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Original Article

Hypogonadism among HIV-positive men who have sex with men in Taiwan: Prevalence and associated factors

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KEYWORDS
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Abstract *Background:* Male hypogonadism is not uncommon in people with HIV (PWH), with estimated prevalence ranging from 9% to 16%. Existing data are limited on the serum testosterone levels in PWH in Asian populations.
Methods: We enrolled HIV-positive men who have sex with men (MSM) and had been on stable antiretroviral therapy and MSM without HIV between February 2021 and November 2022. Serum free testosterone levels, sex hormone-binding globulins and other associated hormones were measured. Multiple linear regression analysis was performed to assess the association between serum free testosterone levels and clinical variables collected.

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Pre-exposure prophylaxis;
Quality of life

Results: A total of 447 MSM with HIV and 124 MSM without HIV were enrolled. Compared with MSM without HIV, MSM with HIV had a higher age (median, 41 versus 29.5 years) and prevalence of symptomatic hypogonadism (8.3% versus 1.6%). Among MSM who were aged <35 years, there were no significant differences in the serum free testosterone levels and prevalences of hypogonadism between the two groups. In multiple linear regression analysis, serum free testosterone level significantly decreased with advanced age (a decrease of 1.14 pg/mL per 1-year increase) and a higher body-mass index (BMI) (a decrease of 1.07 pg/mL per 1-kg/m^2 increase), but was not associated with HIV serostatus.
Conclusion: We found that MSM with HIV had a higher prevalence of symptomatic hypogonadism than MSM without HIV in Taiwan, which could be attributed to age difference. Serum free testosterone levels were negatively correlated with age and BMI, but did not show a significant correlation with HIV serostatus.

Introduction

Early diagnosis of HIV infection and initiation of combination antiretroviral therapy (ART) have resulted in improved survival and a higher rate of retention in care among people with HIV (PWH) in Taiwan.[1,2] Recent studies have increasingly focused on the quality of life among PWH, with endocrine issues emerging as an intriguing research topic.[3] Hypogonadism is a well-documented but under-diagnosed health problem among PWH. Early epidemiological studies revealed a high prevalence of hypogonadism of around 30%—50%, especially among those with AIDS-related wasting syndrome.[4–7] Direct viral effects, ART, chronic inflammation, co-infections and metabolic derangement have all been implicated in the pathogenesis of hypogonadism among PWH.[8] Clinical manifestations of adult male hypogonadism include decreased libido, erectile dysfunction, low bone mass, decreased muscle strength, reduced lean body mass, depression, and metabolic syndrome.[9] Studies regarding androgen deficiency in PWH showed loss of lean body and muscle mass, deterioration in exercise functional capacity, frailty, and poor health status.[6,10,11] The diagnosis of male hypogonadism requires the presence of symptoms and signs of testosterone deficiency and low serum testosterone levels.[9] The Androgen Deficiency in Aging Men (ADAM) questionnaire, a widely used tool for screening symptoms of androgen deficiency, has been validated in the Chinese population.[12]

In the era of combination ART with high rates of viral suppression among PWH who are engaged in care, the prevalence of hypogonadism has significantly decreased, but remains not uncommon among PWH. A cross-sectional study in Italy reported an estimated prevalence of biochemical hypogonadism of 16%, using a serum total testosterone cut-off value of 300 ng/dL.[13] In the Multicenter AIDS Cohort Study, the prevalences of biochemical hypogonadism were similar between HIV-positive (9.3%) and HIV-negative (7.2%) groups.[14] However, the prevalence increased substantially to 24% in the HIV-positive group when men on testosterone replacement therapy were included.[14] A more recent, albeit smaller study, reported a prevalence of hypogonadism of 12.4% among PWH, twice the rate reported in the general population,[15] though a longitudinal study revealed that testosterone levels in PWH decreased with age at a rate comparable to that observed in the general population.[16]

It is important to note several potential pitfalls in previous studies regarding the prevalence of hypogonadism in PWH. First, many studies used total testosterone levels with a cut-off value of 10.4 nmol/L (300 ng/dL). However, HIV infection is known to increase the levels of sex-hormone-binding globulin (SHBG) and therefore, serum free testosterone levels may be a better indicator of androgen deficiency among PWH.[8,14,15] Guidelines and recent expert panels have recommended the measurement of free testosterone in PWH, with a cut-off value of 220 pmol/L (63.5 pg/mL) of serum free testosterone level to define hypogonadism.[8,9] Second, because serum testosterone levels exhibit diurnal variation, blood samples should be obtained in the morning and during a fasting state.[9] Inappropriate timing of blood sampling may lead to misinterpretation of low testosterone levels. Third, few studies recruited participants without HIV infection for comparisons, making it difficult to accurately compare testosterone levels between PWH and people without HIV.

