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Brief Report

Endocrine regulation of cardiac repolarization: early QTc shortening after testosterone in healthy AFAB adults

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Abstract

Testosterone modulates ventricular repolarization, yet the early time course of its effects in humans remains unclear. We conducted a prospective, single-center study in 10 healthy adults assigned female at birth initiating gender-affirming hormone therapy with daily transdermal testosterone gel. Standard 12-lead ECGs at baseline and 3 months showed no change in uncorrected QT, but significant QTc shortening by Bazett (−32 ms; $P = .002$) and Fridericia (−14 ms; $P = .010$) formulas, despite a concurrent heart rate reduction and with no association to changes in serum testosterone. These findings demonstrate rapid ventricular repolarization remodeling after testosterone initiation, with a magnitude comparable to the sex-based QTc gap. This study contributes to the characterization of early electrophysiologic adaptation to androgens in a standardized clinical model, and may inform cardiovascular monitoring strategies during abrupt hormonal transitions.

Keywords: testosterone, androgens, QT interval, ventricular repolarization, gender-affirming hormone therapy, electrocardiography

Significance

Testosterone is a key endocrine regulator of cardiac repolarization, yet the early dynamics of its effects in humans have remained undefined. In this prospective, single-center study, we quantified the magnitude and timing of QTc interval changes in healthy adults assigned female at birth initiating standardized testosterone therapy. Within 3 months, QTc shortening of a magnitude comparable to the sex-based gap was observed, despite a concomitant heart rate reduction. These results provide an early characterization of rapid androgen-induced electrophysiologic adaptation in humans, contributing to the link between endocrine physiology and cardiovascular risk assessment. Although limited by the small sample size and lack of a control group, the findings have direct implications for monitoring strategies during abrupt hormonal transitions, including gender-affirming therapy and other endocrine interventions.

Introduction

The QT interval is a key electrocardiographic marker of ventricular repolarization and arrhythmic risk, clinically associated with malignant arrhythmias and sudden cardiac death.[1] In population studies, cisgender men have shorter QTc values than women, an observation largely attributed to androgen-mediated modulation of repolarizing potassium currents and calcium handling.[2,3] Recent systematic reviews confirm that testosterone (T) shortens the QT interval across both humans and animal models.[4] Conversely, transient inflammatory hypotestosteronemia has been linked to prolonged QT and torsade de pointes in men.[5] Despite robust preclinical and translational evidence, the early time course of T's effects on ventricular repolarization, particularly in the context of endocrine interventions, remains undefined in humans. Grouthier et al.[6] reported QTc shortening in transgender men receiving gender-affirming hormone therapy (GAHT), but heterogeneity in comorbidities, dosing regimens, and follow-up limited the precision of their estimates. We aimed to provide a precise quantification of the magnitude and early time course of T-induced QTc changes in a standardized and relatively homogenous clinical model.

Methods

We consecutively enrolled 10 healthy, young adults assigned female at birth (AFAB; median age 23.5 years, interquartile range 20–24) initiating GAHT with 50 mg/day transdermal T gel. This was a convenience sample, and no a priori power calculation was performed. Exclusion criteria were cardiovascular or systemic disease, history of arrhythmia, use of QT-prolonging medications, abnormal body mass index, electrolyte disturbances, prior exposure to sex steroids, and history of cardiac surgery. Standard 12-lead electrocardiograms

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were obtained in the fasting state, at rest, and in the supine position at baseline and after 3 months. QT intervals were measured manually in lead II or V5 using the tangent method by blinded assessors and corrected using both Bazett's (QTcB) and Fridericia's (QTcF) formulas. Statistical analyses included paired Wilcoxon signed-rank tests, calculation of effect sizes (Cohen's *d*) and post hoc statistical power, and Spearman correlation between ΔT and ΔQTc. This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Results

Heart rate decreased significantly from a median of 79 bpm (IQR 77-81) at baseline to 66 bpm (IQR 61-73) at 3 months ($P = .027$). The uncorrected QT interval showed no significant change (351 ms [IQR 348-366] vs 352 ms [IQR 329-391]; $P = 1.000$). In contrast, corrected QT intervals were markedly reduced: QTcB by a median of 32 ms (412 ms [IQR 402-421] to 380 ms [IQR 363-397]; $P = .002$; Cohen's $d = 1.67$; post hoc power = 99.6%) and QTcF by 14 ms (388 ms [IQR 385-413] to 374 ms [IQR 349-392]; $P = .010$; d = 1.13; power = 88.9%) (Figure 1). PR interval, QRS duration, and T-wave axis remained unchanged. No correlation was observed between ΔT and ΔQTc (Figure 2).

