The impact of testosterone on the QT interval: A Systematic review

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Abstract

Background: Humans and mammals have sex-specific differences in cardiac electrophysiology, linked to the action of sex hormones in the cardiac muscle. These hormones can either increase or decrease the expression of ionic channels modulating the cardiac cycle through genomic and non-genomic interactions. Methods: Systematic search in PubMed, Medline and EMBASE including keywords pertaining to testosterone and QT interval. Included experimental studies, observation studies and case reports presenting the results of testosterone administration, excess or deficiency in humans and animals. Results: Testosterone has been shown to shorten the action potential duration, by enhancing the expression of K+ channels and downregulating ICaL increasing the repolarization reserve of the cardiac muscle. This increased repolarization reserve also protects the heart against the effects of QT prolonging drugs and arrhythmogenesis. This effect has been observed in both genders and animals. Conclusions: Testosterone deficient states can promote arrhythmogenesis. The evidence in this paper may be used to guide clinical consideration relating to testosterone levels and QT prolonging states and medications, such as increased clinical surveillance of patients in testosterone deficient states using ECG.

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Methods: Systematic search in PubMed, Medline and EMBASE including keywords pertaining to testosterone and QT interval. Included experimental studies, observation studies and case reports presenting the results of testosterone administration, excess or deficiency in humans and animals.

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Conclusions: Testosterone deficient states can promote arrhythmogenesis. The evidence in this paper may be used to guide clinical consideration relating to testosterone levels and QT prolonging states and medications, such as increased clinical surveillance of patients in testosterone deficient states using ECG.

Key words: testosterone; QT interval; QTc; arrhythmia; sex hormones

1.0 Introduction

Men and women have several cardiovascular and cardiac electrophysiologic differences. (1). This suggests an important interplay between cardiac physiology and sex hormones. Relevant to this difference, as testosterone levels increase, men experience a shortening of the QT interval (1). QT length is very closely related to arrhythmogenic risk (for instance Torsades de Pointes – TdP), which is why women are at a higher risk than men for developing drug-related TdP, ventricular arrhythmias, drug-induced QT prolongation (DiLQTS) and lethal arrhythmias (2). The QT interval or action potential duration (APD) is defined as the length between the start of the QRS complex (ventricular contraction) and the end of the T wave (ventricular relaxation) shown on ECG. (2,3). As summarized in **Figure 1** , the APD is determined by the action of the outward K^+ currents and the inward Na^+ and Ca^{2+} currents, which work together to contract and relax the heart through the cardiac cycle (3).

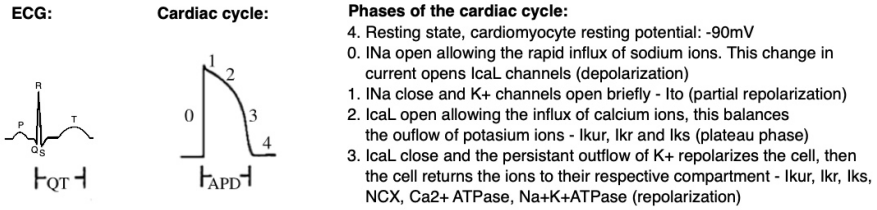

Figure 1. Diagram comparing the cardiac action potential measured by an ECG (left) and represented by the changes in ionic currents (right - Cardiac cycle). The QT and the APD, represent the same process

(3).**Abbreviations:** INa – Na+ current, ICaL – L-type Ca2+ current, IKur – delayed rectifier ultra-rapid K+ current, IKr – delayed rectifier rapid K+ current, IKs – delayed rectifier slow K+ current, NCX – Na+/Ca2+ exchanger.

Prolongation of the QTc (specially values greater than 500ms) can result in life-threatening cardiac events (3). Abnormalities can be caused by genetic conditions, such as long QT syndrome (LQTS), certain medications (e.g., certain anti-arrhythmic, antimicrobials and psychotropic drugs – refer to **Table 3** for an extensive list of QT prolonging drugs) and hormones (3). For instance, according to the literature, low levels of testosterone result in the inhibition of the expression of repolarizing currents in the heart and thus, it is one of the main causes of QT interval prolongation (4) – **Figure 2** (4–6). Thus, the aims of this systematic review are to explore the effects of testosterone on the length of the QT interval and make a strong case for the clinical importance of testosterone as a key factor in determining the patient's susceptibility to arrhythmogenesis.