Data on the serum testosterone levels in PWH in Asia are limited, with most research on hypogonadism conducted in Caucasian PWH. A Japanese study include 25 treatment-naïve PWH and found 52% had low free testosterone levels. However, data related to the symptoms of hypogonadism were not available.[17] In this study, we aimed to know the prevalence of low testosterone levels in men who have sex with men (MSM) who were PWH presenting with symptoms suggestive of hypogonadism and the association between HIV infection and hypogonadism and we also sought to explore the factors associated with serum free testosterone levels among PWH.

Methods

Study population

This was a single-center, cross-sectional study. Between February 2021 and November 2022, adult MSM and were on stable ART with a suppressed plasma HIV-1 RNA level (defined as plasma HIV-1 RNA <200 copies/ml)[18] were

enrolled at the infectious clinics of the National Taiwan University Hospital (NTUH) and NTUH Yunlin Branch. For comparisons, we also enrolled MSM without HIV infection who sought anonymous HIV testing services and those who participated in the government-funded program of pre-exposure prophylaxis (PrEP) against HIV. The exclusion criteria were people with obvious causes of hypogonadism such as known pituitary, adrenal or gonadal disorders that were unrelated to HIV infection, those who had undergone pituitary radiotherapy or systemic chemotherapy, those with acute illnesses, and those receiving medications that could potentially interfere with hypothalamic–pituitary–gonadal axis. These included individuals using testosterone preparations without a well-documented diagnosis of hypogonadism, anabolic steroids, or opioids.

The information on the clinical characteristics, including age, height, weight, and comorbidities, was collected through individual self-administered questionnaire interview and review of electronic medical records. Current smokers were defined as individuals who had smoked at least 100 cigarettes during their lifetime and were still actively smoking at the time of study enrollment.[19] The presence of hypertension, diabetes or dyslipidemia was recorded through access to medical records and medication review. A history of viral hepatitis B and hepatitis C was defined based on the presence of hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV), respectively. For PWH, the duration of HIV infection, current CD4 count, and antiretroviral medications were recorded. The study was approved by NTUH Research Ethics Committee (protocol number 202010105RIND and 202109144RINA), and informed consent was obtained from all study participants. The study was also registered with ClinicalTrials.gov (identifier NCT04760574).

Diagnosis of hypogonadism

Blood samples were obtained in the early morning after an overnight fasting to test for serum total testosterone, SHBG, and gonadotropin hormones, which were measured by the Access Chemiluminescent Immunoassay (Beckman coulter, U.S.A.). Serum free testosterone was calculated by the Vermeulen equation.[8] Thyroid function and prolactin levels were also examined. Hyperprolactinemia was defined as serum prolactin levels >20 ng/mL. Overt hyperthyroidism was defined as elevated serum free T4 levels (>1.12 ng/dL) with suppressed TSH levels, and subclinical hypothyroidism was defined as elevated serum TSH levels (>5.33 uIU/mL), with normal serum free T4 levels (0.61–1.12 ng/dL). To evaluate the symptoms of androgen deficiency, the ADAM questionnaire was administered to all participants.[12] A positive response was defined as a "yes" answer to the question related to sexual dysfunction, or any three other questions in the questionnaire (Supplementary Table 1). Physical activity levels were assessed using the International Physical Activity Questionnaire-Short Form (IPAQ-SF), which categorizes activity levels as low, moderate, or high based on the amount of metabolic equivalent of task-minutes per week.[20]

Biochemical hypogonadism was defined as a morning fasting serum free testosterone level <63.5 pg/mL.[8] Primary hypogonadism was defined as low free testosterone levels and elevated luteinizing hormone (LH) levels (cut-off value, 8.62 mIU/mL). Secondary hypogonadism was defined as low serum free testosterone and subnormal or inappropriate normal serum LH levels. Subclinical hypogonadism was defined as normal serum free testosterone but elevated LH levels. Symptomatic hypogonadism was defined as a low serum free testosterone level combined with a positive screening result on the ADAM questionnaire interview. Participants with a low free testosterone level were advised to have a repeated testosterone measurement according to current guidelines.[9]

