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REVIEW ARTICLE

Testosterone Level and Coronary Artery Disease in Iranian Men; a Systematic Review

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Abstract: Introduction: Coronary artery disease (CAD) is among the most common cardiovascular diseases (CVDs), caused by the formation of plaques of lipids, calcium, and inflammatory cells. In Iran, CAD is responsible for about 50% of all deaths per year. There is also a probability of the role of androgens deficiency in CAD in men. We aimed to systematically review all the related original studies to achieve an overall insight into the associations of testosterone and CAD in Iranian men. Methods: MedLine, Web of Science, Scopus, and Google scholar databases were searched from inception to January 2021. All types of studies on Iranian men older than 40 years of age, reporting results of comparing testosterone in normal individuals and those with CAD were included. The main findings of the articles were compared to achieve an overall statement. Results: Ultimately, six studies were included. Most (66.7%) had directly stated that lower levels of testosterone are associated with CAD or the level of testosterone is lower in patients with proven CAD. Among them, in 3 (50%) studies, the mean age of the participants had no significant difference between patients with CAD and the normal group. Conclusion: It is clear that low testosterone level is associated with increased risk of cardiovascular events but it is not definitely determined whether it is independent of age in Iranian men. Further well-designed studies are needed to clearly exclude all confounding variables including age and show the net effect of testosterone on CAD.

Keywords: Coronary artery disease; Testosterone; Atherosclerosis; Men

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1. Introduction

Coronary artery disease (CAD) is one the most common cardiovascular diseases (CVDs), caused by the formation of plaques of lipids, calcium, and inflammatory cells. These arterial plaques lead to narrowing the blood supply of heart muscles and cause angina pectoralis (1). CAD involves all the people around the world and more than 18.2 million individuals are living with this disease in the USA. This disease is also one of the most important causes of mortality throughout the world (2-4). In Iran, CAD is responsible for about 50% of all death per year (5). Diabetes, hypertension, hyperlipidemia, obesity, Homocystinuria, smoking, psychological distresses, and age are among the most common risk factors of CAD (4, 6, 7). In men, there is also a probability of the role of androgens deficiency in CAD (8). Testosterone as an important androgen plays a special role in the health of the cardiovascular system. Moreover, there is a footprint of significant testosterone deficiency in many chronic diseases (9, 10).

Recent studies have focused on the association between reduced androgens (mostly testosterone) and CAD but their results have lots of controversies. For example, some studies have mentioned that the level of testosterone is correlated with the incidence and the severity of CAD (11), or hypogonadism and low testosterone level are risk factors of mortalities because of CVDs (10, 12). On the other hand, there are some studies that show different results and reject any association between the level of testosterone and incidence and prognosis of CAD (13, 14).

According to these controversial results and lack of integrated data in this field, this study aimed to systematically

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review all the related original studies to achieve an overall insight about the associations of testosterone and CAD in Iranian men to be considered as a base for some preventive measures such as testosterone replacement therapy (TRT).

2. Methods

2.1. Search strategy

Two researchers with a medical background conducted an independent electronic search. Medline, Web of Science, Scopus and, Google scholar from inception to January 2021 were searched. The search keywords were Testosterone OR Androgenic AND Coronary or myocardial AND Iran. The search strategy for PubMed was: ((("Coronary"[All Fields] or "myocardial"[All Fields]) AND ("Testosterone"[All Fields]) OR ("Androgenic"[All Fields])) AND Iran). Databases in Persian including scientific information database (SID) and Magiran were also searched.

2.2. Inclusion and exclusion criteria

To find original articles about the association of testosterone level and CAD incidence or severity in the Iranian adult population, the eligibility criteria based on PICOS (i.e., participants, interventions, comparisons, outcomes, and study design) were all types of studies on men older than 40 years of age, with any effect size about comparing testosterone in normal individuals and those with CAD. Articles with no full text and studies that had defined the CAD rather than standard clinical criteria were excluded.

2.3. Data extraction and reporting

We collected the author's identification, year of publication, province of the study, Study type, CAD criteria, number and age of the participants (CAD vs normal), main measurements, and main findings of articles in a table and then compared them in result section to achieve an overall statement. Quality assessment of the studies was performed using the Newcastle-Ottawa Scale (NOS) checklist (15). Since there was no common effect size among the included studies, Meta-analysis was not applicable.

3. Results

The initial search identified 563 studies, then 95 duplications were removed and the remaining 468 studies were evaluated. Among them, 15 studies matched the inclusion criteria. Finally, six studies were included (figure 1). The search results had an almost perfect agreement (kappa= 0.91) between the two researchers.