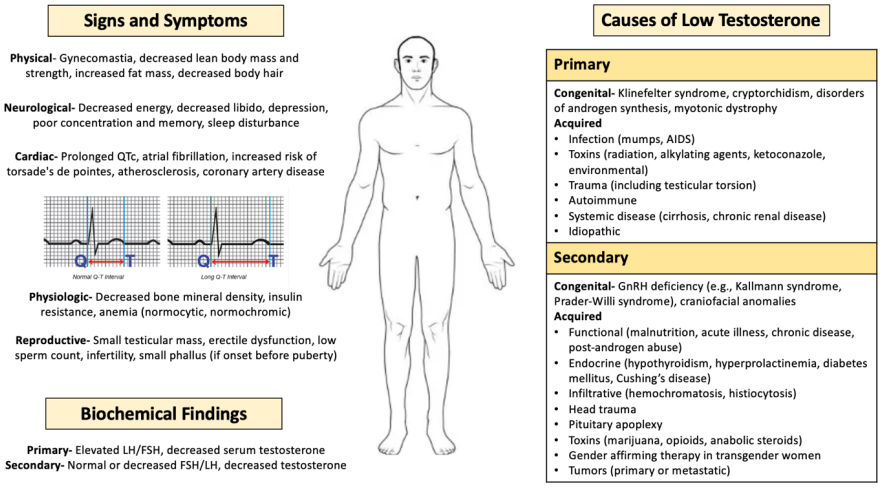

Figure 2. Signs and symptoms of low testosterone, biochemical findings and primary and secondary causes of low testosterone (4–6)

2.0 Methods

This review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An electronic literature review was conducted looking at the effect of testosterone (endogenous and exogenous) on the QT interval in humans and animals. The literature search was completed using PubMed, Medline, and EMBASE. Medical Subject Headings (MeSH) terminology and specific keywords related to Testosterone and QT interval were used to develop our literature search as appropriate: Testosterone (MeSH term) OR Hypogonadism (MeSH term) OR Androgens (MeSH term) OR Gonadal steroid hormones (MeSH term) OR Hyperandrogenism (MeSH term) OR Orchiectomy (MeSH term) OR Androgen deprivation therapy OR Low testosterone OR High testosterone OR Dihydrotestosterone OR Androgen deficiency. The following keywords were used to search the literature for articles pertaining to QT interval and arrhythmias: Long QT syndrome (MeSH term) OR Arrhythmia, cardiac (MeSH term) OR Torsades de Pointes (MeSH term) OR Tachycardia (MeSH term) OR Electrocardiography (MeSH term) OR Heart conduction system (MeSH term) OR Action potential (MeSH term) OR QTc interval OR Short QT syndrome OR Action potential duration.

To be considered for this review, studies had to meet the following inclusion criteria: (i) publication from inception until January 5th, 2021, (ii) human and animal studies (iii) studies involving the administration of sex hormones, sex hormone deprivation/enhancing therapies and sex hormone abnormalities and their effect on the QT interval (iv) English and Spanish language. Papers were excluded if they didn't include

QT interval or androgen involvement, if they were review articles and if they included the use of synthetic androgens.

We employed Covidence to review the articles. Following our search, 3006 studies were imported into the program for screening. There were 1146 duplicates that were automatically removed. The remaining articles were reviewed by two investigators (GG and RW) independently, Kappa Interobserver was determined (k = 0.92) and disagreements were solved by consensus. There were 1678 studies excluded after abstract screening, and then considering the inclusion/exclusion criteria during full text review, 106 studies were selected and included in this paper (PRISMA flow diagram in **Figure 2**). Relevant articles found in the references of the included papers were also added to this review (4 papers added).

The primary outcomes of this article are: (i) to synthesize the knowledge of the effect of testosterone on the QT interval (ii) to further the clinical understanding that low testosterone states are a potential risk factor for arrhythmia development (iii) encourage clinicians to consider testosterone levels and QTc interval when prescribing potentially arrhythmogenic drugs.