Statistical analysis

Descriptive statistics were used to analyze the demographic and clinical characteristics of the study participants. Continuous variables with a normal distribution were expressed as mean ± standard deviation, and unpaired t-tests were performed to compare means between HIV-positive and HIV-negative groups. Continuous variables without a normal distribution were expressed as median (interquartile range), and between-group comparisons were performed using the Mann–Whitney U test. Categorical variables were expressed as absolute numbers and percentages, and Chi-square tests were used to compare between-group differences. Significance was set at a two-tailed p-value of <0.05. Stepwise regression analysis was performed to assess the association between serum free testosterone levels and different variables, such as age, body-mass index (BMI), HIV serostatus, and comorbidities. Further subgroup analysis was performed within the HIV-positive group to assess additional associated factors, such as duration of HIV infection, CD4 count, and ART. Three-way analysis of variance (ANOVA) was performed to compare serum free testosterone levels across different physical activity levels. All data were analyzed using Stata/SE 17.0 for Windows (StataCorp LP, College Station, TX).

Results

Baseline characteristics

A total of 447 MSM with HIV and 124 MSM without HIV were enrolled in the study. The median age was significantly higher in MSM with HIV compared to MSM without HIV (41 versus 29.5 years) (Table 1). Compared with MSM without HIV, MSM with HIV had higher rates of HBsAg and anti-HCV positivity, hypertension, diabetes, and hyperlipidemia.

Among MSM with HIV, the median duration of HIV infection was 8.5 years, the median CD4 count was 482 cells/μL, and all had achieved viral suppression with plasma HIV-1 RNA <200 copies/ml. The majority of MSM with HIV (89.7%) were receiving a combination of two nucleoside reverse-transcriptase inhibitors (NRTIs) and an integrase inhibitor when the survey was conducted. The most frequently prescribed NRTI combinations were emtricitabine plus tenofovir alafenamide (89.9%), with a

Table 1 Baseline characteristics of MSM with or without HIV.

	MSM with HIV (N = 447)	MSM without HIV (N = 124)	*P*
Age (years)	41 [31–50]	29.5 [27–33]	<0.001
BMI (kg/m^2)	23.7 [21.7–26.1]	23.7 [21.5–25.1]	0.401
Current smoker	125 (28.0%)	25 (20.2%)	0.081
Current CD4 (cells/μL)	482 [357–681]		
Duration of HIV infection (years)	8.5 [5.1–13.3]		
Types of current anti-retroviral therapy			
Nucleoside reverse-transcriptase inhibitors	432 (96.6%)	40 (32.3%)	
Non-nucleoside reverse-transcriptase inhibitors	33 (7.4%)		
Integrase inhibitors	428 (95.8%)		
Protease inhibitors	1 (0.2%)		
Co-infections			
Hepatitis B surface antigen positivity	75 (16.8%)	10 (8.1%)	0.016
Anti-hepatitis C antibody positivity	72 (16.1%)	2 (1.6%)	<0.001
Systemic disease			
Hypertension	65 (14.5%)	3 (2.4%)	<0.001
Diabetes	22 (4.9%)	1 (0.8%)	0.039
Hyperlipidemia	270 (60.4%)	6 (4.8%)	<0.001
Chronic kidney disease	13 (2.9%)	0	0.058
Depression	17 (3.8%)	7 (5.7%)	0.366
Cardiovascular disease	16 (3.6%)	2 (1.6%)	0.267
Prolactin (ng/mL)	10.3 ± 0.3	10.6 ± 0.4	0.301
Hyperprolactinemia[a]	24 (5.5%)	6 (4.9%)	0.801
Overt hyperthyroidism[b]	1 (0.2%)	0	1.000
Subclinical hypothyroidism[c]	2 (0.5%)	4 (3.3%)	0.023

[a] Hyperprolactinemia is defined as serum prolactin levels >20 ng/mL.
[b] Overt hyperthyroidism is defined as elevated serum free T4 with suppressed TSH levels.
[c] Subclinical hypothyroidism is defined as serum TSH levels >5.33 uIU/mL, with normal serum free T4 levels.
Continuous variables with a normal distribution are presented as mean ± standard deviation. Continuous variables not normally distributed are presented as median (interquartile range). Categorical variables are presented as absolute numbers (percentages).
Abbreviations: BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; MSM, men who have sex with men.

small percentage of participants (3.6%) receiving lamivudine plus abacavir. Among the integrase inhibitors, bictegravir was the most commonly prescribed (55.7%), followed by cobicistat-boosted elvitegravir (30.4%) and dolutegravir (9.8%). Non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, was prescribed in 6.9% of MSM with HIV. In MSM without HIV, 40 participants (32.3%) were on oral PrEP with coformulated tenofovir disoproxil fumarate/emtricitabine. Following the assessment of thyroid function and prolactin levels, one participant (0.2%) had overt hyperthyroidism and two (0.5%) had subclinical hypothyroidism. Twenty-four participants (5.5%) had mild hyperprolactinemia, with levels exceeding 20 ng/mL but less than 50 ng/mL.

