Circulation

RESEARCH LETTER

Hypogonadism as a Reversible Cause of Torsades de Pointes in Men

Joe-Elie Salem, MD, PhD
Xavier Waintraub, MD
Carine Courtillot, MD
Christian M. Shaffer, BS
Estelle Gandjbakhch, MD, PhD
Carole Maupain, MD
Javid J. Moslehi, MD
Fabio Badilini, PhD
Julien Haroche, MD, PhD
Paul Gougis, MD
Veronique Fressart, MD, PhD
Andrew M. Glazer, PhD
Francoise Hidden-Lucet, MD
Philippe Touraine, MD, PhD
Benedicte Lebrun-Vignes, MD
Dan M. Roden, MD
Anne Bachelot, MD, PhD
Christian Funck-Brentano, MD, PhD

Long QT intervals corrected for rate (QTc) >480 to 500 milliseconds predispose to the polymorphic ventricular tachycardia torsades de pointes (TdP).[1] Because QTc is shorter and TdP is less frequent in men than in women and because testosterone shortens ventricular repolarization, we examined the effect of hypogonadism and androgen deprivation therapy (ADT) on QTc and TdP risk.[2]

We prospectively evaluated testosterone and related plasma levels in each man seen with TdP (n=7) over 19 months at a single university hospital (Hôpital Pitié-Salpétrière, Paris, France, Commission nationale de l'informatique et des libertés No. 1491960v0, patients' informed consent obtained). We then analyzed the European pharmacovigilance database (up to June 2017, URL: https://clinicaltrials.gov, Unique identifier: NCT03193138) searching for QTc/TdP adverse drug reactions (*Medical Dictionary for Regulatory Activities* terms: long-QT syndrome [LQT], ECG QT-prolonged, and TdP) associated with ADT, and we performed a cross-sectional analysis of the association between the *International Classification of Diseases* revisions 9 and 10 codes for LQT/TdP and hypogonadism in 1.1 million men in a US electronic health record cohort (up to November 2017, Vanderbilt University Medical Center, Institutional Review Board approval no. 171796).[3]

Hypogonadism was diagnosed in 7 of 7 cases of TdP (Table). After correction of low testosterone levels, QTc shortened and there was no TdP recurrence. Three patients had spontaneous reversal of hypogonadism after resolution of a severe critical illness; 3 patients needed testosterone supplementation for chronic hypogonadism; and 1 patient died. LQT genetic screening was negative in 6 of the 6 tested patients.

The European pharmacovigilance database (http://www.adrreports.eu/fr/search.html) analysis identified 43 of 34 221 individual case safety reports of men with drug-induced (di) LQT (diLQT) and 15 of 34 221 with diTdP suspected to be attributable to ADT versus none (0 of 10 847) reported during testosterone replacement therapy. ADT included the following pharmacological classes of drugs: gonadotrophin-releasing hormone receptor agonists (leuprolide, buserelin, goserelin, triptorelin), gonadotrophin-releasing hormone receptor antagonist (degarelix), cytochrome-17 inhibitor (abiraterone), nonsteroidal androgen receptor antagonists (bicalutamide, flutamide, nilutamide, enzalutamide), and 5α-reductase inhibitors (finasteride, dutasteride). Disproportionality analysis showed higher reporting odds ratios (ORs)[4] comparing ADT and testosterone for diLQT and diTdP (reporting OR, 3.75–∞, $P<0.0001$; reporting OR, 1.3–∞, $P=0.03$; respectively). Degarelix and abiraterone carried the highest reporting rate for diLQT (n=4 of 769 [0.52%] for degarelix; n=7 of 4723 [0.15%] for abiraterone) and diTdP (n=2 of 769 [0.26%] for degarelix; n=5 of 4723 [0.11%] for abiraterone) compared with other ADTs (n=32 of 28 729 [0.11%] for diLQT; n=8 of 28 729 [0.03%] for diTdP; both $P<0.05$).

