Testosterone treatment in chronic heart failure. Review of literature and future perspectives

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Abstract

Mounting evidence suggests that hormonal deficiencies (HD) have an important role in chronic heart failure (CHF). In particular, androgen depletion is common in men with CHF and is associated with increased morbidity and mortality. This review summarizes the current understanding of the complex relationship between CHF and testosterone, focusing on evidence derived from clinical trials that have investigated the role of testosterone in the treatment of CHF. A greater comprehension of this area will allow researchers and clinicians to plan future studies that improve current strategies to reduce mortality in this high-risk population. Online databases PubMed (Medline), Web of Science, and Scopus were searched for manuscripts published prior to June 2018 using key words “heart failure” AND “testosterone” OR “anabolism” OR “hormone” OR “replacement treatment”. Manuscripts were collated, studied and carried forward for discussion where appropriate. In summary, findings from the literature demonstrate that testosterone treatment in CHF is a promising topic that requires further investigation.

Introduction

Since the previous view of chronic heart failure (CHF) as a syndrome merely based on disordered hemodynamic and fluid balance has switched into a view of the disease involving different molecular pathways in disarray, our understanding of CHF has improved dramatically [1,2]. CHF is now considered not only as a “cardiac disease” caused by alterations in the structure and function of the heart but as a “systemic disease” in which the interplay between myocardial factors, systemic inflammation, comorbidities, and neurohormonal activation plays a pivotal role [3]. With the aim of improving the assessment and treatment of patients with CHF, the current vision has progressed from a focus on the recovery and support of solely hemodynamic aspects of the patient’s condition, to a more targeted view aimed at modifying the maladaptive molecular processes that contribute to progression of disease [4-6].

In this context, mounting evidence suggests that hormonal deficiencies (HD) have an important role in CHF [7-11]. In particular, androgen depletion is common in men with CHF and is associated with increased morbidity and mortality [12,13]. In this review, we summarize clinical data and potential applications of testosterone treatment in CHF.

Testosterone and heart failure. Pathophysiological side

The interaction between hormones and cardiac structure and function is an area that is well understood [14-18]. In this context, there are several studies sought to investigate the pathophysiological mechanisms underpinning this relationship.

The fact that androgen receptors (AR) are expressed in atrial and ventricular myocardial cells suggests that testosterone may act directly
at the cellular level [19]. Testosterone and its active counterpart dihydrotestosterone exhibit biological effects by interacting with AR expressed on cell surfaces as well as in the cytosol. Androgens can mediate different response depending on the type of interaction with the receptor. AR expressed on the surface seem to be more responsible for the activation of ion channels and signaling pathways, while intracellular AR are involved in the modulation of androgen target genes that regulate myocardial and vascular cell activity [20]. In addition, polymorphisms of AR seem to play a role, in particular on metabolic profile [21]. Independently from its genomic effect, however, testosterone interacts with myocardial cells by regulating intracellular calcium (Ca2+) homeostasis. Experiments performed on cardiomyocytes of rats showed that testosterone inhibits voltage-dependent Ca2+ channels, resulting in a rapid vaso-relaxation in both large arteries and smaller resistance vessels [20]. Moreover, it has been evaluated whether testosterone may have effects on the action potential duration (APD). Some observations suggest that low testosterone levels prolong APD, increase intracellular Ca2+ release and, consequently, the duration of contraction [22]. On the other hand, results obtained in gonadectomized female mice showed an increased neutrophil infiltration in the border zone of injured tissue after induction of myocardial infarction when compared with the same group supplemented with testosterone. These data suggest that testosterone is able to increase inflammation through neutrophil local infiltration after acute myocardial infarction. Moreover, this inflammatory status results also in a higher rupture rate during left ventricular remodeling and higher mortality rate secondary to cardiac rupture [23]. There are no clear data about the role and the importance of this inflammation.

Of note, evidence emerging form studies on testosterone deficiency suggest that testosterone is linked to the regulation of metabolic profile. In particular, endogenous testosterone levels improve lipid profile and reduce insulin resistance. Currently, there is no clear consensus on the association between endogenous testosterone levels and the effect of lipid profile, even though evidence suggests that testosterone inhibits the maturation of preadipocytes into mature adipocytes, reduces total fat mass and increases net lean mass [24,25]. In addition, recent evidence suggests that testosterone is a metabolic hormone that differentially regulates the expression of key targets of lipid and glucose metabolism in a tissue-specific manner to potentially reduce fat deposition in pathologically relevant locations such as the liver and arterial tree [26]. Moreover, testosterone improves fasting glucose levels and glucose tolerance. Indeed, it has been reported that men with low testosterone levels have double the risk of developing new onset type 2 diabetes and metabolic syndrome [27].