Discussion

Our findings demonstrate that GAHT with T induces rapid and marked QTc shortening already within the first 3 months of administration. Notably, no correlation was observed between ΔT and ΔQTc, which may reflect the limited sample size and variability of serum concentrations rather than the absence of a

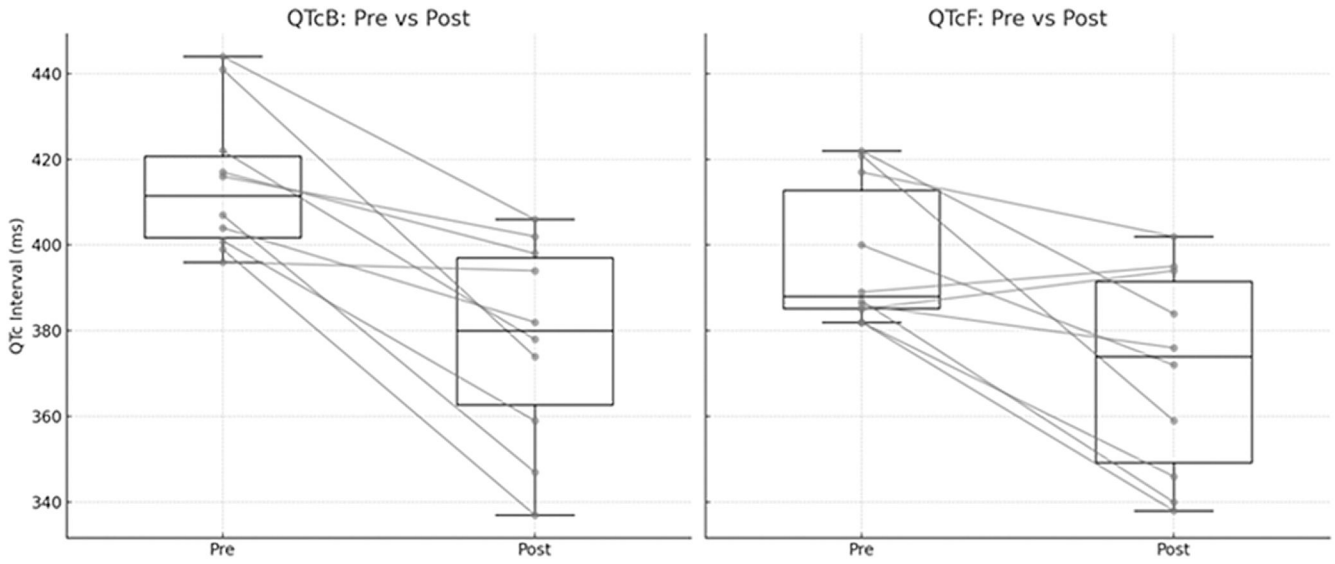

Figure 1. Change in corrected QT interval (Bazett and Fridericia) before and after T-based gender-affirming hormone therapy.

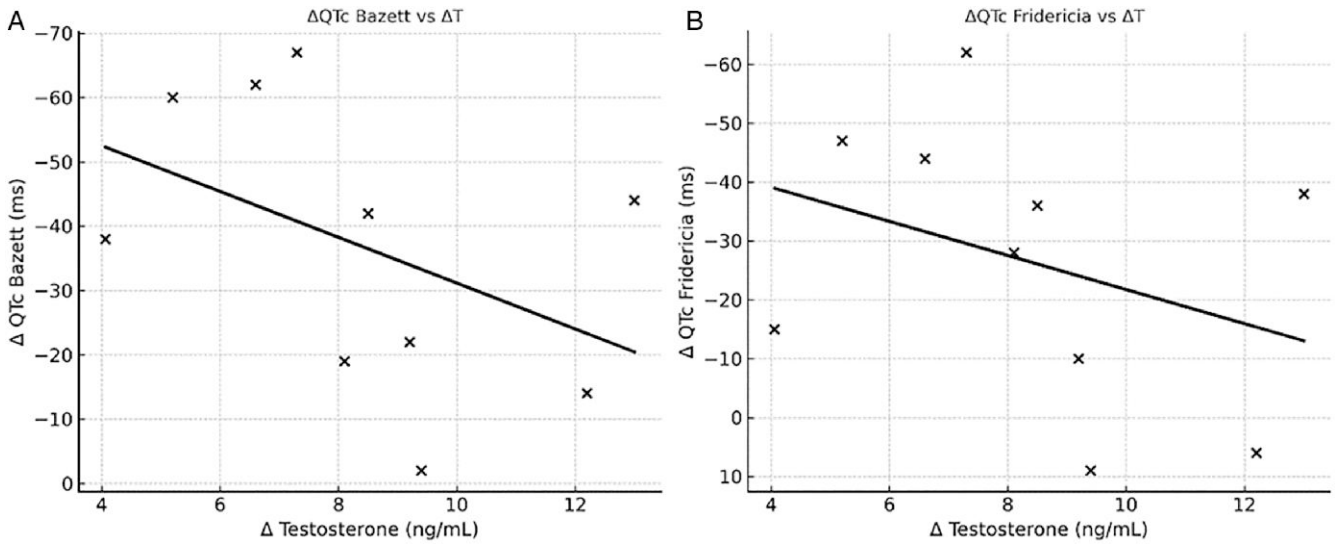

Figure 2. Meta-regression between changes in serum testosterone (ΔT) and QTc, with ΔQTcBazett (A) and ΔQTcFridericia (B). The Y-axis is inverted so that greater QTc shortening with higher testosterone increase appears as a downward slope.