Key Words: androgen antagonists ■ androgens ■ antineoplastic agents ■ hypogonadism ■ men ■ testosterone ■ torsades de pointes

https://www.ahajournals.org/journal/circ

Table. Details of the 7 Cases of TdP Identified With Hypogonadism

Patient No.	Patient Age, y	Medical History	Clinical Presentation	Characterization of Hypogonadism*	Other Liable Drugs or Conditions for TdP†	Outcome
1	72	Hypertension, normal EF, ischemic cardiomyopathy on β-blockers, Non-Langerhans, Langerhans cell histiocytosis infiltrating multiple organs with BRAF mutation (ECD) for 2 y treated by interferon-α	Respiratory distress and recurrent episodes of TdP requiring 6 cardioversions for post-TdP ventricular fibrillation	No sexual activity with no erection for the past 6–8 mo	Plasma electrolytes and troponins normal	ICD implanted
		QTc ≈440 ms before ECD; progressive prolongation after ECD: QTc ≈550 ms concomitant to hypogonadism onset	QTc >550 ms while on long-term β-blocker	Clinical examination: bilateral hypotrophic testes, gynecomastia	Lung infection treated by spiramycin (but after first episode of syncope)	Testosterone started for sustained hypogonadism related to his histiocytosis
				Mixed central and peripheral hypogonadism, Bio-T: 0.5 ng/mL, FSH: 9.5 IU/L, LH: 11.6 IU/L		QTc normalization within 4 d and no TdP recurrence at 1.5 y despite vemurafenib introduction (ECD)
2	78	Paroxysmal atrial fibrillation on sotalol and digoxin, normal EF, progressive QTc prolongation over 4 y: QTc ≈460–480 ms	Syncopal TdP episodes 2 d after mitral valve replacement for endocarditis	Progressive apparition of sexual symptoms over the past 5 y, probably caused by late-onset hypogonadism	Normal electrolytes and no acute ischemia	Temporary pacing
			QTc >600 ms, paroxysmal atrioventricular blocks	Mixed central and peripheral hypogonadism: Bio-T <0.1 ng/mL, FSH: 16.6 IU/L, LH: 10.6 IU/L	Bradycardia, paroxysmal atrioventricular blocks	Persistence of QTc ≈500 ms 2 mo after surgery
					Sotalol withdrawn before surgery; time lag between withdrawal and TdP >5 d	Testosterone administration at 3 mo with normalization of sexual symptoms and QTc with no TdP recurrence at 1 y
3	75	Pacemaker for paroxysmal bradycardia-tachycardia syndrome on amiodarone and bisoprolol (QTc ≈530 ms), ischemic cardiomyopathy, EF=35%–45%, moderate renal failure	Cardiac arrest on TdP 12 h after elective pacemaker replacement	Chronic clinical signs of hypogonadism, probably caused by late-onset hypogonadism	Normal electrolytes and no acute ischemia	Persistence of QTc ≈550 ms 1 wk after amiodarone and hydroxyzine withdrawal
			QTc=660 ms	Peripheral hypogonadism: Bio-T <0.1 ng/mL, FSH: 44.9 IU/L, LH: 51.3 IU/L	Hydroxyzine before surgery, long-term amiodarone	Testosterone administration 1 wk after TdP with QTc shortening (≈480 ms) and no TdP recurrence at 3 mo
4	90	Hypertension treated with diuretics, normal EF, borderline QTc (≈460 ms), cured prostate cancer, temporal arteritis on corticosteroids	Syncopal TdP episodes requiring cardioversions in the context of paroxysmal atrial fibrillation and sepsis	Mild chronic clinical signs of hypogonadism	Severe hypokalemia (2 mmol/L)	Correction of hypokalemia, withdrawal of liable drugs
			QTc >600 ms	Mixed central and peripheral hypogonadism; Bio-T: 0.2 ng/mL, FSH: 17.5 IU/L, LH: 20 IU/L	Sepsis treated by ciprofloxacin and fluconazole	Spontaneous incomplete reversion of Bio-T: 0.7 ng/mL, shortening of QTc (486 ms) within 10 d
						Testosterone not given (history of prostate cancer)

(*Continued*)

