Original Research Article

SAGE Open Medicine

SAGE Open Medicine
Volume 9: 1–9

DOI: 10.1177/20503121211051546
journals.sagepub.com/home/smo
SAGE

Effects of testosterone treatment on transgender males: A single-institution study

Sira Korpaisarn[1], Dararat Chiewchalermsri[1], Jiraporn Arunakul[2], Orawee Chinthakanan[3], Preamrudee Poomthavorn[2] and Chutintorn Sriphrapradang[1]

Abstract

Objectives: Data regarding gender-affirming hormone therapy in the Asian population are sparse. We aimed to evaluate the efficacy and safety of testosterone therapy in transgender men.

Methods: A retrospective study chart review was conducted in a single university-based transgender clinic. Transgender men aged >18 years who newly started testosterone therapy during January 2015 to October 2019 were recruited. Physical changes, laboratory results, and adverse events, including cancer, thromboembolism, cardiovascular events, and death after masculinizing hormone therapy, were evaluated.

Results: A total of 39 transgender men (mean age: 27.8 ± 6.0 years) were included. All individuals were treated with intramuscular testosterone injection with a mean follow-up of 25.2 ± 12.9 months. The most common maintenance regimen was testosterone enanthate 250 mg every 4 weeks. Masculinizing effects developed in all transgender men. There were no changes in body weight, and systolic and diastolic blood pressure. Hematocrit levels were 12% significantly increased from 39.9 ± 3.3% to 48.9 ± 2% ($p < 0.001$). Ten individuals (25.6%) had hematocrit >50%. Significant changes were found in decreased fasting plasma glucose, increased creatinine, and increased uric acid levels. A non-significantly increased alanine aminotransferase, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol were observed. No thromboembolism, cancer, stroke, or coronary artery disease occurred.

Conclusions: Gender-affirming hormone therapy is an effective and safe short-term treatment in Thai transgender men. Apart from the standard recommendation, uric acid, plasma glucose, and creatinine level evaluation before and during masculinizing hormone therapy are rational practices. An intramuscular testosterone enanthate 250 mg every 4 weeks is an alternative masculinizing regimen with decent efficacy and safety profile.

Keywords

Transgender persons, gender-affirming hormone, testosterone, gender dysphoria

Date received: 29 July 2021; accepted: 16 September 2021

Introduction

Transgender people are individuals whose gender identity or gender expression differs from what is typically associated with their sex designated at birth.[1] Transgender male (TM) refers to individuals designated female at birth but who expressed or identified themselves as men. Gender dysphoria occurs if their gender identity is incongruous with their assigned birth sex, resulting in emotional and behavioral distress, which puts them at risk of mental health issues such as depression and anxiety disorders.[2,3] Transgender people with gender dysphoria often seek gender-affirming treatment to induce secondary sexual characteristics of their desired gender. The aim of gender-affirming hormone therapy (GHT) is to replace the exogenous sex hormone that matches

[1]Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[2]Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[3]Department of Obstetrics and Gynecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Corresponding author:
Chutintorn Sriphrapradang, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama 6 Road, Bangkok 10400, Thailand.
Email: chutins@gmail.com

their desired gender and reduce the endogenous sex hormone to suppress the secondary sexual characteristics of their assigned sex at birth.

Several studies demonstrated that GHT effectively induces secondary sexual characteristics, relieves gender dysphoria, and improves the quality of life.[4] These data additionally advocated the safety of GHT.[5,6] Testosterone is a mainstay hormonal therapy to achieve masculinizing effects and suppress female secondary sexual characteristics in TM. Masculinizing effects include acne, skin oiliness, deepening of the voice, increasing body and facial hair, increasing muscle mass, and cessation of menses in various durations after hormone initiation. Several preparations are available, including parenteral (intramuscular or subcutaneous), transdermal, or transbuccal. Dosing of testosterone should be adjusted to achieve serum testosterone levels within physiological cis-male ranges.[7,8] Erythrocytosis, sleep apnea, hypertension, weight gain, salt retention, lipid changes, and acne have been observed as common complications from excess testosterone therapy.[1] When adverse effects occur, either dosing of testosterone or injection interval needs to be adjusted, even if serum testosterone is within a target range. Therefore, testosterone should be continued, though there is currently no consensus regarding discontinuation age, to avoid hypogonadism symptoms and maintain the male sexual characteristics.