For this reason, it has been hypothesized that testosterone plays a pivotal role in the prevention of the metabolic syndrome [28].

**Testosterone and heart failure. Clinical side**

Several studies have investigated the role of testosterone in the treatment of CHF (Table 1).

The first of these was conducted in 12 stable male patients by Pugh et al. [29]. After administration of a single dose of testosterone (60 mg orally), the authors monitored central haemodynamic over 6 h using a pulmonary flotation catheter. Subjects received the second treatment on day 2 and haemodynamic monitoring was repeated. They observed an increase in cardiac output in the treated arm, mainly mediated by a reduction in peripheral resistance and left ventricular afterload. It is interesting to note that no side effects were reported and that results were more evident in patients with lower baseline levels of testosterone.

A few years later, the same group performed a double-blind, placebo-controlled study, enrolling 20 male CHF patients [30]. The treatment group (100 mg every 2 weeks for 12 weeks) showed a significant improvement in 6-minute walking distance and in the Minnesota living with heart failure questionnaire score. Following these promising results, they performed a larger randomized, double-blind, placebo-controlled trial in 76 CHF patients [31]. In the treated group (5 mg/day administered by an adhesive skin patch), authors demonstrated an improvement in clinical disease severity as demonstrated by the reduction of at least one NYHA class (30% of patients vs 8% in treated and untreated, respectively). In addition, even if testosterone did not change left ventricular morphology or function, a significant improvement in shuttle walk distance was demonstrated. On the other hand, treatment had no significant effect on measurements of skeletal muscle bulk and strength, heart rate, blood pressure, nor weight. With regard to plasma concentrations of cytokines (e.g., TNFα, IL-1β, and IL-6), of which have demonstrated and emerging role in CHF in recent years [32], no differences were described. This was in line with a previous report [33] where the administration of physiologic concentrations of testosterone to male patients with CHF had no effect on the serum concentrations of TNF-α, whether administered acutely over 6 h or over a longer 12-week period, either via intramuscular injection or transdermal patch.

Of note, even though this research group previously demonstrated that testosterone therapy was able to reduce QT interval duration in men with CHF [34], with these data confirmed by an independent group a few years later [35], further confirmation of these results was not possible in this larger cohort. Finally, testosterone treatment was well tolerated even though some local reactions caused by the patch preparation were described.

Considering that elderly patients display a deterioration of skeletal muscle strength, affecting early fatigue and limiting exercise tolerance [36,37], in a double-blind, randomized, placebo-controlled study focused on these patients, Caminiti et al. [38] demonstrated that testosterone therapy (12 weeks with very long acting intramuscular 1000 mg testosterone undecanoate) improves functional exercise capacity and muscle strength. In 70 elderly patients with stable CHF and median age of 70 yr, peak VO2 and index of muscular strength (e.g., quadriceps maximal voluntary contraction and peak torque) improved in the testosterone group but not in the placebo group. Furthermore, glucose metabolism (HOMA-IR) and baroreflex sensitivity also improved in the testosterone group.

In 2014, Miramadi et al. [39] performed a double-blind, placebo-controlled trial, in which 25 male patients received an intramuscular (gluteral) long-acting androgen injection (1 mL of testosterone enan-thate 250 mg/mL) once every 4 weeks for 12 weeks. When compared with the placebo arm, the treatment group displayed a significant increasing trend in 6-minute walking distance and quality of life.

Further, Stout et al. [40] demonstrated that testosterone supplementation added to a program of exercise rehabilitation was feasible and can positively impact on a range of key health outcomes in elderly male patients with CHF who have a low testosterone status. Indeed, testosterone treatment (an intramuscular (gluteral) injection of 100 mg testosterone once a fortnight for 12 weeks) induced positive changes in aerobic fitness, leg strength, depression, and androgen deficiency symptoms that were not observed in the placebo group. In this context, a very interesting study was performed by dos Santos and colleagues [41]. In this study, 39 male patients with advanced CHF (NYHA class III) and testosterone deficiency were randomized to training (4-month cycleergometer training), testosterone (intramuscular injection of testosterone undecylate for 4 months), and training + testosterone. Authors not only confirmed that testosterone therapy was able to potentiate the beneficial effects of exercise training in patients with CHF, but provided...
interesting information about the effects of the combined therapies on total body composition, functional capacity, hormonal status, and quality of life, supporting the concept that the peripheral effect of testosterone facilitates the improvement in cardiovascular performance.

Considering the important topic of sex differences in disease [42-47], the effect of testosterone treatment has been investigated also in female populations. In 36 female patients treated with testosterone (300 mg, transdermal patch, twice per week), an improvement in 6-minute walking distance and peak oxygen consumption was observed. In this group, a positive effect was further observed on metabolic pattern (via insulin resistance) [48]. In addition, also in female patients, a direct effect of testosterone to shorten ventricular repolarization in vivo was demonstrated [35].

