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Testosterone use and shorter electrocardiographic QT interval duration in men living with and without HIV

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Abstract

Objectives—Testosterone usage (T-use) may alter risk factors for sudden cardiac death in men living with HIV (MLWH). Electrocardiographic QT interval prolongation, which could potentiate ventricular arrhythmias, has previously been associated with HIV infection and, separately, with low testosterone levels. We investigated whether T-use shortens the QT interval duration in MLWH and HIV-uninfected men.

Methods—We utilized data from the Multicenter AIDS Cohort Study, a prospective, longitudinal study of HIV infection among men who have sex with men. Multivariable linear regression analyses were used to evaluate associations between T-use and corrected QT interval (QTc) duration.

Results—Testosterone usage was more common in MLWH compared with HIV-uninfected men (19% *vs.* 9%). In a multivariable regression analysis, T-use was associated with a 5.7 ms shorter

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QT interval [95% confidence interval (CI): −9.5 to −1.9; $P = 0.003$). Furthermore, stronger associations were observed for prolonged duration of T-use and recent timing of T-use.

Conclusions—This study is the first known analysis of T-use and QTc interval in MLWH. Overall, our data demonstrate that recent T-use is associated with a shorter QTc interval. Increased T-use duration above a threshold of ≥ 50% of visits in the preceding 5 years was associated with a shorter QTc interval while lesser T-use duration was not.

Keywords

HIV; QT interval; testosterone usage

Introduction

People living with HIV may be at increased risk for sudden arrhythmic cardiac death (SCD) [1–2]. A risk factor for SCD in the general population is prolongation of the corrected QT interval (QTc), an electrocardiographic measure of ventricular repolarization [3]. We previously reported an independent association between HIV infection and longer QTc [4–5] but did not assess the influence of testosterone usage (T-use). In the general population, low testosterone levels (T-levels) are associated with 4–11 ms QTc prolongation [6–9], whereas high T-levels are associated with lower SCD risk in men [10–11]. Evidence suggests that androgen deprivation therapy is associated with QTc prolongation and arrhythmic risk [12–13]. The association of T-levels with QTc duration is particularly relevant for men living with HIV (MLWH) because of increased prevalence of hypogonadism in MLWH *vs.* HIV-uninfected men (24% *vs.* 7.8%, respectively) [14]. T-use is guideline-recommended for MLWH with symptomatic low T-levels [15] and is higher in MLWH *vs.* HIV-uninfected men (17% *vs.* 5%, respectively) [16]. Currently, no reported data describe the relationship between QT interval duration and T-use specifically in MLWH.

Here, we aimed to investigate the association between T-use and QTc duration in MLWH and HIV-uninfected men.

Methods

We utilized data from the Multicenter AIDS Cohort Study (MACS), a prospective, longitudinal study of HIV infection among men who have sex with men, both MLWH and HIV-uninfected men [4]. Semi-annual study visits occur at four US sites (Baltimore, MD/Washington, DC; Chicago, IL; Pittsburgh, PA; and Los Angeles, CA) [4,17–18]. We included data from participants who, as part of the MACS study, underwent standard resting 12-lead electrocardiograms in 2016–2017 and reported the presence or absence of T-use in the 6 months preceding visits since 2012. For each participant, a standardized QT interval duration was measured digitally and corrected for heart rate using the linear Framingham formula to generate the QTc, as previously described [5]. All participants provided written informed consent, and study procedures were approved by institutional review boards at each site.

Multivariable linear regression analyses were used to evaluate associations between T-use and QTc duration, using models adjusted for age, race, HIV serostatus, MACS site, wave of MACS enrollment (before/after 2001), heart rate, body mass index; use of alcohol, tobacco, opioids and cocaine; blood pressure, serum glucose, medications to treat hypertension or diabetes, renal function, electrocardiographic left ventricular hypertrophy and use of QT prolongation drugs. T-use was defined in four ways, each assessed in separate multivariable regression models:

- Binary T-use at visit closest to the electrocardiogram (last visit).
- Timing of T-use defined categorically as:
  - T-use at last visit, termed ‘recent T-use’;
  - T-use in the preceding 5 years but not at last visit, termed ‘prior T-use’;
  - no T-use in the preceding 5 years, termed ‘no T-use’.•Percentage of visits with reported T-use during the preceding 5 years assessed as:
  - a continuous variable;
  - quartiles of visits (0–24%, 25–49%, 50–74%, 75–100%).