Although expansion in the transgender population has been observed, there is a paucity of information, especially regarding the efficacy and safety of GHT in Asians. Our study aimed to describe the physical changes and metabolic effects of testosterone therapy in TM. Our prespecified hypothesis is that the current masculinizing regimens using in Thai transgender men are effective with a similar safety profile as reported data.

Methods

Participants and study design

This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. It was approved by an institutional review board of the study site, and informed consent was exempted. This study was a retrospective observational study. Data from all TM visiting a transgender clinic of the study site were collected from the electronic medical records between January 2015 and October 2019. A power analysis for sample size calculation was not performed due to a limited number of transgender people visiting the clinic. TM older than 18 years who started GHT and followed up in the transgender clinic during the study period were included. Exclusion criteria were having already started GHT or not having started GHT despite treatment approval. Participants were initially evaluated by mental health providers for diagnosis of gender dysphoria. Then, all participants were referred to endocrinologists for GHT.

Hormonal therapy

All participants were treated with intramuscular testosterone. The dosing of testosterone was adjusted based on serum testosterone levels, clinical outcome, and adverse effects. Our transgender clinic applies the 2017 Endocrine Society Clinical Practice Guideline for the Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons.[1] However, the final decisions were based on several factors, including efficacy, side effects, cost, or patient preference. The recommended dosage is intramuscular testosterone enanthate 50–100 mg every week or 100–200 mg every 2 weeks. Since there is only one preparation of testosterone enanthate in Thailand (single-time use of 250 mg/1 ml per ampule), some TM were prescribed the testosterone every 3- to 4-week interval with a higher dose than the recommended regimen to minimize the medication costs. Otherwise, the remaining medication needs to be discarded due to safety purposes. According to the country's regulation where the study was performed, intramuscular medication needs to be administered by health care providers. TM could have testosterone administered at the study site or any accessible clinic.

The initial hormone regimens and maintenance regimens were recorded. According to the guidelines, the goal for serum testosterone at midway between injection is 400–700 ng/dL and any testosterone level in the normal physiologic range (320–1000 ng/dL).[1] All TM were encouraged to have testosterone measurements midway between injections. However, the actual timings of testosterone measurements depended on the individual's convenience.

Data collection and outcome measurement

Using the template form for monitoring GHT, baseline characteristics including race, age at GHT initiation, body weight, height, body mass index (BMI), as well as self-reported lifestyle factors such as alcohol drinking, smoking, and snoring were recorded. In addition, other comorbidities recorded in the electronic medical records were extracted. The initial laboratory data, including renal and hepatic function, hematocrit level, lipid profiles, fasting glucose, and sex hormone levels, were obtained. The self-reported physical changes, using a template form, including oily skin, acne, fat redistribution, increase muscle mass, cessation of menses, facial and body hair, scalp hair loss, and voice change, as well as laboratory parameters, were subsequently extracted from each follow-up visit every 3–6 months, up to 2 years after GHT initiation. In addition, other laboratory data as part of annual physicals were obtained, including uric acid levels. Finally, adverse events with regard to cancer, thromboembolism, cardiovascular events, and death were recorded.

Statistical analysis

Descriptive data are expressed as counts (%) for categorical variables and mean with ± SD for numerical variables. Only

