



Review Article

Low Testosterone Level in Worsening Symptom of Heart Failure Patients: A Literature ReviewRyan Ardiansyah^{1*}, Akhmad Sandy Sauqy² ¹North Lombok Regional General Hospital, West Nusa Tenggara, Indonesia.²West Nusa Tenggara Regional General Hospital, West Nusa Tenggara, Indonesia.**ARTICLE INFO***Article history:*Submitted Feb 25th 2025Reviewed May 16th – Jun 4th 2025Accepted Jun 4th 2025Available online Sep 30th 2025**Correspondence:*shorinjiryan9@gmail.com*Keywords:*Low Testosterone Level
Worsening Symptom
Heart Failure**ABSTRACT**

Background: Heart failure can be caused by a variety of factors, including high blood pressure, coronary artery disease, diabetes, obesity, smoking, and genetics. Testosterone is the primary male hormone responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis, and fertility. It plays a crucial role in various bodily functions, including the development of male reproductive tissues and the maintenance of muscle mass and bone density. Testosterone levels have been found to be significantly decreased in heart failure patients compared to healthy controls. This suggests that low testosterone levels may play a role in the development or progression of heart failure. The relationship between testosterone and heart failure is complex and warrants further investigation. Additional research is needed to better understand the role of testosterone in heart failure and to determine the optimal therapeutic strategy for its management. Based on these data, we decided to further investigate how low testosterone levels affect the symptoms of heart failure patients. **Aims:** This literature review study aims to examine further how low testosterone levels affect the symptoms of heart failure patients. **Method:** Journals in this literature review used three databases, including Google Scholar, PubMed, and Science Direct, using the keywords "testosterone" and "heart failure." The literature search was adjusted based on the inclusion and exclusion criteria. **Result:** The search results were obtained from 10 international journals. The results showed that testosterone is crucial in maintaining men's health and well-being. Testosterone deficiency was associated with a worsening of HFpEF in men, those with lower testosterone levels had worse symptoms and a lower quality of life. **Conclusion:** Testosterone exerts an important regulation of cardiovascular function through genomic and nongenomic pathways. It influences contractility, energy metabolism of myocardial cells, apoptosis, and the remodeling process. Reduced testosterone levels in men with heart failure are associated with increased mortality and poor prognosis.

Highlights:

1. Testosterone deficiency is associated with worsening symptoms and poorer quality of life in men with heart failure with preserved ejection fraction (HFpEF).
2. The role of testosterone in cardiovascular health is multifaceted—its deficiency may contribute to adverse cardiac remodeling, while excessive levels may increase thromboembolic and inflammatory risks.

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Introduction

Heart failure is a complex clinical syndrome characterized by the inability of the heart to pump enough blood to meet the body's needs. It can be caused by a variety of factors, including high blood pressure, coronary artery disease, diabetes, obesity, smoking, and genetics^[1]. The condition is associated with symptoms such as shortness of breath, ankle swelling, and fatigue, and is diagnosed based on demonstration of underlying cardiac dysfunction. The pathophysiology of heart failure is multifaceted and can be caused by structural or functional cardiac abnormalities.^[2]

According to recent studies, the prevalence of heart failure is increasing, especially in developed countries with aging populations. Heart failure is now one of the most common reasons for hospitalization among the elderly. The prevalence of heart failure varies depending on the population studied, but is estimated to affect approximately 26 million people worldwide^[3]. The prevalence of heart failure has increased over the past 20 years, and this is partly due to the aging of the population and the increasing

prevalence of risk factors such as obesity and diabetes. Mortality rates associated with heart failure remain high, despite improvements in treatment strategies and overall outcomes of heart failure patients. Mortality rates are higher in patients with reduced ejection fraction compared to patients with preserved ejection fraction.^[4]