Table. Continued

Patient No.	Patient Age, y	Medical History	Clinical Presentation	Characterization of Hypogonadism*†	Other Liable Drugs or Conditions for TdP†	Outcome
5	63	Hypertension, prostate adenoma, familial history of sudden death, normal QTc, normal EF, paroxysmal atrial fibrillation	Multiple self-terminating TdP episodes in context of septic and hemorrhagic shocks	No preexisting signs of hypogonadism before shock	Shocks, extracorporeal membrane oxygenation	Spontaneous normalization of testosterone levels (Bio-T: 0.9 ng/mL) and QTc (440 ms) 1 mo after recovery from shock
			QTc: 508 ms	Central hypogonadism triggered by severe acute conditions; Bio-T <0.1 ng/mL, FSH: 6.9 IU/L, LH: 10.7 IU/L	Ventricular arrhythmias and ischemia on inotropes requiring amiodarone	
6	63	Hypertension, paroxysmal atrial fibrillation, systemic aneurysmal vasculopathy leading to multiple strokes complicated by epilepsy and hemiplegia, normal EF, normal QTc	Cardiac arrest caused by TdP leading to ventricular fibrillation (>15 cardioversions)	No preexisting signs of hypogonadism before TdP	Normal electrolytes and no acute ischemia	Septic death 6 d after admission for cardiac arrest
			QTc ≈560 ms	Central hypogonadism triggered by acute severe conditions; Bio-T: 0.3 ng/mL, FSH: 6.4 IU/L, LH: 4.4 IU/L		
7	72	Syncopal sinus node dysfunction with normal QTc requiring pacemaker, hypertension, normal EF, normal QTc	TdP (QTc=470 ms) while hospitalized for transient cerebral ischemia	No preexisting signs of hypogonadism before TdP	Normal electrolytes and no acute ischemia	Spontaneous normalization of testosterone levels (Bio-T: 1.5 ng/mL) and QTc (430 ms) within weeks of acute event resolution
			Recurrence of acquired prolonged QTc: 480 ms in context of endocarditis	Central hypogonadism triggered by acute severe conditions; Bio-T <0.1 ng/mL, FSH: 0.5 IU/L, LH: 1.4 IU/L (for endocarditis event)		ICD upgrading while changing pacemaker

Bio-T indicates bioavailable testosterone; ECD, Erdheim-Chester disease; EF, ejection fraction (left ventricle); FSH, follicle-stimulating hormone; ICD, implantable cardioverter-defibrillator; LH, luteinizing hormone; and TdP, torsades de pointes.

*Hypogonadic men with high FSH and LH were classified as having peripheral hypogonadism, whereas those with inappropriately normal or low FSH and LH were considered to have central hypogonadism. Normal values for adult men in our laboratory are as follows: FSH, 1.5 to 12.4 IU/L; LH, 1.7 to 8.6 IU/L; and Bio-T, 1 to 3.2 ng/mL. A progressive decrease in Bio-T normal values is expected with increasing age (up to 40% at 90 years of age).

†According to the CredibleMeds website (https://crediblemeds.org/).

In the electronic health record cohort, conditions or drugs leading to hypogonadism were associated with LQT/TdP (86 of 38 041 cases versus 649 of 1 082 891 controls; crude OR, 3.8 [95% confidence interval, 3–4.7]; age-adjusted OR, 4.8 [95% confidence interval, 3.8–6.1]). Men with hypogonadism secondary to endocrine conditions carried the highest association with LQT/TdP compared with ADT users and all other men (30 of 9202 [0.33%] versus 56 of 28 839 [0.19%] versus 649 of 1 082 891 [0.06%], respectively, $P<0.0001$).

Taken together, these data provide consistent support for an association between hypogonadism in men and LQT/TdP. The association appears to be causal because correction of hypogonadism by testosterone replacement therapy can treat or prevent TdP and ADT can lead to LQT/TdP. These results provide strong justification for a clinical recommendation to investigate the possibility of hypogonadism when TdP occurs in men. Hypogonadism should be added to the list of risk factors for TdP, and an increased awareness should prompt correction of other TdP risk factors in men receiving ADT.

Our findings support the hypothesis that hypogonadism is a correctable and readily identifiable risk factor for TdP in men. There should be a high index of suspicion when symptoms such as erectile dysfunction, testicular hypotrophy, and hot flashes are present, particularly when the prevalence of hypogonadism is expected to be high such as in elderly men. It has been shown that hypothalamic-pituitary-gonadal axis physiology is dramatically altered during critical illnesses and after major surgery or brain injury and can lead to tran-

sient functional hypogonadism[5]; therefore, the distinction between transient hypogonadism in this setting and preexistent hypogonadism may be difficult. For these reasons, we postponed testosterone supplementation in patients 4 through 7 (sepsis, surgery, or stroke; Table), awaiting a spontaneous normalization of pituitary function. Late-onset hypogonadism has recently been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms associated with higher cardiovascular mortality in the presence of low testosterone levels (eg, patients 2 and 3).[5] In our case series, TdP did not recur after testosterone supplementation. The basic mechanisms are not completely defined, but preclinical studies show that testosterone increases the repolarizing potassium currents I_{Kr} and I_{Ks} and decreases the depolarizing L-type calcium current.[2]

ADT is a cornerstone of the treatment of prostate cancer. Among ADTs, the website crediblemeds.org currently lists only degarelix and leuprolide as possible risks for TdP, so further guideline updates may be needed for newer drugs such as abiraterone.

A limitation of the analyses of the pharmacovigilance database and the electronic health record is that the data come from uncontrolled sources. Nevertheless, the case series and the population analyses provide orthogonal validation for the causal, and treatable, relationship we postulate between male hypogonadism and TdP risk.