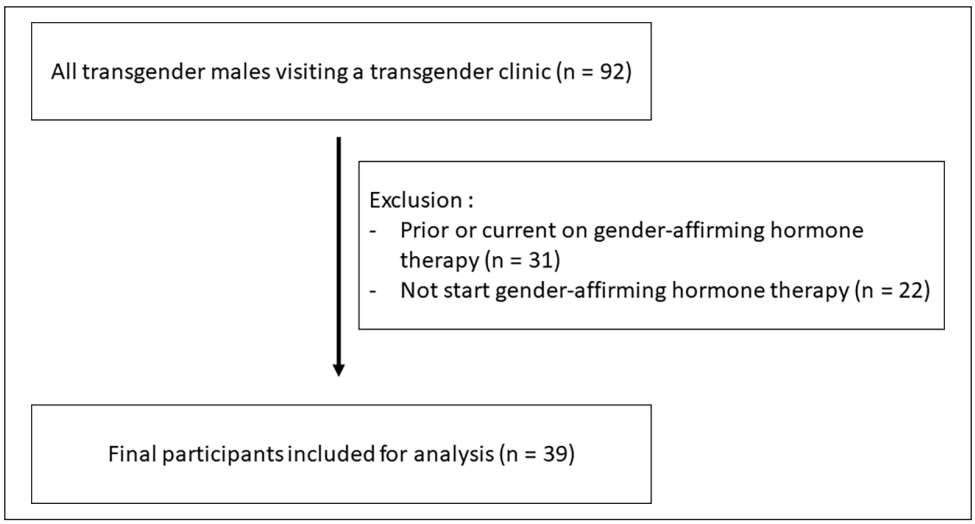

Figure 1. Study flow chart.

cases in which data could be extracted from the medical records were analyzed for any missing values. Statistics of means were evaluated using the one-way analysis of variance (ANOVA) to compare data, and significance was set at $p < 0.05$. Data were analyzed using SPSS statistical software version 18 (SPSS Inc, Chicago, IL).

Results

Baseline characteristics

The electronic medical records of 92 TM were reviewed. Fifty-three TM were excluded (22 TM did not start GHT and 31 TM priorly or currently received GHT). A final 39 participants were included for analysis (Figure 1). Baseline characteristics of the study population are summarized in Table 1. The mean age at the start of hormone therapy was 27.8 ± 6.0 years. Most participants are Thai (97.4%), with a mean BMI of 23.6 ± 4.5 kg/m^2. The prevalence of comorbidities and lifestyle factors is shown in Table 1.

All individuals were treated with intramuscular testosterone enanthate injection. One TM started with testosterone undecanoate, and then subsequently switched to testosterone enanthate due to a financial issue. A significant variety of hormonal regimens were used in the present cohort, including 8 initial hormone regimens and 12 maintenance regimens (Table 2). The most common initial regimen was testosterone enanthate 50 mg every 2 weeks (40.5%). The most common maintenance regimen was testosterone enanthate 250 mg every 4 weeks (23%), followed by 100 mg every 2 weeks (18%). After administration of GHT, serum testosterone levels significantly increased from the baseline ($p < 0.05$). Most of the participants achieved serum testosterone levels within the reference range. Fifteen TM (38%) had serum testosterone levels exceed the upper limit of reference values (>1000 ng/dL).

Table 1. Baseline characteristics of the study population.

	Mean	Max	Min	SD
Age (years)	27.8	44.0	19.0	6.0
Height (cm)	159.6	170.0	150.9	4.2
Weight (kg)	60.4	90.3	37.7	12.6
BMI (kg/m^2)	23.6	35.8	15.2	4.5
		N (total = 39)		
Thai		38		
Comorbidities				
• Diabetes mellitus		0		
• Hypertension		1		
• Aortic root dilatation		1		
• Alcoholic hepatitis		1		
• Chronic myelogenous leukemia survivor		1		
• Thyroid diseases		3		
• Active cancer		0		
Personal history				
• Alcohol drinking		13		
• Smoking		11		
Clinical manifestation of sleep apnea				
• Observed apnea		1		
• Snoring		8		
• Daytime somnolence		2		

BMI: body mass index.

Physical changes

Masculinizing effects developed in all TM (Figure 2). Skin oiliness (Figure 2(a)), acne (Figure 2(b)), cessation of menses (Figure 2(c)), increased facial hair (Figure 2(d)), and deepening of the voice (Figure 2(e)) within the first 6 months, and increased muscle mass (Figure 2(f)) and body hair (Figure 2(g)) at 6–12 months after testosterone treatment. However, few TM developed fat redistribution (Figure 2(h))

Table 2. Testosterone level, hematocrit, and the number of patients with polycythemia in various maintenance testosterone dosages.