biological relationship. These results are consistent with recent systematic reviews[7] and experimental evidence supporting androgen-mediated modulation of cardiac electrophysiology,[8] and align with broader position statements affirming the cardiovascular safety of testosterone therapy in hypogonadal individuals.[9] In a complementary pattern to our findings, Angus et al.[10] reported a mean QTc prolongation of 19 ms over 6 months in AMAB individuals undergoing feminizing hormone therapy with marked testosterone suppression. Taken together, these bidirectional observations provide converging evidence for androgen-dependent modulation of ventricular repolarization in humans. While QTc shortening may be protective against torsades in some contexts, its impact on other arrhythmogenic substrates remains uncertain.[11] The small sample size and short follow-up are clear limitations, and regression to the mean cannot be excluded. Nevertheless, the magnitude of effect was large (Cohen's $d > 1$ for both QTcB and QTcF), and post hoc power exceeded .99, making a false positive finding unlikely. Our study therefore provides a benchmark for the early electrophysiologic adaptations to testosterone and may inform monitoring protocols and risk assessment strategies in endocrine and cardiovascular care, particularly in scenarios involving rapid hormonal shifts.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical review and approval were waived by the Institutional Review Board of the University of L'Aquila, as the study involved healthy volunteers, fully anonymized data, and no interventions beyond standard clinical procedures. All participants provided written informed consent prior to enrollment.

Authors' contributions

Daniele Tienforti (Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing—original draft), Giovanni Terrana (Investigation, Data curation, Writing—review & editing), Luca Spagnolo (Investigation, Data curation, Writing—review & editing), Beatrice Fusco (Resources, Data curation, Writing—review & editing), Marco Baroni (Supervision, Methodology, Writing—review & editing), and Arcangelo Barbonetti (Conceptualization, Supervision, Project administration, Writing—review & editing)

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Davies RA, Ladouceur VB, Green MS, Joza J, Juurlink DN, Krahn AD, *et al*. The 2023 Canadian cardiovascular society clinical practice update on management of the patient with a prolonged QT interval. *Can J Cardiol*. 2023;39(10):1285–1301. https://doi.org/10.1016/j.cjca.2023.06.011
2. Bai CX, Kurokawa J, Tamagawa M, Nakaya H, Furukawa T. Nontranscriptional regulation of cardiac repolarization currents by testosterone. *Circulation*. 2005;112(12):1701-1710. https://doi.org/10.1161/CIRCULATIONAHA.104.523217
3. Costa S, Saguner AM, Gasperetti A, Akdis D, Brunckhorst C, Duru F. The link between sex hormones and susceptibility to cardiac arrhythmias: from molecular basis to clinical implications. *Front Cardiovasc Med*. 2021;8:644279. https://doi.org/10.3389/fcvm.2021.644279
4. Salvi V, Karnad DR, Panicker GK, Kothari S. The impact of testosterone on the QT interval: a systematic review. *Curr Probl Cardiol*. 2021;47(9):100882. https://doi.org/10.1016/j.cpcardiol.2021.100882
5. Lazzerini PE, Cantara S, Bertolozzi I, *et al*. Transient hypogonadism is associated with heart rate–corrected QT prolongation and torsades de pointes risk during active systemic inflammation in men. *J Am Heart Assoc*. 2022;11(1):e023371. https://doi.org/10.1161/JAHA.121.023371
6. Grouthier V, Matamala M, Tabarin A, Galioot A, Couffinhal T, Vaglio M, *et al*. Transgender-affirming hormone therapies, QT prolongation, and cardiac repolarization. *JAMA Netw Open*. 2025;8(7):e2524124. https://doi.org/10.1001/jamanetworkopen.2025.24124
7. Gutierrez G, Wamboldt R, Baranchuk A. The impact of testosterone on the QT interval: a systematic Review. *Curr Probl Cardiol*. 2022;47(9):100882. https://doi.org/10.1016/j.cpcardiol.2021.100882
8. Kaur H, Werstuck GH. The effect of testosterone on cardiovascular disease and cardiovascular risk factors in men: a review of clinical and preclinical data. *CJC Open*. 2021;3(10):1238-1248. https://doi.org/10.1016/j.cjco.2021.05.007
9. Zitzmann M, Rastrelli G, Murray RD, Edwards D, Reisman Y, Rao PM, *et al*. Cardiovascular safety of testosterone therapy—insights from the TRAVERSE trial and beyond: a position statement of the European expert panel for testosterone research. *Andrology*. 2025. https://doi.org/10.1111/andr.70062.
10. Angus LM, Lin T, Leemaqz SY, Cheung AS. Effect of feminizing hormone therapy on QTc interval: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2024;7(3):e243994. https://doi.org/10.1001/jamanetworkopen.2024.3994
11. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. *Circ Arrhythm Electrophysiol*. 2012;5(4):868-877. https://doi.org/10.1161/CIRCEP.111.962019 Erratum in: Circ Arrhythm Electrophysiol. 2012;5(6):e119-20.