Although there was a remarkable heterogeneity among the included studies, as shown in table 1, most (66.7%) had directly stated that lower levels of testosterone were associated with CAD or the level of Testosterone is lower in patients with proven CAD. There was only one (16.7%) study showing no significant correlation between two forms of testosterone (TT and FT) and the presence or severity of CAD. Another study showed that a higher level of TT (22.1 to 43.3 ng/l) was a risk factor for CAD. Four (66.7%) studies were cross-sectional and two (33.3%) studies had a case-control design. The most common criterion used for categorization of patients into CAD or normal groups was having ≥1 affected (≥50% stenosis) coronary vessels (4 studies [66.7%]). In 3 (50%) studies the mean age of the participants had no significant difference between CAD patients and the normal group, so based on these studies it can be stated that the risk of low testosterone for CAD may be independent of age.

4. Discussion

Based on our review low testosterone level can be considered as a potential risk factor for CAD, there are some included studies among our results that show the independent effect of testosterone on this disease. Although testosterone deficiency is not considered as a major risk factor for CAD, it is generally accepted that the male factor is a major risk factor to develop cardiovascular disease and testosterone level gradually declines with increasing age (9). Cardiovascular disease is three folds more common in men than women and it develops a decade earlier in men (21). There is compelling evidence that showed low testosterone level is associated not only with increased risk of cardiovascular events but also with cardiac mortality and overall mortality (20, 22, 23). Allameh and colleagues reported that serum free testosterone level is lower in patients with CAD (13) this relationship might be attributed to the effects of age and diabetes mellitus on the androgen level. Multiple studies showed that there is an inverse relationship between coronary artery calcium (CAC) score and testosterone level (24, 25). Testosterone level is an independent predictor of CAD severity when assessed via Gensini score (23, 26). Men younger than 45 years with premature CAD have also been found with low testosterone levels compared with controls (27). Separham and co-workers reported that there was a significant positive correlation between left ventricular function and free testosterone (17). Davoodi and colleagues (18) showed that serum testosterone level is significantly lower in patients with severe heart failure. Men in the highest tertiles of testosterone and bioavailable testosterone had a lower relative risk of abdominal aortic atherosclerosis than men in the lowest tertile (28). Some studies have shown a negative correlation between the degree of angiographic coronary disease and testosterone levels (29). Despite many studies showing the relationship between testosterone level and cardiovascular disease, several studies such as Davoodi and colleagues (19)

failed to show a cause and effect relationship between testosterone level and cardiovascular events because testosterone could be a marker for general well-being and quality of health (23) so it might have no direct effect on CAD and CVD events. Malkin and co-workers reported that low testosterone level increases the risk of cardiovascular events and it influences life expectancy and showed that testosterone level could be a prognostic factor in patients with cardiovascular disease (30). On the other hand, Fallah and colleagues (16) reported that although testosterone has a preventive effect at the low standard level, higher testosterone levels increase the risk of cardiac events. Budoff and co-workers showed that testosterone therapy was associated with increased non-calcified plaque compared with placebo in the coronary artery but it did not increase CAC score or major cardiac events (31). Some other studies showed that testosterone therapy could increase the risk of cardiac events in patients with known cardiac disease (32). Several Meta-analyses reported that testosterone therapy had neutral effects on the occurrence of major cardiovascular events, and had various small effects on lipid levels (33-35).

5. Conclusion

It is clear that low testosterone level is associated with increased risk of cardiovascular events but it is not definitely determined that is independent of age in Iranian men. Further well-designed studies are needed to clearly exclude all confounding variables including age and show the net effect of testosterone on CAD.

6. Appendix

6.1. Acknowledgements

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6.2. Conflict of interest

None.

6.3. Funding and support

This study was a part of an ongoing project, with no independent financial support.

6.4. Author contribution

The authors declare that they have no competing interests.