Testosterone dose and interval	*N* (%)	Testosterone level at midway, ng/dL[a]	Trough testosterone level, ng/dL[a]	Hematocrit level, %[b]	Number of patients with polycythemia (%)
250 mg every 4 weeks	9 (23.1)	795 (39–>1862)	249 (182–326)	47.4 (41.7–52.0)	2 (20)
250 mg every 3 weeks	1 (2.6)	1369 (1222–1515)	N/A	48.7 (48.6–48.8)	0
250 mg every 2 weeks	2 (5.1)	937 (809–1082)	427 (222–631)	48.6 (46.4–52.7)	1 (10)
200 mg every 4 weeks	3 (7.7)	696 (300–931)	361 (270–594)	47.31 (43.2–50.9)	1 (10)
200 mg every 3 weeks	1 (2.6)	765 (446–864)	N/A	46.9 (44.9–48.2)	0
200 mg every 2 weeks	1 (2.6)	>1862	812 (812–812)	47.5 (46.7–48.0)	0
150 mg every 3 weeks	2 (5.1)	N/A	194 (97–682)	48.6 (47.8–49.4)	0
150 mg every 2 weeks	5 (12.8)	1479 (758–1703)	642 (148–1481)	46.7 (38.9–51.8)	2 (20)
125 mg every 2 weeks	6 (15.4)	942 (370–>1862)	465 (215–1481)	46.0 (41.0–49.6)	0
100 mg every 2 weeks	7 (17.9)	811 (545–1202)	662 (335–677)	47.5 (42.3–53.4)	4 (40)
75 mg every 2 weeks	1 (2.6)	647 (579–1065)	N/A	45.3 (43.1–48.1)	0
50 mg every 2 weeks	1 (2.6)	972 (972–972)	N/A	46.4 (45.9–46.8)	0

[a]The upper limit of detectable testosterone level is 1862 ng/dL. Data are presented as the median with range.
[b]Data are presented as the mean with range.

and scalp hair loss (Figure 2(i)) during 24-month follow-up. At 6 months, acne presented in 81% of TM, deepening of voice in 72%, skin oiliness in 61%, increased facial hair in 56%, cessation of menses in 53%, body hair in 42%, increased muscle mass presented in 33%, fat redistribution in 14%, and scalp hair loss in 11%. At 12 months, acne presented in all TM, deepening of voice in 97%, skin oiliness in 75%, increased facial hair in 75%, cessation of menses in 78%, body hair in 47%, increased muscle mass presented in 53%, fat redistribution in 19%, and scalp hair loss in 9.4%. At 24 months, acne and deepening of voice presented in all TM, skin oiliness in 77%, increased facial hair in 94%, cessation of menses in 79%, body hair in 77%, increased muscle mass in 65%, fat redistribution in 24%, and scalp hair loss in 29%. There were no significant changes in body weight, and systolic and diastolic blood pressure.

Metabolic changes

Hematocrit levels were 12% significantly increased from baseline ($39.9 \pm 3.3\%$–$48.9 \pm 1.9\%$; $p < 0.001$) (Figure 3(a)). Ten individuals (25.6%) had erythrocytosis (hematocrit >50%) without symptoms. The prevalence of erythrocytosis for each testosterone regimen is shown in Table 2. Hematocrit levels returned to normal with dose adjustment. Significant changes were observed in increased creatinine (0.68 ± 0.11–0.89 ± 0.01 mg/dL; $p = 0.007$) (Figure 3(b)), decreased fasting plasma glucose (91.8 ± 9.6–82.8 ± 8.5 mg/dL; $p = 0.02$) (Figure 3(c)), and increased uric acid levels (5.1 ± 1.0–6.7 ± 3.4 mg/dL; $p = 0.03$) (Figure 3(d)). There was a non-significant increase in aspartate aminotransferase (AST) (26.0 ± 24.3–28.2 ± 10.0 U/L; $p = 0.7$), alanine aminotransferase (ALT) levels (20.6 ± 20.6–31.5 ± 19.8 U/L; $p = 0.09$), low-density lipoprotein cholesterol (LDL-c) levels (131.7 ± 36.8–157.5 ± 32.4 mg/dL; $p = 0.19$), and a non-significant decrease in high-density lipoprotein cholesterol (HDL-c) levels (57.2 ± 13.1–51.6 ± 7.7 mg/dL; $p = 0.2$). Other parameters did not change during observation. Metabolic changes of TM are summarized in Table 3.

Adverse drug reactions

During the follow-up period, no participants reported severe adverse events (e.g. thromboembolism, hormone-related cancer, stroke, coronary artery disease, or death).