Testosterone is the primary male hormone responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis, and fertility. It plays a crucial role in various bodily functions, including the development of male reproductive tissues and the maintenance of muscle mass and bone density. Testosterone levels can be indicative of a range of conditions, and it is essential to understand the normal ranges and implications of low levels. The normal range for testosterone levels in adult men is typically between 280 to 1,100 nanograms per decilitre (ng/dL). However, the American Urological Association (AUA) guideline suggests using a cut-off

for low testosterone of 300 ng/dL when evaluating adult men.^[5]

Studies have shown that heart failure is more prevalent in elderly populations and is often associated with uncontrolled hypertension. Testosterone levels have been found to be significantly decreased in heart failure patients compared to healthy controls^[6]. This suggests that low testosterone levels may play a role in the development or progression of heart failure.

Furthermore, sarcopenia, or the loss of muscle mass, is a common feature in heart failure patients and affects 20-47% of them. Sarcopenia is an independent predictor of impaired functional capacity in heart failure patients, even after adjusting for clinically relevant variables. Lower testosterone levels have been associated with increased sarcopenia in heart failure patients, indicating that testosterone therapy might help improve muscle mass and physical performance.^[7]

The relationship between testosterone and heart failure is complex and warrants further investigation. However, existing evidence suggests that testosterone therapy might have potential benefits in heart failure patients, particularly in improving muscle mass and physical performance. Additional research is needed to better understand the role of testosterone in heart failure and to determine the optimal therapeutic strategy for its management. Based on these data, we decided to further

investigate how low testosterone levels affect the symptoms of heart failure patients.

Methods

The research design used is the Literature Study method with a Literature Review type. The reference or literature search strategy was carried out through the Google Scholar, PubMed, and Science Direct databases using the keywords "testosterone" and "heart failure." The literature search was adjusted based on the inclusion and exclusion criteria. Inclusion criteria included: 1) the period of journal publication from 2010-present, 2) the theme or content of the research journal is related to how low testosterone levels affect the symptoms of heart failure patients, 3) the type of journal used is a research journal, not a literature study, 4) national or international journals, 5) the journal is a full-text journal. The exclusion data includes 1) journals published under 2010, 2) journals that only show abstract text, and 3) journals that do not discuss how low testosterone levels affect the symptoms of heart failure patients.

Journal searches using Google Scholar found 169,000 journals, PubMed 400 journals, and Science Direct 17,923. So, that is a total of 187,323 journals. Then, screening was carried out to obtain journals based on inclusion and exclusion criteria. The screening results amounted to 21 journals. The journals analyzed and used as data in this study were ten journals, all of which were international.

The patient was discharged after seven days of IV antibiotic administration. Echocardiography evaluation before discharge showed improvement of LVEF to 55% with residual moderate pericardial effusion and bouncing interventricular septum. Therefore, a diagnosis of purulent bacterial myopericarditis was made. A cardiac magnetic resonance imaging (MRI) done one month later found residual sign of pericarditis and signs of constrictive pericarditis with pericardial thickening at basal- mid lateral IV, fibrin deposit and *late gadolinium enhancement* (LGE) at the same segments, with systolic jerk interventricular motion.

Surgical pericardiectomy was then performed with excellent result.

Analysis of 10 journals on how low testosterone levels affect the symptoms of heart failure patients showed that there were four studies^[8–11] that displayed Hazard Ratio (HR) values, all of which showed that testosterone levels were associated with worsening symptoms in heart failure patients (Table 1). Ewa A. Jankowska et al.^[8] showed that patients who had decreased testosterone levels had a risk of worsening 2.64 times than those who did not, while Elisabeth Wehr et al.^[9] showed that the lower the testosterone level, the higher the chance of worsening heart failure symptoms.

Table 1. Results of each journal on how low testosterone levels affect the symptoms of heart failure patients.