Serum androgen levels and prevalence of hypogonadism

The mean serum total testosterone levels in MSM with HIV and MSM without HIV were 4.63 ng/mL and 5.20 ng/mL, respectively, while the mean serum free testosterone levels were 98.8 pg/mL and 115.2 pg/mL, respectively (Table 2). The symptoms of hypogonadism, as screened by ADAM questionnaire, were relatively common in the participants, with 62.0% in MSM with HIV and 58.9% in MSM without HIV who reported positive symptoms of hypogonadism. There were no significant differences in serum free testosterone levels among the participants in different categories of physical activity levels according to IPAQ-SF (Supplementary Table 2).

The prevalence of biochemical hypogonadism, defined as a morning fasting free testosterone <63.5 pg/mL, was 11.6% in MSM with HIV and 1.6% in MSM without HIV. Similarly, the prevalence of symptomatic hypogonadism was higher in MSM with HIV (8.3%) compared to MSM without HIV (1.6%). Because of a significant difference in age between the two groups of participants, which might contribute to the difference of serum testosterone levels and the prevalence of hypogonadism observed, we conducted an additional analysis to compare serum testosterone levels and the prevalence of hypogonadism in participants aged <35 years in both groups (Table 3). In this subgroup analysis, both MSM with HIV and MSM without HIV had a similar median age (29 years, *p*-value 0.06). There were no significant differences in the serum free testosterone levels and prevalence of hypogonadism between two groups aged <35 years.

The most common form of biochemical hypogonadism among MSM with HIV was secondary hypogonadism, which was identified in 40 participants (8.9%). Subclinical hypogonadism and primary hypogonadism were identified in

Table 2 Serum testosterone levels and related symptoms across all age groups.

	MSM with HIV (N = 447)	MSM without HIV (N = 124)	*P*
Total testosterone (ng/mL)	4.63 ± 1.41	5.20 ± 1.54	<0.001
Free testosterone (pg/mL)	98.8 ± 31.2	115.2 ± 30.0	<0.001
SHBG (nmol/L)	33.4 ± 17.1	29.7 ± 15.9	0.033
Albumin (g/dL)	4.33 ± 0.34	4.50 ± 0.26	<0.001
Positive result on the ADAM questionnaire	276 (62.0%)	73 (58.9%)	0.524
Physical activity category according to IPAQ-SF			0.439
Low	58 (17.7%)	13 (13.1%)	
Moderate	153 (46.7%)	45 (45.5%)	
High	117 (35.7%)	41 (41.4)	
Prevalence of low free testosterone	52 (11.6%)	2 (1.6%)	0.001
Prevalence of symptomatic hypogonadism	37 (8.3%)	2 (1.6%)	0.009

Continuous variables with a normal distribution are presented as mean ± standard deviation. Categorical variables are presented as absolute numbers (percentages).
Abbreviations: ADAM, The Androgen Deficiency in Ageing Males; HIV, human immunodeficiency virus; IPAQ-SF, International Physical Activity Questionnaire - Short Form; SHBG, sex hormone-binding globulin.

Table 3 Serum testosterone levels and prevalence of hypogonadism in participants aged <35 years.

	MSM with HIV (N = 150)	MSM without HIV (N = 101)	*P*
Age (years)	29 [26–31]	29 [27–31]	0.057
BMI (kg/m^2)	21.1 [23.1–25.3]	21.3 [22.9–25.1]	0.776
Total testosterone (ng/mL)	4.95 ± 1.25	5.29 ± 1.53	0.050
Free testosterone (pg/mL)	114.4 ± 30.0	117.9 ± 30.5	0.368
SHBG (nmol/L)	27.8 ± 10.2	29.3 ± 15.0	0.340
Albumin (g/dL)	4.40 ± 0.30	4.54 ± 0.25	<0.001
Prevalence of low free testosterone	7 (4.7%)	1 (1.0%)	0.149
Prevalence of symptomatic hypogonadism	5 (3.3%)	1 (1.0%)	0.406

Continuous variables not normally distributed are presented as median (interquartile range). Continuous variables with a normal distribution are presented as mean ± standard deviation. Categorical variables are presented as absolute numbers (percentages).
Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; SHBG, sex hormone-binding globulin.