Discussion

GHT for transgender people is effective in inducing secondary sexual characteristics aligning with the desired

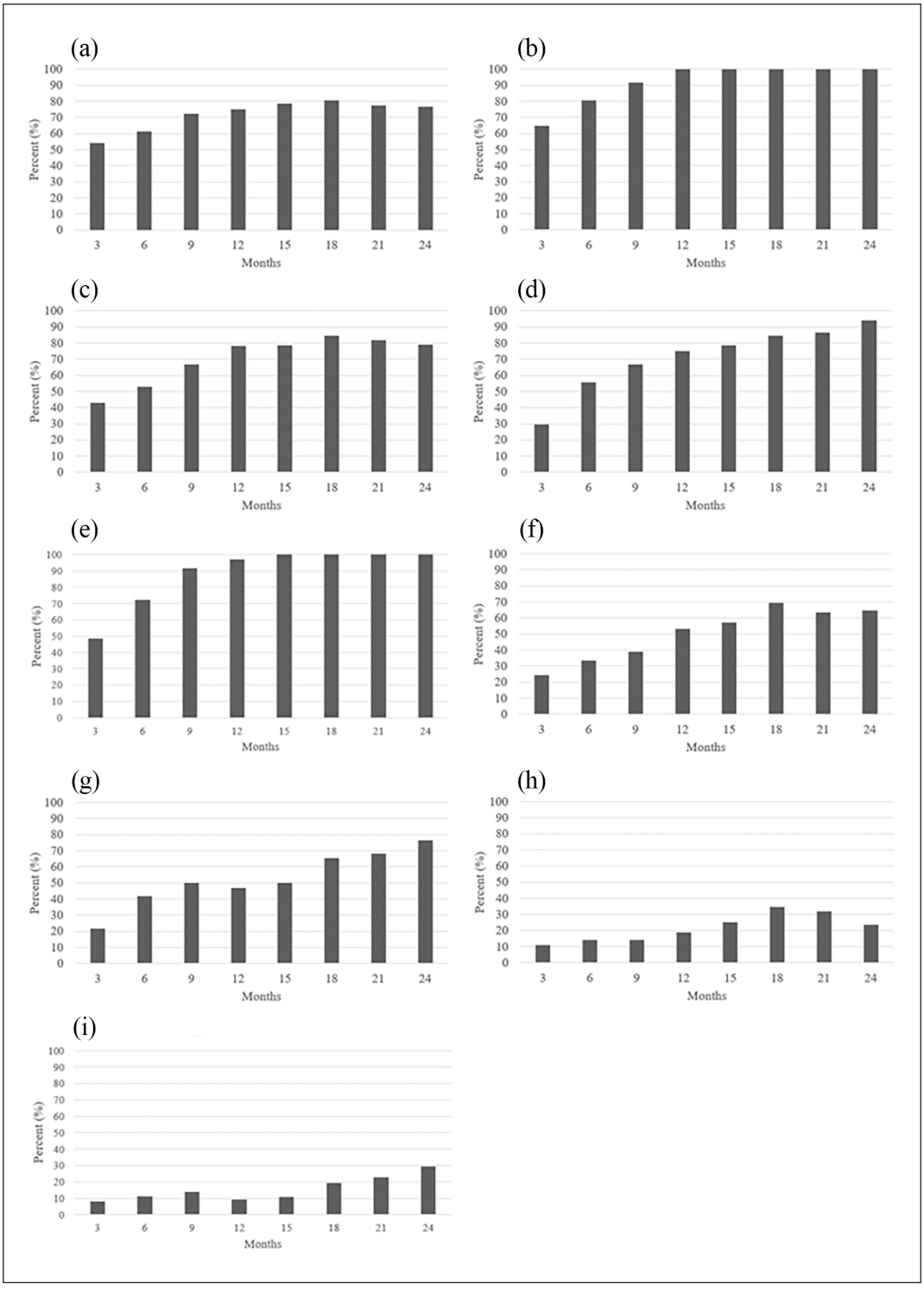

Figure 2. The prevalence of masculinizing physical changes from each follow-up visit during 24 months of testosterone therapy. (a) Oily skin, (b) acne, (c) amenorrhea, (d) facial hair, (e) voice change, (f) increased muscle mass, (g) body hair, (h) fat redistribution, and (i) scalp hair loss.