No.	Author	Prognosticators	HR	Patients without testosterone deficiency	Patients with testosterone deficiency	Before Testosterone Supplementation	After Testosterone Supplementation
1.	Ewa A. Jankowska et al ⁸	TT deficiency, yes vs. no	2.64				
2.	Elisabeth Wehr et al ⁹	Total testosterone (mg/L) ≤3.6	1.00 (reference)				
		Total testosterone (mg/L) 3.7-4.7	0.80				
		Total testosterone (mg/L) 4.8-6.1	0.59				
		Total testosterone (mg/L) >6.1	0.70				
		Risk for 1 SD increase in TT	0.50				
3.	Hai-Yun Wu et al ¹⁰	TT, increased per 1 nmol	0.97				
4.	Anna Florvaag et al ¹²	IVSd (mm)		12	11		
		Ejection fraction (%)		39	38		
		PAP (mmHg + CVP)		27	25		
5.	Martin Stout et al ¹³	NYHA				2.5	1.8
6.	Ahmad Mirdamadi et al ¹⁴	Quality of life (Short Form Health Survey questionnaire)				128.96	130.95
		Ejection fraction				34.52	37.12
7.	Marcelo Rodrigues dos Santos et al ¹¹	Readmission within 90 days	2.77				
		Mortality	4.65				
8.	Akiomi Yoshihisa et al ¹⁵	In the Kaplan–Meier analysis, all-cause mortality progressively increased from the first to the fourth quartile (log-rank, p = 0.010). Patients were divided into quartiles based on their TTlevels: first (632 ng/dl ≤ TT, n = 154), second (463 ≤ TT ≤ 631, n = 155), third (462 ≤ TT ≤ 301, n = 156), and fourth quartiles (TT ≤ 300, n = 153). The TT of ≤ 300 ng/dl is generally considered as low TT levels.					

9.	Marina Navarro-Pen˜alver et al. ¹⁶	NYHA class			2.18	2.8
		LVEF, %			29.88	29.90
10.	Ahmed Hamam et al. ¹⁷	NYHA III (n)	16	20		
		Testosterone levels be used as independent predictors of NYHA class III				P value = 0.008

Hai-Yun Wu et al.^[10] showed that each one nmol increase in testosterone levels decreased the risk of worsening heart failure symptoms by 0.97 times. In addition, Marcelo Rodrigues dos Santos et al.^[11] showed that testosterone levels are associated with death and readmission within 90 days. Heart failure patients who experience decreased testosterone levels will have a 90-day readmission risk of 2.77 times and will have a mortality risk of 4.65 times.

Anna Florvaag et al.^[12] compared patients with testosterone deficiency with those who did not; they found that IVSd, ejection fraction, and PAP of the group that did not have testosterone deficiency had better values than the group with testosterone deficiency. Ahmed Hamam et al.^[17] also compared the number of NYHA III cases between patients who had testosterone deficiency and those who did not, and the results were found to be more in the testosterone-deficient group. In addition, this study also found that testosterone levels can be used as independent predictors of NYHA class III (p-value = 0.008).

Three studies examined the effect of testosterone levels on symptoms of heart failure patients while providing interventions in the form of testosterone supplementation. Martin Stout et al.^[13] showed that

the NYHA grade decreased after testosterone supplementation. In contrast, Ahmad Mirdamadi et al.^[14] showed that the quality of life and ejection fraction of patients who received testosterone supplementation improved. Marina Navarro-Pen˜alver et al.^[16] showed that after testosterone supplementation, there was a decrease in NYHA degree and an increase in LVEF. One study¹⁵ found that all-cause mortality progressively increased from the first to the fourth quartile (log-rank, $p = 0.010$).

Discussion

Testosterone levels begin to decrease after age 40, and this decrease has been associated with an increase in all-cause mortality and cardiovascular disease (CVD)^[18]. Heart failure, a chronic condition characterized by the inability of the heart to pump enough blood to meet the body's needs, is often accompanied by other health issues, including hormonal imbalances. One such hormone is testosterone, which plays a crucial role in maintaining men's health and well-being. Endogenous and exogenous testosterone can have both positive and negative effects on the cardiovascular system. On one hand, testosterone has been shown to have cardioprotective effects, such as reducing the risk of heart attack and stroke.