ARTICLE INFORMATION

The online-only Data Supplement is available with this article at https://www.ahajournals.org/journal/circ/doi/suppl/10.1161/CIRCULATIONAHA.118.034282.

Data sharing: The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Correspondence

Joe-Elie Salem, MD, PhD, Centre d'Investigation Clinique Paris-Est, Hôpital La Pitié-Salpêtrière, 47–83 Bld de l'hôpital, 75651 Paris Cedex 13; or Department of Medicine and Pharmacology, Cardio-Oncology Program, Vanderbilt University Medical Center, 1211 Medical Center Dr, Nashville, TN 37232. E-mail joe-elie.salem@aphp.fr or joe-elie.salem@vanderbilt.edu

Affiliations

Department of Pharmacology, Pharmacovigilance Unit (J.-E.S., P.G., B.L.-V., C.F.-B.), Department of Cardiology, CIC 1421, Cardiogenetic Unit, Arrhythmology Unit (J.-E.S., X.W., E.G., C.M., V.F., F.H.-L.), Department of Internal Medicine (J.H.), and Department of Endocrinology and Reproductive Medicine (C.C., P.T., A.B.), AP-HP, Pitié-Salpêtrière Hospital, Paris, France. Centre de Référence des Maladies Endocriniennes Rares de la Croissance et Centre des Pathologies Gynécologiques Rares (C.C., P.T., A.B.), Institut National de la Santé et de la Recherche Médicale (J.-E.S., P.G., B.L.-V., C.F.-B.), UMR Institute of Cardiometabolism and Nutrition (J.-E.S., X.W., E.G., C.M., V.F., F.H.-L.), Paris, France. Sorbonne Université, Faculty of Medicine, Paris, France (J.-E.S., P.G., B.L.-V., C.F.-B., A.B., P.T., E.G.). Departments of Medicine, Pharmacology, and Biomedical Informatics (J.-E.S., C.M.S., A.M.G., D.M.R.) and Departments of Medicine, Cardiology, and Cardio-Oncology Program, Vanderbilt University Medical Center, Nashville, TN (J.-E.S., J.J.M.). AMPS LLC, New York, NY (F.B.). Sorbonne Université, Faculty of Medicine, Paris, France (J.H.).

Sources of Funding

This study was supported by the Cancer Institut Thématique Multi-Organisme of the French National Alliance for Life and Health Sciences: Plan Cancer 2014 to 2019. The Vanderbilt deidentified electronic medical record has been supported by numerous sources: institutional funding, private agencies, and federal grants. These include the National Institutes of Health–funded Shared Instrumentation Grant S10RR025141 and Clinical and Translational Science Awards grants UL1TR002243, UL1TR000445, and UL1RR024975.

Disclosures

Dr Moslehi has been a consultant to Novartis, Pfizer, Bristol Myers Squibb, and Takeda. The other authors report no conflicts.

APPENDIX

Investigators

Marie Bretagne, Pauline Dureau, Valentin Saqué, Aida Zarhrate-Ghoul, Clément Bourguignon, Monique Leban, Virginie Grouthier, Martino Vaglio.

REFERENCES

1. Curtis MJ, Hancox JC, Farkas A, Wainwright CL, Stables CL, Saint DA, Clements-Jewery H, Lambiase PD, Billman GE, Janse MJ, Pugsley MK, Ng GA, Roden DM, Camm AJ, Walker MJ. The Lambeth Conventions (II): guidelines for the study of animal and human ventricular and supraventricular arrhythmias. *Pharmacol Ther*. 2013;139:213–248. doi: 10.1016/j.pharmthera.2013.04.008.
2. Salem JE, Alexandre J, Bachelot A, Funck-Brentano C. Influence of steroid hormones on ventricular repolarization. *Pharmacol Ther*. 2016;167:38–47. doi: 10.1016/j.pharmthera.2016.07.005.
3. Roden DM, Pulley JM, Basford MA, Bernard GR, Clayton EW, Balser JR, Masys DR. Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin Pharmacol Ther*. 2008;84:362–369. doi: 10.1038/clpt.2008.89.
4. De Bruin ML, Pettersson M, Meyboom RH, Hoes AW, Leufkens HG. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. *Eur Heart J*. 2005;26:590–597. doi: 10.1093/eurheartj/ehi092.
5. Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P, Aszpis S, Pacenza N, Stewart Usher J, Bergadá I, Campo SM. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. *Andrology*. 2013;1:3–16. doi: 10.1111/j.2047-2927.2012.00008.x.