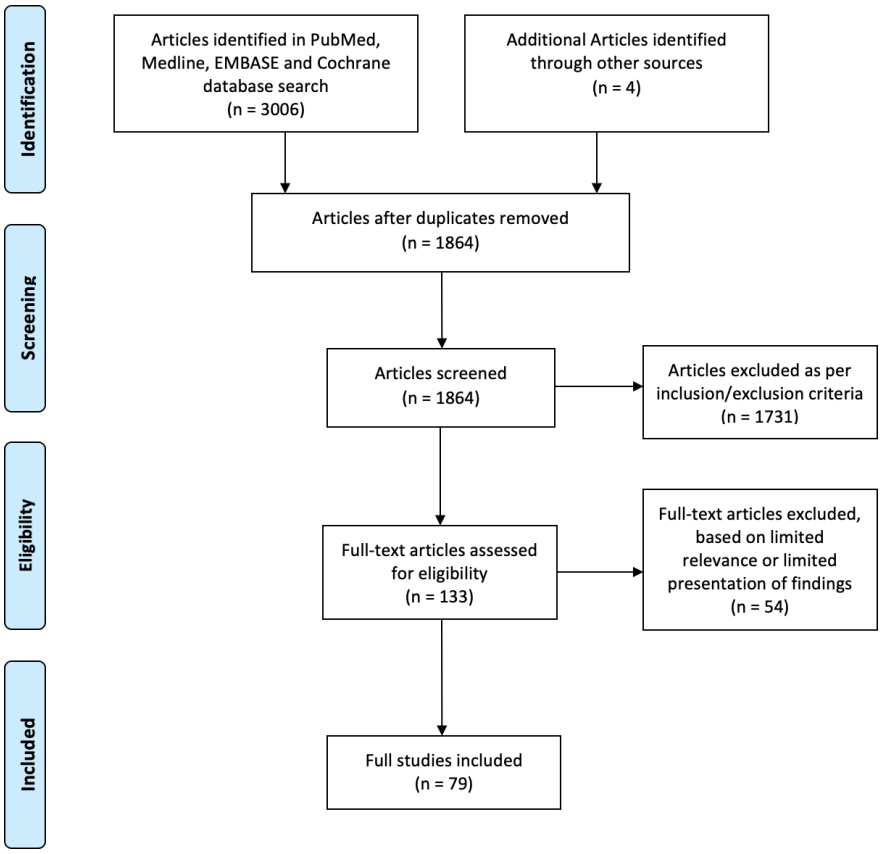

Figure 3. PRISMA flow diagram obtained from Covidence showing the process of study selection for this literature review (7).

3.0 Results

3.1 Effects of testosterone on the QT interval of humans

In men, testosterone ranges from 9-38 nmol/L and has QT shortening effects in a dose dependent manner, which become evident as testosterone rises with puberty (1). In different patient populations high testosterone levels (exogenous and endogenous) resulted in significant QT interval shortening in both men and

women (8–10). For instance,*Schwartz et al* (8), showed that older men and women exposed to testosterone for 12 weeks presented with significant QT interval shortening (for men: 385 ± 28ms to 382 ± 28ms, p < 0.002; and for women: 400 ± 25ms to 397 ± 23ms, p = 0.06), when compared to placebo. Additionally, testosterone increases the repolarization reserve (redundancy of repolarization currents in cardiac cells) which protects the heart against the effects of QT prolonging drugs such as Quinidine (11). Women taking Drospirenone – an anti-androgenic pill, have higher incidences of drug induced QT prolongation (12). In comparison, prostate cancer therapy which involves the use of androgen depravation therapy is associated with considerable cardiovascular risk and QT lengthening (12–17). In a comparable fashion breast cancer therapy can also modify the QT interval. For instance, aromatase inhibitors (AIs), cause the accumulation of testosterone resulting in QT shortening (12,18). As**Table 1** shows, research conducted on testosterone in humans explains that the shortening of the QTc interval occurs through the upregulation and downregulation of ion channel expression and function in the presence of testosterone.

3.1.1Conditions affecting testosterone levels and the QT interval

Different genetic, congenital and metabolic conditions can affect testosterone levels in men and women. For instance, men with congenital adrenal hyperplasia (CAH) present with longer QTcF (corrected with the Fridericia equation) and significantly lower serum total testosterone levels (19). In comparison women with CAH, were found to have a shorter QTcF compared to controls (404±2 msec vs. 413±2.1 msec, p<0.001) and these patients present with higher blood levels of total testosterone and significantly lower FSH levels (P<0.05) (19). Patients with Klinefelter syndrome (KS) receiving testosterone replacement therapy had shorter QTc compared to untreated KS patients and healthy controls (20). Hypogonadal men tend to have longer QT intervals and are almost twice as likely to suffer LQT than eugonadal men; this effect is further exacerbated in obese hypogonadal males (21–24). Men with decompensated cirrhosis exhibit significant QT interval prolongation as well as profoundly diminished free testosterone; likely secondary to increased levels of sex hormone binding globulin (25). Women with PCOS, which have higher levels of testosterone and estrogen present with QTc shortening (401±61ms vs 467±61ms in controls; p=0.007) and increased QT dispersion (the difference between the longest and shortest QT interval on an ECG) (26,27). Male patients with Cushing's syndrome presented with QT prolongation (426.9 ± 9.27 vs. 389.7 ± 8.31, p < 0.05). The high level of cortisol in these patients causes a lowering in testosterone levels (28). In the case of testosterone deficiency, the QT prolongation and other physiologic changes were resolved by testosterone administration.