On the other hand, high testosterone levels can contribute to the development of atherosclerosis, a condition in which the arteries become clogged with plaque, leading to reduced blood flow and increased risk of heart attack and stroke.^[19]

Depression and anxiety are common in patients with heart failure, and low testosterone levels have been linked to increased depression severity. In a study of 78 Caucasian male patients with dilated cardiomyopathy and chronic heart failure, researchers found a correlation between testosterone levels and depression severity, as assessed using the PHQ-9 Depression Test Questionnaire^[20]. This suggests that addressing testosterone deficiency may help improve mood and overall quality of life in heart failure patients.

A recent study published in the Journal of Cardiovascular Development and Disease investigated the relationship between testosterone deficiency and HFpEF in men. The study found that testosterone deficiency was associated with a worsening of HFpEF in men. The researchers measured testosterone levels in 100 men with HFpEF and found that those with lower testosterone levels had worse symptoms and a lower quality of life.^[17]

Testosterone deficiency is common in men with heart failure, and studies have shown an association between low testosterone levels and poor cardiovascular outcomes. Testosterone exerts an

important regulation of cardiovascular function through genomic and nongenomic pathways. It influences contractility, energy metabolism of myocardial cells, apoptosis, and the remodelling process. Reduced testosterone levels in men with heart failure are associated with increased mortality and poor prognosis. Testosterone replacement therapy has been shown to improve myocardial ischemia, exercise capacity, and serum glucose levels in men with heart failure. However, the effects of testosterone on the cardiovascular system are still not fully understood and may be different under normal physiological conditions and in disease states.^[18,21]

One study published in 2012 found that low testosterone levels in men were associated with an increased risk of cardiovascular disease, including heart failure. The study suggested that testosterone may have a protective effect on the heart, and that low levels of testosterone may contribute to the development of heart failure^[22]. Another study published in 2021 explored the relationship between testosterone and cardiovascular risk factors, including subclinical atherosclerosis, lipoprotein function, and heart failure. The study found that low testosterone levels were associated with an increased risk of heart failure, and that testosterone replacement therapy may be a potential treatment option for men with heart failure.^[23]

Research has shown that there is a link between low testosterone levels and heart failure.²⁴ Testosterone is a hormone that is important for the development and maintenance of male sexual characteristics, but it also plays a role in the cardiovascular system. Low levels of testosterone have been associated with an increased risk of cardiovascular disease, including heart failure. On the other hand, there is also

evidence that high levels of testosterone may be harmful to the cardiovascular system. A study published in The Lancet found that genetically predicted high levels of testosterone were associated with an increased risk of thromboembolism, heart failure, and myocardial infarction.^[25]