We also assessed the interaction between HIV serostatus and T-use at last visit with a multiplicative term (HIV × T-use) in a separate model. Statistical significance was defined as $P < 0.05$. All analyses were performed using Stata v.15.1 (StataCorp, TX, USA).

Results

We included data from 1427 participants, of whom 54% were MLWH ($n = 774$) and 59% were white, with a mean age of 56 ± 12 years. Overall, 14% ($n = 202$) of men had prior or recent T-use (19% among MLWH, 9% among HIV-uninfected men); 7.9% ($n = 113$) had recent T-use (of these, 73% were MLWH); and 6.2% ($n = 89$) had prior T-use. Within our study, 99% of individuals reported testosterone as a prescribed medication during the years 2012–2018. Of the individuals with recent testosterone use, 84.1% reported T-use for the indication of low serum testosterone levels, and 13.3% reported T-use for the indication of wasting or unintentional weight loss. We previously reported the study characteristics by HIV serostatus and have included baseline characteristics of the study cohort by T-use in Table 1. Absolute QTc was 411.8 ± 19.6 ms in those with no T-use, 415.0 ± 20.4 ms in those with prior T-use, and 408.8 ± 18.8 ms in those with recent T-use.

After multivariable adjustment, recent T-use compared with no T-use was associated with a 5.7 ms shorter QTc (95% CI: −9.5 to −1.9, $P = 0.003$) *vs.* a 4.3 ms longer QTc (95% CI: 2.1–6.5, $P < 0.001$) in MLWH compared with HIV-uninfected men (Table 2). There was no interaction between recent T-use and HIV serostatus ($P = 0.22$). Recent T-use, compared with prior T-use, was also associated with a 6.9 ms shorter QTc (95% CI: −13 to −1.1, $P = 0.02$). By contrast, there was no significant difference in QTc (beta = 0.98 ms, $P = 0.65$) between men with no T-use and men with prior T-use.

Percentage of visits with T-use, as a continuous variable, was also significantly associated with QTc duration (1 ms shorter per decile of visits; 95% CI: −1.9 to − 0.016, $P = 0.046$). When stratifying participants by increasing fractions of visits with T-use, the QTc duration was significantly shorter in those with T-use at ≥ 50% ($P = 0.04$) and ≥ 75% of visits ($P = 0.036$), whereas QTc duration was not significantly different in those with T-use at ≥ 25% of visits ($P = 0.33$), compared to those with T-use at < 25% of visits. In the individuals with T-use at > 35% of visits, there appears to be an inverse linear relationship between increasing visits with T-use and lower QTc value. The correlation coefficient for QTc and percentage of T-use visits above a threshold of 35% is $R = −0.49$ ($P = 0.01$).

Discussion

This study is the first known analysis of T-use and QTc interval in MLWH. Overall, our data demonstrate that recent T-use is associated with a shorter QTc interval. Increased T-use duration above a threshold of ≥ 50% of visits in the preceding 5 years was associated with a shorter QTc interval, while lesser T-use duration was not.

Limitations of the study include unavailability of concurrent serum T-levels, absence of data regarding testosterone usage supplementation dosages, and cross-sectional study design with potential for residual confounding. Notably, measured serum testosterone levels can fluctuate based on factors including time of day and medication administration method, timing of hormonal assessment with respect to testosterone administration, and treatment adherence. Therefore, serum testosterone data may also pose analytic limitations. The analysis is additionally limited by the absence of baseline QTc interval for each participant.

Our findings may have clinical implications, particularly when clinicians and patients consider testosterone discontinuation and initiation. The safety of T-use came under scrutiny following reports demonstrating elevated risks of heart attack, plaque volume, stroke and elevated serum prostate-specific antigen levels in men with T-use [19,20]. Our findings demonstrate that T-use is associated with shorter electrocardiographic QTc duration independent of HIV serostatus. This finding may be particularly relevant for MLWH, as MLWH are less likely to discontinue testosterone and more likely to have QT prolongation associated with HIV infection [5,16]. Longer QTc duration has been associated with HIV infection. [4]. In addition, MLWH are more likely to receive therapy with QTc-prolonging medications, including antiretrovirals such as efavirenz, rilpivirine and protease inhibitors [1,4].