Negative Studies on QT interval in hypogonadal men

Several studies have failed to show an association between testosterone deficient states and QTc prolongation. *Kirilmaz et al* (29) and*La Fountaine et al* (30) found no significant change in the QT interval of hypogonadal patients compared to healthy controls.*Lubart et al* (31) and *Olsson et al* (32), both did not find QT prolongation after ADT treatment. And *Zhao et al* (33), was not able to find an association between testosterone and QT, or a protective role for testosterone, in a large cohort of older Chinese men (4212 men).

Table 1. Biochemical effect of testosterone on humans and human derived tissue (34–42)

Literature	Study design
Gagliano-Jucá et al. 2017 [35]	RCT: Testosterone replacement therapy effect on QTc
Gagliano-Jucá et al. 2018 [36]	Prospective cohort study: Changes in QT with ADT (control: prostatectomy no ADT treat
Huo et al. 2019 [37]	Experimental study: Study sex hormonal influences on human iPSCs derived cardiomyocyt
LaFountaine et al. 2011 [38]	Cross-sectional study: Testosterone replacement therapy in males with hypogonadism and S
Piccirillo et al. 2019 [39]	Intervention study: Testosterone replacement therapy in males with hypogonadism (control
Salem et al. 2018 [40]	Prospective cohort study: Testosterone replacement therapy in males with hypogonadism a
Salem et al. 2019 [41]	Experimental study: ADT – Enzalutamide (Xtandi®, Astellas Pharma US, Inc., Northbro
Vicente et al. 2014 [42]	Cross-sectional study: Testosterone effects on ECG parameters
Wu et al. 2008 [43]	Experimental study: DHT treatment in HEK293 cells

Abbreviations Table 1

ADT: Androgen deprivation therapy

APD: Action potential duration

AR: Androgen receptor

AR45: Variant of the Androgen receptor

DHT: Dihydrotestosterone

FPD: Field potential duration

G: Gene

hERG: human Ether-à-go-go-Related Gene

Human iPSC: Human induced pluripotent stem cell

IC: Ion channel

I_{CaL}: L-type Ca^{2+} current

I_{Kr}: delayed rectifier rapid K+ current

I_{Ks}: delayed rectifier slow K+ current

QTc: Corrected QT interval

QTcF: Corrected QT interval with the Fredericia equation

QTe: Interval between the q wave the end of T wave

QTp: Interval between the q wave and the peak of T wave

RCT: Randomized controlled trial

SCI: Spinal cord injury

Te: Interval between the peak and the end of T wave

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3.2 Effects of testosterone on the QT interval of animals

Testosterone has been shown to be a major factor contributing to the shortening of the QTc interval and lowering the risk of TdP in a variety of animal models (3). Similarly, to humans QTc shortening can

occur through the upregulation and downregulation of ion channel expression and function in the presence of testosterone (**Table 2**). Several animal models were considered for this study and showed a trend in concordance with human studies. In adult male and female rabbits, testosterone shortens the length of the APD as well as decreases the susceptibility to arrhythmogenesis and triggered activity (43–45). Following this trend, rat models in a testosterone deficient state presented with QT prolongation, which could be restored to normal by testosterone administration (1). For instance, *Lujan et al* (46), showed that ORCX rats have longer QT intervals than normal rats.**Table 2** presents an extensive list of animal models and results further supporting the inverse relation between testosterone and the QT interval.

Table 2. Biochemical effect of testosterone on animals (43,44,47–71)

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Barajas-Martinez et al. 2009 [48]	Experimental study: Testosterone effect on cardiac repolarization in dog cardiomyocytes	Cardiomyocytes from adult mongrel dogs weighting between 30 and 35kg	N/A	I_{Na} amplitude and transmural distribution	Treatment with testosterone: I_{Na} (IC): reduced transmural dispersion.
Fülöp et al. 2006 [49]	Experimental study: Testosterone and Estrogen effect on ECG parameters and cardiac channel expression	Male and female dogs (gonadecto-mized and WT)	20	ECG parameters (HR and QTc) and protein expression analysis	Treatment with testosterone: QT shortening, I_{K1} (IC): upregulation and I_{to} (IC): upregulation.
Bai et al. 2005 [50]	Experimental study: Testosterone effect on cardiac repolarization via a NO-dependent mechanism	White Hartrey guinea pig ventricular myocytes	36	APD and membrane current using patch clamp technique	Treatment with testosterone: APD shortening, I_{Ks} (IC): upregulation, I_{CaL} (IC): downregula-tion and NOS3 (E): phosphorylation.
James et al. 2004 [51]	Experimental study: Ion channel expression and APD in male and female guinea pig cardiomyocytes	Duncan-Hartley male and female guinea pig cardiomyocyte	33	Ion currents and APD	Treatment with testosterone: APD shortening, higher I_{K1} (IC) and higher I_{CaL} (IC)