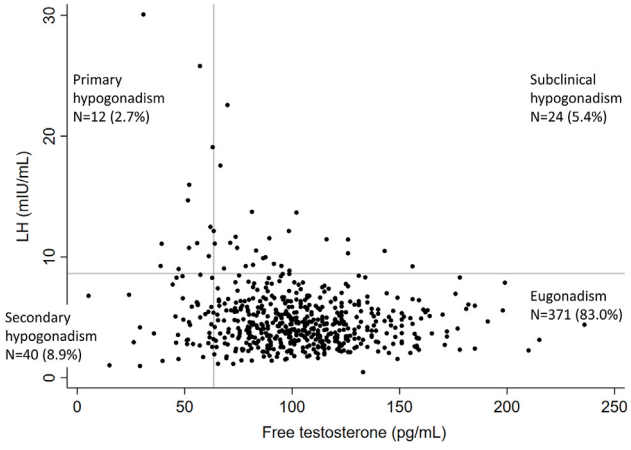

Figure 1. Gonadal status of 447 MSM with HIV according to serum free testosterone threshold of 63.5 pg/mL and LH threshold of 8.62 mIU/mL. LH, luteinizing hormone; MSM, men who have sex with men.

5.4% and 2.7% of MSM with HIV, respectively (Fig. 1). Compared with MSM with HIV who had normal serum free testosterone levels, those with biochemical hypogonadism were significantly older (median age, 48 versus 40 years, $P < 0.05$) and had a longer duration of HIV infection (median time 12.0 versus 8.3 years, $P < 0.05$) (Supplementary Table 2). Moreover, they had a lower proportion of NRTI use (86.5% versus 98.0%, $P < 0.05$) and a higher proportion of non-NRTI use (19.2% versus 5.82%, $P < 0.05$) use. In MSM with HIV, no statistically significant differences were observed in the proportions of other comorbidities between participants with and those without biochemical hypogonadism.

Factors associated with serum free testosterone level

In multiple regression analysis of all participants, serum free testosterone levels were found to significantly decrease with

Table 4 Factors associated with serum free testosterone levels (left column) and serum SHBG levels (right column) in all subjects via simple and multiple linear regression models. (n = 554).

Variables	Free testosterone (pg/mL)				SHBG (nmol/L)			
	Unadjusted model[a]		Adjusted model[b]		Unadjusted model[a]		Adjusted model[b]	
	Regression coefficient	*P* value	Regression coefficient	*P* value	Regression coefficient	*P* value	Regression coefficient	*P* value
HIV serostatus[c]	−16.44	<0.001	−4.32	0.172	3.66	0.033	0.65	0.720
Age (years)	−1.24	<0.001	−1.14	<0.001	0.42	<0.001	0.51	<0.001
BMI (kg/m^2)	−1.43	<0.001	−1.07	<0.001	−1.24	<0.001	−1.09	<0.001
Current smoker[d]	0.51	0.866			2.61	0.105		
HBsAg positivity[e]	−13.42	<0.001			12.34	<0.001	9.16	<0.001
Anti-HCV positivity[e]	−8.60	0.029			5.23	0.013	5.18	0.009
Hypertension[f]	−19.29	<0.001			−1.13	0.604	−5.48	0.014
Diabetes[f]	−13.99	0.038			−0.48	0.893		
Hyperlipidemia[f]	−15.11	<0.001			−1.88	0.186	−5.33	<0.001
Chronic kidney diseases[f]	−10.02	0.261			−2.06	0.665		
Free T4 (ng/dL)	16.57	0.050			−3.18	0.484		
Prolactin (ng/mL)	0.13	0.579			−0.15	0.224		

[a] Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using simple linear regression analysis.
[b] Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using multiple linear regression analysis and forward stepwise selection. HIV serostatus was included in the model as a forcing variable.
[c] HIV serostatus: 0, no HIV infection; 1, positive HIV infection.
[d] Current smoker: 0, not active smoking currently; 1, smoking at least 100 cigarettes during lifetime and were still actively smoking at the time of study enrollment.
[e] HBsAg positivity, anti-HCV positivity: 0, no; 1, yes.
[f] Comorbidities: 0, no; 1, yes. Chronic kidney disease defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2.
Abbreviations: Anti-HCV, anti-hepatitis C antibody; BMI, body mass index; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin.

