0.141	10.5 ± 2.8	0.128	12.1 ± 3.5	0.422
LH (mIU/mL)	11.0 ± 2.3	7.5 ± 1.7	0.017	7.0 ± 1.6	0.016	6.6 ± 1.9	0.048
Trans feminine							
Testosterone (ng/mL)	4.3 ± 0.6	1.5 ± 0.4	<0.001	1.1 ± 0.3	<0.001	1.0 ± 0.3	<0.001
E2 (pg/mL)	37.7 ± 5.1	54.9 ± 6.3	0.006	107.0 ± 35.2	0.056	120.5 ± 38.5	0.040
FSH (mIU/mL)	5.4 ± 1.6	1.8 ± 0.8	0.007	1.6 ± 0.8	0.005	2.8 ± 1.5	0.250
LH (mIU/mL)	4.1 ± 1.0	2.0 ± 0.5	0.006	1.6 ± 0.5	0.002	2.5 ± 1.2	0.215

Data are expressed as numbers and percentage for noncontinuous variables and mean ± SD for continuous variables.

p value using paired t test comparing to baseline visiting data.

E2 = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone.

transfer of cholesterol from HDL to VLDL, catalyzed by cholesteryl ester transfer protein.[24] Changes in the estrogen level in trans masculine patients may also be related to decreased renal function due to attenuated protective effects of estrogen. For trans feminine subjects, decreased creatinine was observed in our study. It may relate to the physiological mechanism of estrogen in the renal system. Estrogen and progesterone could modulate sodium and chloride reabsorption along the mammalian nephron and alter the physiological hydroelectrolyte balance. It may also implied that there is no difference between sex about the effects of estrogen, no matter it is innate or acquired.

Cross-sex HT resulted in a decrease in the markers of insulin resistance (HOMA-IR) in the trans masculine population, which may result from increased skeletal muscle caused by testosterone use. In addition, decreased HbA1c was also identified in the trans feminine individuals after the use of gender affirming HT for 3 months (p = 0.017). The administration of testosterone in HT for the trans masculine population is associated with the increases in hemoglobin and hematocrit.[25–28] We observed significant increases in hemoglobin and hematocrit at all follow-up examinations. These changes reflected a shift in these populations, but they were still within the normal cisgender range. For the trans feminine population, there were no changes in hemogram results after cross-sex HT.

There are some limitations in the present study that should be considered. First, as this is a retrospective review, data were restricted by availability and varied by patients. Second, the study lacked sufficient power to compare the adverse effects of cross-sex HT to the general population. The individuals in our study were relatively young and the risks could be different compared to the general population on gender affirming HT. Third, the length of time between follow-up visits after the initiation of HT was different. Some individuals had longer intervals between visits than others. Individuals lost to follow up were not included though. Finally, the plasma levels of testosterone and estradiol were in the normal physiologic range for the affirmed gender based on clinical guidelines.[6] However, even we adjusted the dose used, the timing of achieving the normal physiologic range was still different in each case. Thus, it might be difficult to show the efficacy of the HT.

In conclusion, the use of gender-affirming HT increased BMI, LDL-c, and hemoglobin in trans masculine transgender individuals and could associate with increased risk of cardiovascular disease in Taiwan.

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