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Yang et al. 2010 [52]	Simulation – experimental study: Testosterone effect on a guinea pig computational model	Guinea pig computational model	N/A	Sexual hormone effects on simulated cardiac tissue	Treatment with testosterone: QT shortening.
Raghu et al. 2009 [53]	Experimental study: Haloperidol (Haldol®, Janssen Pharmaceuticals, Inc., Titusville, NJ) effect on cardiac electrophysiology	Albino male guinea pig hearts	9	AP duration	Treatment with testosterone: APD prolongation.
Argenziano et al. 2014 [54]	Experimental study: DHT effect on cardiac ion channel expression	Immortalized mouse cardiomyocyte (HL-1)	N/A	Androgenic control of gene expression	Treatment with DHT: APD shortening, NCX (IC): upregulation and Kv4.3 (G): upregulation.
Brouillette et al. 2005 [55]	Experimental study: Comparing testosterone levels and current density between the 2 mice strains	CD-1 and C57BL/6 mice isolated ventricular myocytes	59 CD-1 and 35 C57BL/6 mice	Testosterone levels and current density using whole-cell voltage clamp recoding	Higher levels of testosterone: Shorter APD and higher I_{Kur} (IC) in the CD-1 strain.
Brouillette et al. 2003 [56]	Experimental study: Compare the cardiac electrophysiology differences in gonadectomized and control mice	CD-1 male mice	42	ECG parameters (APD and QTc) and protein expression	Testosterone deficiency: QT prolongation and I_{Kur} (IC): downregulation.

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Crump et al. 2016 [57]	Experimental study: Effect of KCNE4 deletion in mice isolated cardiomyocytes	Isolated cardiomyocytes from KCNE4 knockout C57BL/6 mice	24	Electrophysiological activity of mice cardiomyocytes	KCNE4 deletion: QT prolongation.
Hu et al. 2018 [58]	Experimental study: APD measurements in KCNE4 knockout male and female mice (control: wild-type mice)	KCNE4 knockout mice ventricular myocytes	62	ECG parameters (QT) and testosterone measurements	KCNE4 deletion: QT prolongation.
Sun et al. 2018 [59]	Experimental study: Effects of Valsartan on Gonadectomized mice	Male ICR mice	12	Path-clamp measurements of cardiac electrophysiology	Gonadectomy: APD prolongation, I_{to} (IC): downregulation, I_{Kur} (IC): downregulation, I_{Na} (IC): upregulation and Connexin 43 (P): downregulation.
Tsai et al. 2015 [60]	Experimental study: Study the effects of ARKO on cardiac arrhythmogenesis (control: wild-type mice)	Right ventricular outflow track tissue from ARKO mice	12	Cardiac electrophysiology and arrhythmogenesis	Androgen receptor knockout: APD prolongation, I_{CaL} (IC): upregulation, NCX (IC): upregulation, RyR2 (R): upregulation, Phospholamban (R): upregulation, CAMKII (G): upregulation and GRK2 (G): upregulation.

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Tsai et al. 2013 [61]	Experimental study: Study the effects of ARKO in the modulation of atrial electrophysiology and arrhythmogenesis (control: wild-type mice)	ARKO mice left atrium	20	Cardiac electrophysiology and protein expression	Treatment with Isoproterenol: QT prolongation.
Zhang et al. 2017 [62]	Experimental study: Gonadectomy and susceptibility to atrial fibrillation	Male ICR mice	18	Susceptibility to atrial fibrillation	Gonadectomy: QT prolongation and I_{Na} (IC): upregulation. Gonadectomy increased the incidence of atrial fibrillation. Parameters returned to normal after DHT administration.
Drici et al. 1996 [63]	Experimental study: Effect of sexual hormones on cardiac repolarization (control: no DHT or E2 treatment)	Female albino New Zealand white rabbit hearts	24	ECG parameters (QT), mRNA expression and cardiac electrophysiology	Quinidine (Quinidex®, Wyeth Pharms Inc., Philadelphia, PA) treatment: QT prolongation and I_{Kr} (IC): downregulation. Treatment with DHT or E2 in OVX rabbits: QT prolongation, I_{Ks} (IC): downregulation and I_{Kur} (IC): downregulation.