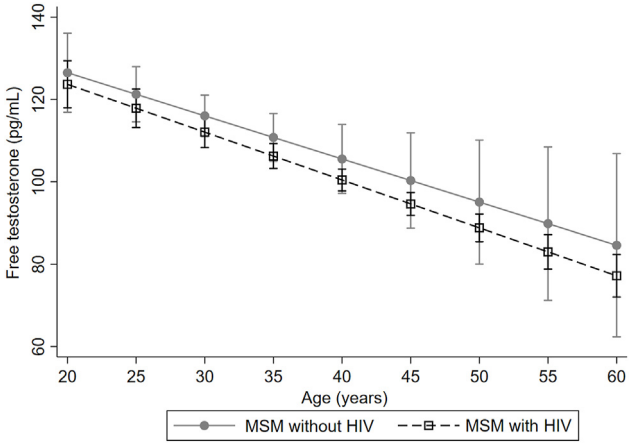

Figure 2. Age-predicted serum free testosterone decline in MSM with or without HIV. P value for interactions between HIV serostatus and age was 0.774.

advanced age and higher BMI (Table 4). There was no significant association between serum free testosterone levels, HIV serostatus, thyroid function, prolactin levels or comorbidities, including hypertension, hyperlipidemia, diabetes, and the presence of HBsAg or anti-HCV. On the other hand, serum SHBG levels significantly increased with age and were positively associated with the presence of HBsAg and anti-HCV, and negatively associated with BMI, hypertension, and hyperlipidemia. In the linear regression models, there were no statistically significant differences observed in the age-predicted serum free testosterone levels and the rate of age-related free testosterone decline between MSM with HIV and MSM without HIV (Fig. 2).

Among MSM with HIV, the serum free testosterone levels significantly decreased with advanced age, higher BMI and longer duration of HIV infection (Table 5). The serum free testosterone levels were positively associated with use of NRTIs. The serum free testosterone levels were not significantly associated with CD4 count, thyroid function, prolactin levels or comorbidities such as hypertension, hyperlipidemia, diabetes, or viral hepatitis B or hepatitis C serostatus. Similar to the results including all study participants, the serum SHBG levels in MSM with HIV significantly increased with age and the presence of HBsAg and anti-HCV, and were negatively associated with BMI, hypertension, and hyperlipidemia.

Discussion

This is the largest Chinese Han cohort to date investigating the clinical manifestations and prevalence of hypogonadism in MSM. We adhered to current practice guidelines by using morning fasting free testosterone levels as the diagnostic criteria for hypogonadism.[9] The results showed that MSM with HIV had a prevalence of symptomatic hypogonadism of 8.3%, whereas MSM without HIV had a prevalence of 1.6%.

Table 5 Factors associated with serum free testosterone levels (left column) and serum SHBG levels (right column) in MSM with HIV via simple and multiple linear regression models. (n = 420).

Variables	Free testosterone (pg/mL)				SHBG (nmol/L)			
	Unadjusted model[a]		Adjusted model[b]		Unadjusted model[a]		Adjusted model[b]	
	Univariate coefficient	*P* value	Multivariate coefficient	*P* value	Univariate coefficient	*P* value	Multivariate coefficient	*P* value
Age (years)	−1.18	<0.001	−0.89	<0.001	0.43	<0.001	0.54	<0.001
BMI (kg/m^2)	−1.24	0.001	−1.03	0.003	−1.16	<0.001	−0.96	<0.001
Current smoker[c]	1.50	0.650			2.62	0.147		
Current CD4 (cells/μL)	0.004	0.468			−0.006	0.045		
Duration of HIV infection (years)	−1.79	<0.001	−0.84	0.002	0.45	0.001		
NRTI use[d]	24.57	0.003	28.0	<0.001	2.62	0.561		
NNRTI use[d]	−14.04	0.013			−2.97	0.338		
II use[d]	3.67	0.616			2.33	0.562		
HBsAg positivity[e]	−12.75	0.001			10.23	<0.001	7.04	<0.001
Anti-HCV positivity[e]	−5.26	0.191			4.95	0.025	5.23	0.012
Hypertension[f]	−16.67	<0.001			−1.22	0.595	−5.13	0.034
Diabetes[f]	−12.14	0.075			−0.70	0.851		
Hyperlipidemia[f]	−10.85	<0.001			−4.29	0.009	−5.43	0.001
Chronic kidney diseases[f]	−6.41	0.466			−2.83	0.558		
Free T4 (ng/dL)	18.66	0.041			−4.01	0.429		
Prolactin (ng/mL)	0.13	0.588			−0.17	0.214		