gender. Several published guidelines have recommended the appropriate hormone regimen.[1,9] However, most data supporting these guidelines are from the Caucasian population. To our knowledge, the studies of the testosterone effect among Asian TM are sparse. A very recent study from Japan demonstrated a 1-year efficacy and safety of intramuscular testosterone enanthate (250 mg intramuscular every 2 weeks) in TM.[10] Another Japanese study

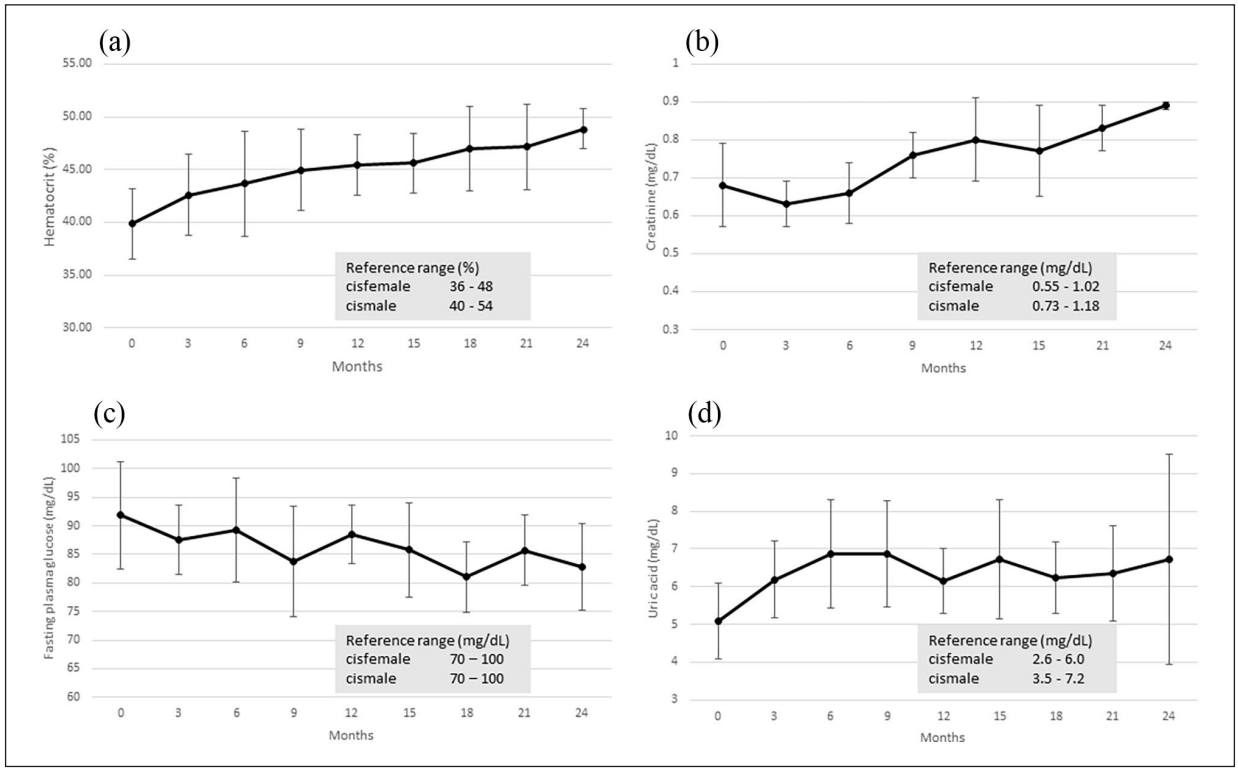

Figure 3. The changes of biochemistry data during 24 months of testosterone therapy. (a) Hematocrit, (b) creatinine, (c) fasting plasma glucose, and (d) uric acid. Data are presented as mean ± standard deviation (SD). At 24 months, all four parameters are significantly changed from baseline ($p < 0.05$).

Table 3. Laboratory data during 24 month of testosterone therapy in transgender men.