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Lang et al. 2016 [64]	Experimental study: Specific differences in cardiac electrophysiology in a rabbit model (control: no DHT or E2 treatment)	Male and female rabbits	43	ECG measurements (QT)	Ovariectomy in female rabbits: SERCA (IC): downregulation. Testosterone treatment: I_{Kr} (IC): upregulation, I_{K1} (IC): upregulation and I_{Ks} (IC): upregulation.
Liu et al. 2003 [45]	Experimental study: DHT treatment in ORX rabbits (control: no DHT treatment)	Hearts isolated from ORX New Zealand male white rabbits	35	ECG and patch-clamp recordings	Treatment with DHT in ORX rabbits: QT shortening, I_{K1} (IC): upregulation and I_{Kr} (IC): upregulation.
Pham et al. 2002 [65]	Experimental study: DHT or E2 treatments on gonadectomized rabbits (control: no DHT or E2 treatment)	Epicardial and endocardial myocytes isolated from New Zealand White rabbits gonadectomized at age 50–60 days	36	I_{CaL} density and function using patch clamp technique	Treatment with DHT or E2 in OVX rabbits: QT prolongation and I_{CaL} (IC): Increased transmural dispersion.
Pham et al. 2001 [66]	Experimental study: Dofetilide exposure in gonadectomized rabbits (control: no gonadectomy)	Isolated right ventricular endocardium from control and gonadectomized rabbits	16	APD measurements using microelectrodes	Exposure to Dofetilide (Tikosyn®, Pfizer, NY, NY) in gonadectomized rabbits: APD prolongation and I_{Kr} (IC): blocking.
Pham et al. 2002 [67]	Experimental study: DHT treatment in female rabbits (control: no DHT treatment)	Ventricular myocardium from female rabbits	61	ECG parameters using microelectrodes (APD)	Treatment with DHT: APD shortening and I_{Kr} (IC): upregulation.

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Valverde et al. 2003 [44]	Experimental study: Gender differences in cardiac repolarization in rabbits	New Zealand white rabbits	44	ECG parameters and microelectrode recordings (APD)	Testosterone in male rabbits: APD shortening.
Argenziano et al. 2017 [68]	Experimental study: Androgenic inhibition in male rats (control: placebo instead of androgenic inhibition)	Right ventricular free wall from male Wistar rats	20	ECG (APD) and electro-physiology measures	Androgenic inhibition with Finasteride (5a-reductase inhibitor) or Flutamide: QT prolongation, I_{to} (IC): down-regulation and NCX (IC): downregulation.
Ayaz et al. 2015 [69]	Experimental study: ORCX rats treated with E2 (control: no gonadectomy and no E2 treatment)	Left ventricular tissue from Male Wistar rats	27	APD and contraction measurements and expression of Ca^{2+} and K+ channels	Orchiectomy: APD prolongation, K^+ channel: downregula-tion and I_{CaL} (IC): upregulation.
Eleawa et al. 2013 [70]	Experimental study: Gonadectomy and testosterone treatment in male rats (control: no testosterone treatment)	Male rats	104	ECG parameters (QT) and protein expression	Orchiectomy: QT prolongation, I_{K1} (IC): downregula-tion and I_{Na} (IC): downregulation.
Masuda et al. 2018 [8]	Experimental study: Testosterone treatment in gonadec-tomized rats	Male and female rats	6	ECG parameters (QTc) and I_{Ks} expression and density	Treatment with testosterone: QT shortening and I_{Ks} (IC): upregulation.

Literature	Study design	Sample characteristics	Sample size (n)	Outcome measures	Relevant findings
Shuba et al. 2001 [71]	Experimental study: Testosterone and neuroleptic – Haloperidol Pimozide and Fluspirilene treatment in Xenopous oocytes	hERG expressing Xenopous oocytes	32	hERG expression	Treatment with neuroleptics: QT prolongation and hERG (G): downregulation.