[a] Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using simple linear regression analysis.
[b] Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using multiple linear regression analysis and forward stepwise selection.
[c] Current smoker: 0, not active smoking currently; 1, smoking at least 100 cigarettes during lifetime and were still actively smoking at the time of study enrollment.
[d] NRTI use, NNRTI use, II use: 0, no; 1: yes.
[e] HBsAg positivity, anti-HCV positivity: 0, no; 1, yes.
[f] Comorbidities: 0, no; 1, yes. Chronic kidney disease defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2.
Abbreviations: Anti-HCV, anti-hepatitis C antibody; BMI, body mass index; CD4, cluster of differentiation 4; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IIs, integrase inhibitors; MSM, men who have sex with men; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; SHBG, sex hormone-binding globulin.

MSM with HIV showed similar age-predicted serum free testosterone levels and age-related free testosterone declines compared to MSM without HIV infection. Our study found that older age, higher BMI and longer duration of HIV infection were associated with lower serum free testosterone levels. Moreover, HBsAg and anti-HCV positivity were associated with higher serum SHBG levels but did not have significant impact on the free testosterone levels. Hypertension and hyperlipidemia were associated with lower serum SHBG levels but did not have significant impact on the free testosterone levels.

The prevalence of hypogonadism in MSM with HIV in our study was lower compared to the prevalence reported in previous literature, which ranged from 9.3% to 52%.[14,15,17,21] The wide variation in the prevalence of hypogonadism observed in these studies may be attributed to differences in the age distribution of the study populations included and definitions used for hypogonadism. Our study population had a similar mean age and BMI to a study in France, which reported a hypogonadism prevalence of 12% in MSM with HIV.[15] Another contributing factor for lower prevalence of hypogonadism may be improved general health in MSM with HIV. The number of comorbidities and frailty index had been shown to correlate inversely with serum testosterone levels.[11] Our study population had a lower prevalence of viral hepatitis, hypertension, hyperlipidemia, and diabetes compared to those in previous studies, indicating a better overall health status in our participants.

Our study did not find significant association between HIV serostatus and serum free testosterone levels. HIV infection has been proposed to interfere with testicular steroidogenesis by direct viral effect or excess cytokine related chronic inflammation, which may lead to primary hypogonadism.[8] In our cohort, 2.7% of MSM with HIV were diagnosed with primary hypogonadism, which is similar to the proportion observed in a large cohort study in Italy.[13] The pathogenesis of secondary hypogonadism in PWH is likely multifactorial, including poor health status, malnutrition, chronic inflammation, comorbidities, premature aging and medications that interfere with hypothalamic–pituitary–gonadal axis.[8] The lower prevalence of secondary hypogonadism (8.9%) observed in our study compared to those in previous literature might be attributed to improved general health, suppressed viral loads and

the exclusion of people taking potentially interfering medications. Limited studies have included a comparison group to investigate the prevalence of hypogonadism in MSM with HIV. Our study results were comparable to the results of the Multicenter AIDS Cohort Study (MACS), as both revealed a similar rate of age-related free testosterone decline in MSM with HIV compared to MSM without HIV.[14,16] It is worth noting that our study enrolled MSM without HIV as the control group, which may share similar lifestyle behaviors with MSM with HIV when compared to the general population. Additionally, the general health status of MSM with HIV may have improved over time compared to the participants in the MACS study, which was conducted more than 10 years before our study.

The impact of exposure to current ART on the testosterone level is unclear and needs more investigations. In this study, we observed a positive association between the use of NRTIs and serum free testosterone levels. Fifteen participants who did not receive NRTIs were exclusively treated with a combination regimen of dolutegravir and rilpivirine. These two antiretrovirals have not been reported to be associated with low testosterone levels or shown to interfere with testosterone metabolism in the literature. A recent study revealed that switch to co-formulated bictegravir, emtricitabine and tenofovir alafenamide reduced HIV-related symptoms among virally suppressed PWH.[22] This regimen was prescribed to 55% of PWH in our cohort. Considering the highly prevalent use of NRTIs (96.6%) in our study, this association may be incidental and warrants further investigation.