The magnitude of QTc reduction arising from T-use observed in our analysis is consistent with that reported by prior studies investigating the relationship between QTc and T-use in the general population [6–9]. Notably, in the present analysis, the absolute change in QTc associated with T-use was larger than that associated with HIV seropositivity. Given the association of longer QTc with HIV infection and the increased prevalence of hypogonadism and low T-levels in MLWH [4–5,14], the shorter QTc associated with T-use observed in this study might support a protective effect on ventricular repolarization that could counteract the potentially deleterious prolongation seen with HIV infection. In light of our findings, QTc duration data may be helpful when evaluating initiation and discontinuation of T-use,

particularly in MLWH without cardiovascular disease and those taking QTc-prolonging medications. ECG-based information may contribute to the consideration of previously reported risks and benefits of testosterone therapy [19,20] during individualized and patient-centred decision-making regarding T-use. Further research is needed to investigate prognostic implications of T-use on clinical arrhythmic outcomes in MLWH.

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Table 1

Baseline characteristics of the study cohort by testosterone usage (T-use)

	No recent T-use	Recent T-use
HIV-infected [*n* (%)]	682 (52.7%)	83 (73.5%)
Age per 5 years	55.4 ± 12.2	58.4 ± 8.53
Race [*n* (%)]		
Black	353 (27%)	17 (15%)
Caucasian	758 (58%)	78 (69%)
Enrolled after 2001		
Heart rate (beats/min)	66.4 ± 12.0	66.8 ± 11.2
Body mass index (kg/m^2)	26.9 ± 5.11	27.2 ± 4.95
Alcohol use >13 drinks per week [*n* (%)]	49 (3.8%)	7 (6.3%)
Smoking (per 10 cumulative pack-years) (mg/dL)	12.2 ± 19.2	10.7 ± 18.4
Opioid use [*n* (%)]	87 (6.7%)	12 (11%)
Systolic blood pressure (mmHg)	130 ± 15.8	131 ± 15.3
Fasting glucose (mg/dL)	98 ± 33	97 ± 22
On hypertension medications [*n* (%)]	433 (34%)	59 (52%)
On diabetes medications [*n* (%)]	112 (8.7%)	18 (16%)
eGFR (mL/min/1.73 m^2)	86.3 ± 19.6	77.2 ± 16.2
Left ventricular hypertrophy [*n* (%)]	18 (1.4%)	1 (0.88%)
QT prolongation drugs (known + possible *vs.* conditional + none) [*n* (%)]	122 (9.4%)	17 (15%)
Cocaine use	124 (9.7%)	10 (9.0%)
HAART, cumulative years	10.8 ± 6.3	13.3 ± 5.4
QTc Framingham (msec)	411.8 ± 19.6	408.8 ± 18.8
QTc >450 msec	38 (2.9%)	2 (1.8%)

eGFR, estimated glomerular filtration rate.

Table 2

Adjusted* mean differences in corrected QT interval (QTc) duration by testosterone usage definitions (each assessed in separate multivariable models)

	Difference in QTc (ms) [mean (95% CI)]	*P*-value
HIV infected (*vs.* uninfected)	4.3 (2.1–6.5)	< 0.001†
Testosterone use at last visit *vs.* no use at last visit	−5.7 (−9.5 to −1.9)	**0.003**‡
Timing of testosterone use‡		
Last visit *vs.* no use in preceding 5 years	−2.7 (−4.6 to −0.77)	**0.006**‡
Last visit *vs.* use in preceding 5 years but not at last visit	−6.9 (−13 to −1.1)	**0.02**‡
Preceding 5 years *vs.* no use in preceding 5 years	0.98 (−3.2–5.2)	0.65
Percentage of testosterone use visits‡		
Percentage of testosterone use visits as continuous variable	−0.98 (−1.9 to −0.016)	**0.046**‡
≤ 25% *vs.* > 25%	−3.7 (−11 −3.8)	0.33‡
≤ 50% *vs.* > 50%	−6.7 (−13 to −0.31)	**0.04**‡
≤ 75% *vs.* > 75%	−6.5 (−12 to −0.44)	**0.036**‡

*Adjustment for covariates included HIV serostatus, age, race, enrolment time, heart rate, body mass index, alcohol use, smoking opioid use, systolic blood pressure, blood glucose, estimated glomerular filtration rate, LVH, cocaine use, and the usage of hypertension, diabetes or QTc-prolonging medications. The model was further controlled for Multicenter AIDS Cohort Study enrolment site.

†Significant *P*-values with $P < 0.05$, involving testosterone usage variables, are in bold.

‡$P < 0.01$, HIV-positive compared with HIV-uninfected for all testosterone usage variables.