Abbreviations Table 2

APD: Action potential duration

ARKO: Androgen receptor knockout

DHT: Dihydrotestosterone

E: Enzyme

E2: Estradiol

G: Gene

IC: Ion channel

I_{CaL}: L-type Ca^{2+} current

I_{K1}: inward rectifying current

I_{Kr}: delayed rectifier rapid K+ current

I_{Ks}: delayed rectifier slow K+ current

I_{Kur}: delayed rectifier ultra-rapid K+ current

I_{NaL}: late Na current

I_{to}: transient outward K current

NCX: Na^{+}/Ca^{2+} exchanger

ORX: Orchiectomized

P: Protein

QTc: Corrected QT interval

RyR2: Ryanodine Receptor 2

SERCA: Sarcoplasmic reticulum Ca^{2+}-ATPase

4.0 Discussion

4.1 Effect of testosterone on QT interval

The current literature supports the QTc shortening effect of testosterone in both men and women through the upregulation of K^+ currents and the suppression of Ca^{2+} currents. (**Tables 1 and 2**). QTc prolongation can also be the result of genetic, congenital and acquired causes including medications, heart blocks, endocrine abnormalities, electrolyte abnormalities or CNS injury (**Table 3**). Regardless of the mechanism, a prolonged QT interval is predictive for arrhythmogenesis, such as increased PVCs and TdP (1). The findings encountered in animal models support those in humans, portraying similar mechanisms of action for testosterone (**Table 2**). This further supports that testosterone levels are inversely correlated with the QT interval and that testosterone is protective against arrhythmogenesis (46,47,69). It is important to note that some studies have found the opposite result or a negative result when studying testosterone effects in humans and animal models (37,61,72,73).

Table 3, Drug and non-drug causes of QT prolongation or increased QT prolongation risk (29,30,34,36,41,42,44,83,120,126,127)

Drug induced QT prolongation	Drug induced QT prolongation	Physiologically induced QT prolongation	Physiologically induced QT prolongation
Class	**Drug**	**Category**	**Cause**
Antiandrogens	Apalutamide AR inhibitors CYP inhibitors Degarelix Enzalutamide Finasteride Flutamide GnRH agonists and antagonists	**Cardiac**	Bradycardia Heart failure Hypertension Myocardial infarction Ventricular hypertrophy
Antiarrhythmics	Amiodarone Disopyramide Dofetilide Ibutilide Procainamide Quinidine Sotalol	**Electrolytes**	Hypocalcemia Hypokalemia, Hypomagnesemia
Antibiotics	Clarithromycin Erythromycin Grepafloxacin Levofloxacin Moxifloxacin Pentamidine Sparfloxacin	**Endocrine**	Cushing's Diabetes mellitus Hyperthyroidism
Antidepressants	Amitriptyline Desipramine Doxepin Fluoxetine Imipramine Maprotiline Sertraline	**Genetic**	Congenital adrenal hyperplasia Kalman syndrome Klinefelter syndrome LQTS: LQT1 (KCNQ1), LQT2 (KCNH2) and LQT3 (SCN5A) Prader-Willi syndrome
Antihistamine	Astemizole Terfenadine	**Hepatic**	Cirrhosis
Antimalarial	Chloroquine Halofantrine	**Patient factors**	Advanced age Female gender High body mass index High cholesterol Low testosterone

Drug induced QT prolongation	Drug induced QT prolongation	Physiologically induced QT prolongation	Physiologically induced QT prolongation
Antipsychotic	Chlorpromazine Citalopram Clozapine Droperidol Haloperidol Mesoridazine Pimozide Risperidone Sertindole Thioridazine Ziprasidone	**Renal**	Chronic renal disfunction
GI drugs	Cisapride Domperidone	**Trauma**	Testicular torsion
Opiate agonists	Methadone		
Other	Arsenic trioxide Bepridil DECA Diuretics Probucol		

Abbreviations Table 3

AR: Androgen receptor

GnRH: Gonadotropin releasing hormone

LQTS: Long QT syndrome

4.2 Clinical evidence of arrhythmia in low testosterone states

Due to the inverse relation between testosterone levels and the length of the QT interval, testosterone deficient states can lead to QT interval prolongation, promoting arrhythmogenesis. In humans, testosterone deficient states can occur in the context of disease (e.g. CAH (19), hypogonadism (21), Cushing's syndrome (28), decompensated cirrhosis (25), etc.) and androgen deprivation therapy for the treatment of prostate cancer (13,16,35,40). In all of these cases, testosterone administration and/or stopping ADT were able to return the QT interval back to normal levels. In animals, similarly to humans, testosterone deficient states such as after orchiectomy or by knocking out the cardiac androgen receptor (ARKO mice), prolong the QT interval and increase the risk of arrhythmogenesis and the effect of QT prolonging drugs (53,65,77) (**Table 2**).