HCV infection was associated with increased serum SHBG levels and decreased free testosterone levels.[23,24] Few studies have examined the effect of HBV infection on serum sex-hormone levels.[25] Our study revealed that people with viral hepatitis had significantly increased serum SHBG levels without affecting free testosterone levels in MSM with HIV with normal liver functions. This finding is consistent with those of previous studies that co-infection with viral hepatitis was not a predictor of serum testosterone levels.[11,13] In obese individuals, the presence of inflammatory cytokines and comorbidities is associated with decreased gonadotropin frequencies, resulting in lower SHBG and free testosterone levels.[26] Our study found a significant negative correlation between BMI and both serum SHBG and free testosterone levels in MSM with HIV. Previous study had also identified BMI as a predictor for serum testosterone levels.[13] We observed that 18.3% of MSM with HIV who had obesity had subnormal free testosterone levels. This subgroup may represent a specific population that could benefit from screening for male hypogonadism.

Hyperprolactinemia may interfere with gonadotropin-releasing hormones and the production of testosterone.[9] In our study, 23 participants (4.5%) had mild elevations of serum prolactin level, ranging from 20 to 50 ng/mL. We investigated whether these individuals were more likely to develop male hypogonadism. However, in multiple linear regression models, neither serum prolactin levels nor the presence of hyperprolactinemia was associated with serum free testosterone levels. Therefore, it was reasonable to include these individuals with mild hyperprolactinemia in our study. On the other hand, primary hypothyroidism has been reported to be associated with hypogonadism by reducing LH response to gonadotropin-releasing hormone.[27] In our study, where only a few participants presented with subclinical hypothyroidism, serum free T4 levels were not associated with free testosterone levels in multiple regression analysis.

There are several limitations of our study and the results should be interpreted cautiously. First, the discrepancy in age between the two groups of participants was significant. In the study setting, to enroll more MSM without HIV of a similar age to MSM with HIV was difficult because participants from government-funded PrEP program, in which MSM <35 years were eligible, and anonymous HIV testing services, were younger than MSM with HIV. To address this issue, we performed regression analysis adjusting for age; moreover, we performed subgroup analysis of participants aged <35 years. We found no statistically significant differences in the serum free testosterone levels and prevalence of hypogonadism between MSM with and MSM without HIV. Second, the single testosterone testing might have led to an overestimation of the prevalence of hypogonadism. This is because serum testosterone levels exhibit physiological daily variations. However, since most epidemiologic studies on hypogonadism in MSM with HIV used single testosterone measurement, our results can be reasonably compared with those of previous published studies,[13,14,17] although a longitudinal follow-up study of participants with subnormal free testosterone levels is warranted. Third, our study excluded individuals on testosterone replacement therapy, which might have led to an underestimation of the true prevalence of hypogonadism in MSM populations. We excluded these individuals receiving testosterone replacement therapy because we could not ascertain their diagnosis and prior serum testosterone levels before initiation of testosterone therapy. Moreover, previous literature has shown that testosterone prescriptions often did not adhere to the guidelines, and therefore, these patients might not truly have hypogonadism.[28]

In conclusion, our study found the prevalence of hypogonadism (8.3%) remains low in MSM with HIV in Taiwan, with secondary hypogonadism being the most common form. Serum free testosterone levels negatively correlated with age and BMI, while did not significantly correlate with HIV serostatus. Both MSM with HIV and MSM without HIV showed a similar age-related decline in serum free testosterone levels.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT in order to improve readability and language. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

CRediT authorship contribution statement

Kuan-Yu Lin: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing — original draft, Writing — review & editing. **Hsin-Yun Sun:**

Conceptualization, Data curation, Project administration, Resources. **Wang-Da Liu:** Conceptualization, Data curation, Project administration, Resources. **Chi-Ying Lin:** Conceptualization, Data curation, Project administration, Resources. **Ming-Jui Tsai:** Conceptualization, Data curation, Project administration, Resources. **Yu-Chung Chuang:** Data curation, Project administration, Resources. **Hung-Yuan Li:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. **Jou-Wei Lin:** Data curation, Formal analysis, Methodology, Resources. **Wen-Chun Liu:** Data curation, Project administration, Resources. **Pei-Ying Wu:** Data curation, Project administration, Resources. **Ling-Ya Chen:** Data curation, Project administration, Resources. **Hsi-Yen Chang:** Data curation, Project administration, Resources. **Yu-Zhen Luo:** Data curation, Project administration, Resources. **Yi-Ting Chen:** Data curation, Project administration, Resources. **Guei-Chi Li:** Data curation, Project administration, Resources. **Shyang-Rong Shih:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing — review & editing. **Chien-Ching Hung:** Conceptualization, Data curation, Supervision, Writing — review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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