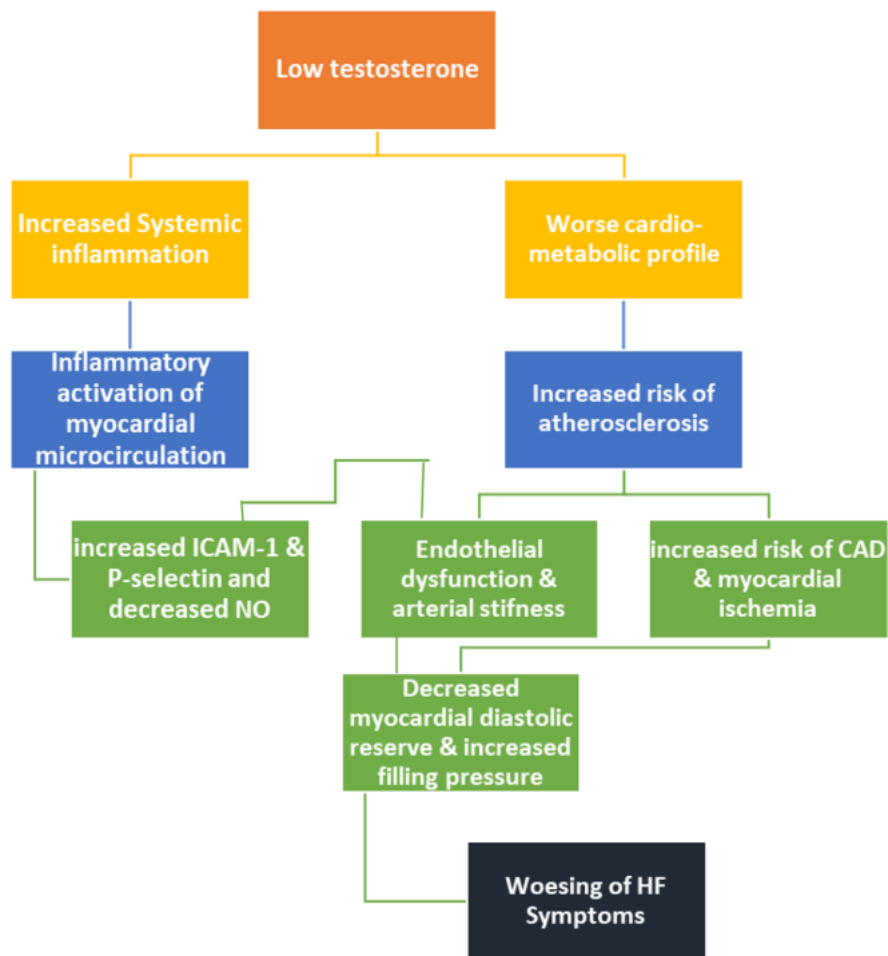


Figure 1. Illustration of the possible mechanism that links testosterone deficiency to the worsening symptoms of HFpEF^[17]

Several mechanisms have been proposed to explain the relationship between testosterone and cardiovascular health. These include 1) Testosterone's effect on thromboxane A2 receptors, 2) Vascular adhesion molecule 1 receptors, 3) Erythropoiesis and 4) Obstructive sleep apnea^[26]. Epidemiological studies have shown that testosterone concentrations greater than 500 ng/dL have been associated with an increased risk of cardiovascular disease. However, the relationship between testosterone and cardiovascular risk is complex and may depend on various factors, including age and the presence of other risk factors for cardiovascular disease. Testosterone has been found to have both positive and negative effects on cardiovascular health. On one hand, testosterone has been shown to have anti-inflammatory and antithrombotic effects, which could potentially reduce the risk of cardiovascular disease. On the other hand, higher testosterone concentrations have been associated with increased levels of C-reactive protein (CRP), a marker of inflammation, which could contribute to the development of cardiovascular disease.^[25]

Central effects of testosterone involve its influence on cardiomyocytes and electrophysiology. Testosterone modulates cardiac contraction and calcium homeostasis, which are essential for maintaining the proper functioning of the heart. Additionally, testosterone has been shown to affect

electrophysiology, which is crucial for the proper conduction of electrical impulses in the heart. Peripheral effects of testosterone include its influence on blood vessels, baroreceptor reactivity, skeletal muscles, and erythropoiesis. These effects may contribute to the beneficial effects of testosterone in the pathophysiology of HF syndrome. However, the central, or cardiac, effects of testosterone are still to be further explored.^[27]

Conclusion

Testosterone deficiency may worsen HFpEF in men. The role of testosterone in cardiovascular health is multifaceted and depends on various factors. Testosterone plays a complex role in cardiovascular health, with potential benefits and risks for both men and women. While more research is needed to fully understand the relationship between testosterone and heart failure, it is clear that testosterone levels play a role in cardiovascular health.

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