**Clinical implication**

Recently, a meta-analysis performed by Toma and colleagues [49] demonstrated that testosterone supplementation in patients with CHF is associated with a clinically significant improvement in the exercise capacity, expressed as 6-minute walk test distance. Of note, this improvement was greater than that seen with other CHF treatment (e.g., beta-blockers and ACE inhibitors, etc.). Also VO₂peak and NYHA class improved in patients receiving testosterone treatment.

Because this progress is not associated with an improvement in cardiac structure or function, the cause of these findings is most likely due to peripheral mechanisms, as showed by dos Santos et al. [41].

It is important to underline that only small trial data are available from current literature, recruiting patients with differing characteristics and using alternative routes and dosage of testosterone. Further, all studies are focused in the setting of CHF with reduced ejection fraction (EF) and no data are available about CHF with mildly reduced or preserved EF. Finally, all these studies, because of the short term of their duration, are focused only on the investigation of changes in clinical parameters and not on strong clinical outcome, such as mortality and/or hospitalization. Of note, none of the trials showed a significant change in prostate specific antigen. In the studies using topical testosterone, skin reactions were described. Thus, there are no real safety concerns reported in any of the trials.

Another intriguing issue to argue is that the basal testosterone status was not used in all the studies as a parameter of inclusion or exclusion. Recently, in the context of HD in CHF [50-54], the idea that not all the patients need hormone therapy, but only patients with a deficit of the axis of interest, has improved the outcome and represents the most promising option in this field [55-58]. Finally, considering the high frequency of multiple HD in CHF, no data are available about combined hormone treatment.

**Conclusion**

Taken all together, findings from the most recent literature demonstrate that testosterone treatment in CHF is a promising topic that needs further investigation.

<table>
<thead>
<tr>
<th>First author [cit] (year)</th>
<th>Sample size</th>
<th>Sex</th>
<th>Mean age (years)</th>
<th>NYHA class (mean ± SEM)</th>
<th>Testosterone deficiency</th>
<th>Testosterone supplementation</th>
<th>Type of trial</th>
<th>Trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pugh PJ [29] (2003)</td>
<td>12</td>
<td>Male</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>60 mg orally day one and day 2</td>
<td>R, DB, PC, cross-over</td>
<td>2 days</td>
</tr>
<tr>
<td>Malkin CJ [34] (2003)</td>
<td>20</td>
<td>Male</td>
<td>61.5</td>
<td>2.5±0.5</td>
<td>NR</td>
<td>Sustanon 100 mg IM every 2 weeks</td>
<td>R, DB, PC</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Malkin CJ [31] (2006)</td>
<td>76</td>
<td>Male</td>
<td>64</td>
<td>2.5±0.6</td>
<td>NR</td>
<td>Androderm 5 mg every 24 hours</td>
<td>R, DB, PC</td>
<td>12 months</td>
</tr>
<tr>
<td>Caminiti G [38] (2009)</td>
<td>70</td>
<td>Male</td>
<td>70</td>
<td>2.5±0.5</td>
<td>NR</td>
<td>Long-acting testosterone undecanoate (Nebido) IM at 0, 6, 12 weeks</td>
<td>R, DB, PC</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Iellamo F [48] (2010)</td>
<td>32</td>
<td>Female</td>
<td>68.7</td>
<td>3±0</td>
<td>NR</td>
<td>Transdermal testosterone</td>
<td>R, DB, PC</td>
<td>6 months</td>
</tr>
<tr>
<td>Schwartz JB [35] (2011)</td>
<td>84</td>
<td>Male (69%) and Female (31%)</td>
<td>70.4</td>
<td>NR</td>
<td>Long-acting testosterone undecanoate 1,000 mg IM at 0, 6, 12 weeks</td>
<td>R, DB, PC</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Stout M [40] (2012)</td>
<td>41</td>
<td>Male</td>
<td>67.2</td>
<td>2.5±0.5</td>
<td>low testosterone status</td>
<td>Sustanon 100 mg IM every 2 weeks</td>
<td>R, DB, PC</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Mirdamadi A [39] (2014)</td>
<td>50</td>
<td>Male</td>
<td>60</td>
<td>2.4±0.6</td>
<td>NR</td>
<td>Long-acting testosterone enanthate 250 mg IM every 4 weeks</td>
<td>R, DB, PC</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Dos Santos MR [41] (2016)</td>
<td>39</td>
<td>Male</td>
<td>51</td>
<td>3</td>
<td>Testosterone deficiency</td>
<td>Intramuscular injection of long-acting depot testosterone undecylate</td>
<td>R</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

R, randomized; DB, double blind; PC, placebo-controlled; NR, not reported; SEM, standard error of the mean
References