4.3 Clinical recommendations and considerations

This systematic review highlights the importance of testosterone in relation to the electrophysiological function of the heart and makes a strong case for increasing our level of clinical consideration for testosterone as an important factor when deciding therapeutic options and susceptibility for arrhythmogenesis. There are many medications used in the treatment of both common and life-threatening conditions that have QT prolonging effects (eg. anti-arrhythmics, anti-depressants, anti-psychotics etc. – **Table 3**) (75). Hence, recognizing whether these patients are in testosterone deficient state becomes very important to reduce their risk of arrhythmogenesis (**Figure 2**). For instance, special considerations should be taken with patients undergoing androgen depravation therapy, gender transition from male to female and patients with genetic and those with medical conditions that lower their testosterone levels (eg. primary or secondary hypogonadism, liver disease) (13,25,40).

Currently there are no guidelines to perform ECGs prior to starting a potentially arrhythmogenic therapy. Additionally, there are no recommendations in regards to how patient should be counselled regarding the risk of arrhythmia development (78). It is our recommendations to assess for risk factors of QT prolongation before starting potentially arrhythmogenic therapies, if there is any suspicion for a testosterone deficient state. We encourage clinicians to perform routine ECGs before starting potentially arrhythmogenic therapies, especially on patients who may have risk factors for arrhythmogenesis and/or low testosterone (79) (**Figure 4**). For patients starting a QT prolonging medication, the British Medical Journal – Drug and Therapeutics Bulletin recommends a baseline ECG and another ECG once the drug has reached steady state (78). This paper also encourages us to keep looking into the effects of testosterone as a protective hormone against arrhythmogenesis, and its therapeutic potential. Some limitations that should be noted include the omission of gray literature and the exclusion of papers in other languages than English or Spanish.

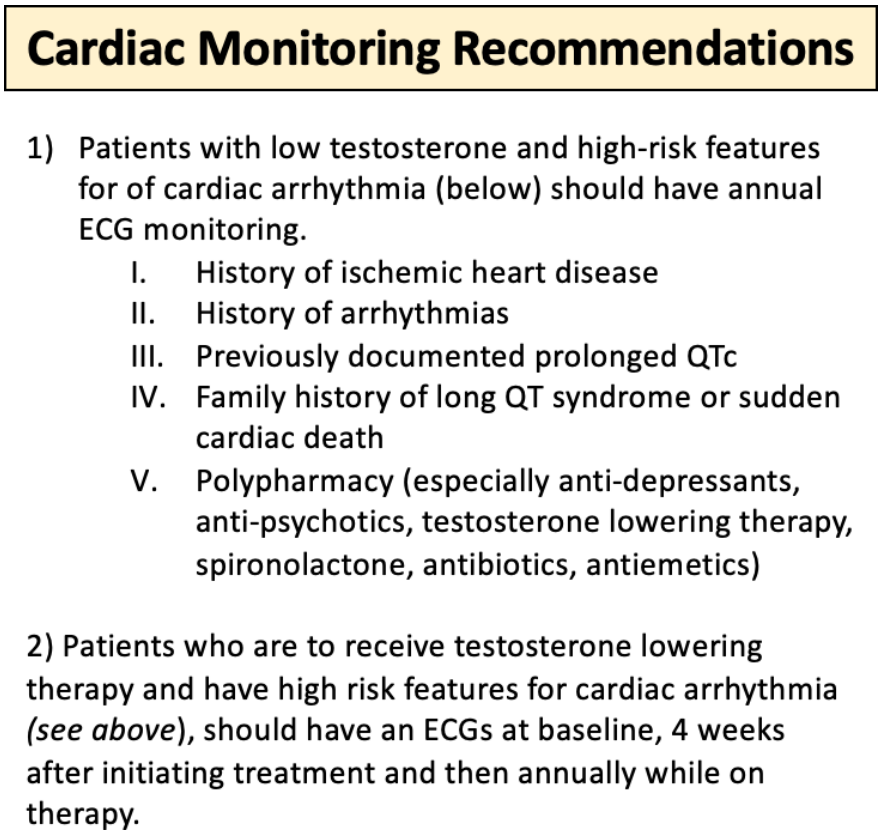

Figure 4. Cardiac monitoring recommendations for patients with low testosterone (4–6)

5.0 Conclusion

There is clear evidence in humans and animals to suggest that testosterone has a shortening effect on the QT interval and that states of testosterone deprivation are associated with QTc prolongation and thus, arrhythmogenesis. This highlights the importance of testosterone in clinical considerations and encourages us to increase our understanding of testosterone deficient states as important factors determining the risk of arrhythmogenesis.

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8.0 Disclosures

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