	At baseline	*n*	24 months	*n*	*p* value*
Hematocrit (%)	39.9 ± 3.4	39	48.9 ± 2.0	14	<0.001
MCV (fL)	83.7 ± 9.9	39	88.3 ± 6.1	13	0.3
WBC count (per cum)	7356 ± 1726.3	39	6879 ± 1453.1	13	0.8
Creatinine (mg/dL)	0.68 ± 0.11	34	0.89 ± 0.01	2	0.007
Aspartate aminotransferase (U/L)	26.0 ± 24.3	37	28.2 ± 10.0	9	0.7
Alanine aminotransferase (U/L)	20.6 ± 20.6	37	31.5 ± 19.8	10	0.09
Fasting plasma glucose (mg/dL)	91.8 ± 9.6	29	82.8 ± 8.5	5	0.02
Cholesterol (mg/dL)	207.4 ± 40.8	37	221.3 ± 33.3	8	0.7
Triglyceride (mg/dL)	86.4 ± 44.4	35	123.5 ± 41.9	8	0.7
LDL-c (mg/dL)	131.7 ± 36.8	34	157.5 ± 32.4	8	0.19
HDL-c (mg/dL)	57.2 ± 13.1	34	51.6 ± 7.7	8	0.2
Uric acid (mg/dL)	5.1 ± 1.0	19	6.7 ± 3.4	3	0.03

MCV: mean corpuscular volume; WBC: white blood cell; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; ANOVA: analysis of variance.
*p value compared between the group means using the one-way ANOVA. The significance was set at $p < 0.05$.

proved the dose-dependent masculinizing efficacy from variable doses of intramuscular testosterone enanthate (250 mg every 2 weeks, 250 mg every 3 weeks, and 125 mg every 2 weeks) with no significant side effects.[11] This study confirms the masculinizing effect of testosterone therapy on TM. In accordance with the Endocrine Society Clinical Practice Guideline,[1] our study showed that skin oiliness, acne, voice change, and cessation of menses occurred during the first 6 months of testosterone therapy. Later effects, including increased muscle mass and body hair growth, occurred at 6–12 months. Few participants documented scalp hair loss or fat redistribution. Male

pattern hair loss usually occurs within a few years after GHT initiation.[12] A prospective study in 20 TM showed that only one TM developed male pattern hair loss within 1 year after testosterone treatment.[13] Concurrently, the 1-year incidence was 17% in another study of 53 TM.[5] Results from most studies showed increased muscle mass in the first 1–2 years of testosterone therapy, but the BMI change varied.[5,14] In our study, there was no significant change in BMI. In accordance with published Asian studies, the use of GHT in TM is safe.[15,16] Neither serious adverse event nor death was reported.

Several maintenance testosterone doses were utilized in this cohort. Most providers started with low-dose testosterone, of which the most common regimen was 50 mg every 2 weeks, then subsequent titration to the maintenance dose over 3–6 months. Testosterone enanthate 250 mg every 4 weeks was the most common maintenance regimen in this study. This dose is higher than the recommended dose from the 2017 Endocrine Society guideline, which recommends intramuscular testosterone enanthate either 50–100 mg every week or 100–200 mg every 2 weeks.[1] However, it is effective in inducing masculinizing effects without significant adverse effects. The main concerning side effect of higher dose testosterone is erythrocytosis. The prevalence of erythrocytosis in testosterone enanthate 250 mg every 4 weeks is comparable to other testosterone regimens in this cohort. Since there is only one preparation of testosterone enanthate in Thailand, 250 mg in a single-use 1-ml ampule, many physicians prescribe 250 mg, the whole ampule, every 4 weeks to minimize cost. Otherwise, the remaining medication would be wasted. Moreover, many TM complain of painful testosterone injections. Therefore, being given less frequent injections with decent efficacy and safety, testosterone enanthate 250 mg every 4 weeks is an alternative regimen, especially in a source-limiting country. However, a long-term study evaluating the safety of this regimen is required.

Testosterone therapy was significantly associated with a 12% relative increase in hematocrit levels from the baseline with a 9% absolute increment. These results are comparable with the previous data. A recent systematic review of seven studies demonstrated that the relative increase in hematocrit levels ranged from 4.4% to 17.6% from baseline.[17] All included studies were conducted in Europe, but one was from the United States. A multicenter prospective cohort study in 192 European hormone-naive TM showed an absolute 4.9% rising in hematocrit at 12 months of follow-up, with the most pronounced increase during the first 3 months.[18] This is nearly a 12% relative increase from the baseline, equivalent to this study. This study revealed that testosterone ester (a mixture of four testosterone esters with a dose of 250 mg every 2 weeks) carried the highest risk for erythrocytosis. In contrast, testosterone undecanoate had the lowest risk, even compared with transdermal testosterone. However, a randomized controlled trial of 56 TM showed no significant difference in hematocrit rising between testosterone enanthate, testosterone undecanoate, and transdermal testosterone. This study revealed a trend that the transdermal route might result in the lowest magnitude of hematocrit rising.[19] Erythrocytosis, defined by hematocrit $>50\%$, occurred in 26%. A prompt adjustment of testosterone dosage or interval solved all erythrocytosis.

The 2017 Endocrine Society guideline does not include uric acid as part of the recommended screening at baseline before GHT or monitoring during GHT.[1] This study revealed a significant increase in uric acid levels, but there was no clinical significance. A prospective cohort of 47 TM found that the uric acid increased significantly, and the fractional excretion of uric acid significantly fell from the baseline.[20] Two studies from Japan demonstrated the same concept of increased uric acid with testosterone therapy in TM.[10,21] This effect was dose dependent. Several mechanisms have been proposed. The increase in uric acid levels may result from reducing estrogen levels and subsequently decreasing urinary uric acid excretion. The other mechanism is increased muscle mass, a significant purine source, and consequently, uric acid production.[21] In this study, none of the TM had hyperuricemia at baseline, according to both cismale and cisfemale reference ranges. Whether TM with hyperuricemia at baseline upon starting testosterone will develop clinically significant hyperuricemia or not needs to be elucidated. Therefore, it is reasonable that hyperuricemia is evaluated prior to GHT as it could be exacerbated by masculinizing hormone therapy. In addition, our study showed an increase in creatinine level, possibly due to increased muscle mass.

The fasting plasma glucose was significantly decreased, with an absolute mean glucose reduction at 9 mg/dL. The studies of masculinizing hormone and glucose metabolism are controversial. A recent study revealed that masculinizing hormone increased insulin sensitivity and incretin response from oral glucose tolerance tests, while there was no change in fasting glucose.[22] A large multicenter randomized, double-blind placebo-controlled study in eight European countries concluded that testosterone therapy in hypogonadal men with type 2 diabetes significantly reduced the homeostatic model of insulin resistance (HOMA-IR) and significantly reduced HbA1c.[23] However, several studies showed worsened glycemic metabolism for transgender adults on GHT.[24] In this study, LDL-c levels and HDL-c levels tended to increase and decrease, respectively. The non-significant results are likely from the small sample size or the short-term follow-up. Several studies showed that testosterone treatment is associated with an adverse change in lipid profile.[25]

There were several limitations. First, the follow-up is short, and most included TM are young, while many

cardiovascular risks may become more pronounced in older TM and long-term use of GHT. Therefore, it is inconclusive with regard to long-term cardiovascular events or malignancy of GHT. Second, the sample sizes were small with missing data, given the nature of the retrospective study. In addition, since a power analysis for sample size calculation was not done, this may not provide enough power to demonstrate significant change. Third, there was no standard protocol for hormone initiation/titration and physical changes assessment. Finally, we do not have a control group to compare the results.

Conclusion

This study reveals the masculinizing hormone effect in the Asian TM population, in which information is sparse. The hematocrit, creatinine, and uric levels were significantly increased, while plasma glucose was significantly decreased after 2 years of testosterone therapy. In the short term, our study demonstrated that GHT was effective and safe for TM. However, several metabolic abnormalities, for example, hyperuricemia, high ALT, and low HDL-c, were observed. The intramuscular testosterone enanthate 250 mg every 4 weeks is an alternative masculinizing regimen with decent efficacy and safety profile.

Acknowledgements

We would like to thank Ms. Sam Ormond for her assistance in proofreading this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from a Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (APPROVAL NUMBER/ MURA2021/426).

Informed consent

Informed consent was not sought for this study because of the retrospective chart review nature of the study.

ORCID iDs

Sira Korpaisarn https://orcid.org/0000-0002-3324-1906
Chutintorn Sriphrapradang https://orcid.org/0000-0001-8294-8601

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