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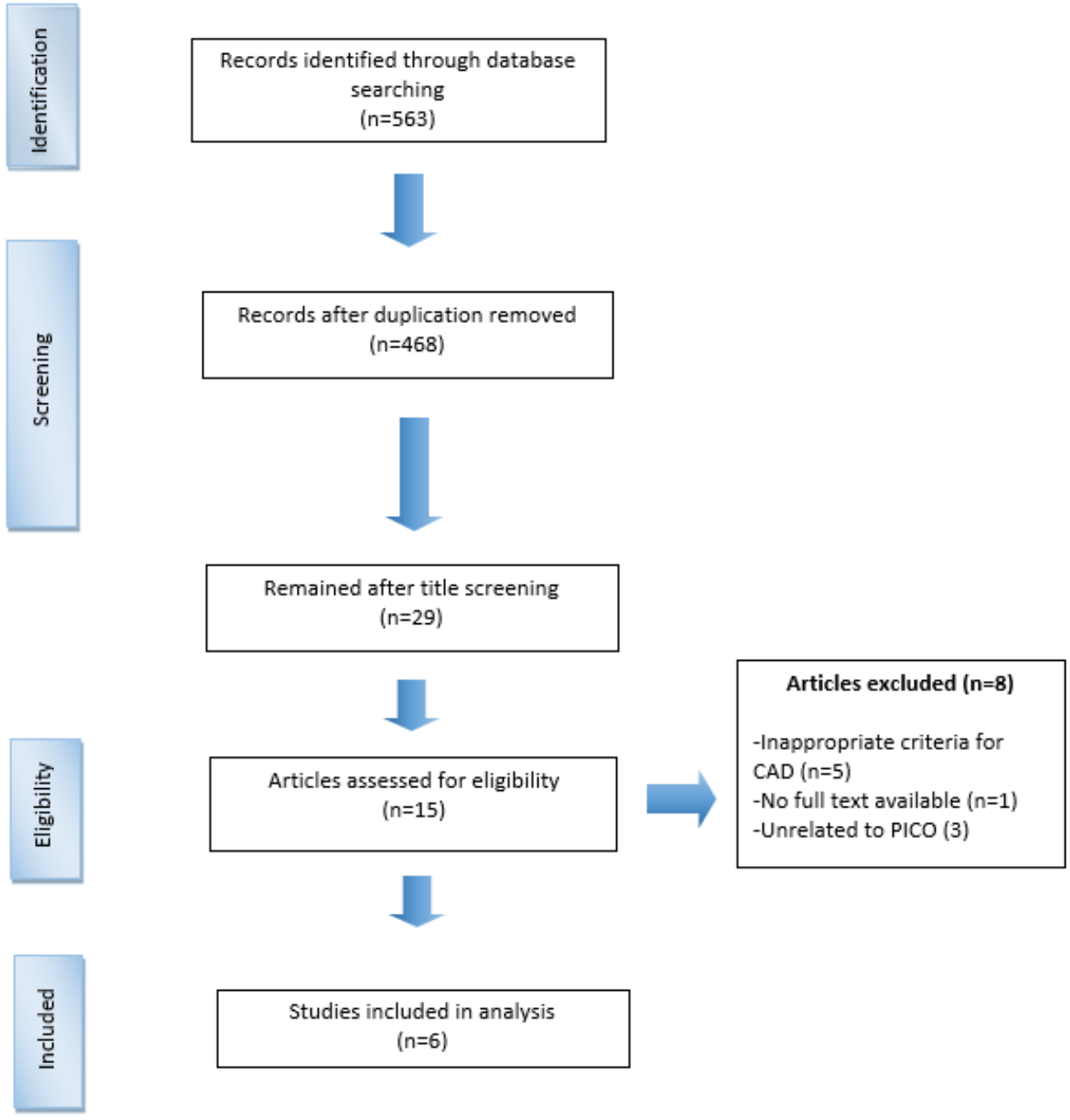

Figure 1: Flow chart of study selection following PRISMA guidelines.

Table 1: Summary of included studies.

First Author [reference]	Study location	Study type	CAD criteria	Number and age of Participants (CAD vs Normal)	Main Measurements	Main findings
Alkamel A, 2014 (11)	Tehran	Cross-sectional	≥1 affected (≥50% stenosis) coronary vessels	191 vs 94 Mane age: 41.6 vs 39.3 (p<0.001)	FT and TT and Coronary angiogram, Gensini score (cut-off for low TT was 2.5 ng/L)	The association between low TT and CAD is significant (p≤0.001). There was a significant negative correlation between Gensini score and TT (r= -0.37) and FT (r= -0.34).
Fallah N , 2009 (16)	Tehran	Cross-sectional	≥1 affected (≥50% stenosis) coronary vessels	388 vs 114 Mane age: 57 vs 52.9 (p<0.001)	TT and FT and coronary angiogram TT level divided into 3 groups; low (0 to 7), medium (7.1 to 22), and high (22.1 to 43.3).	TT showed a significant preventive effect in low levels and a risk factor effect in high levels (p<0.05).
Allameh F , 2016 (13)	Tehran	Case-control	≥1 affected (≥50% stenosis) coronary vessels	200 vs 135 Mane age: 60 vs 55 (p<0.0001)	TT, FT, DHEA-s, SHBG, Diabetes and coronary angiogram	The serum levels of FT & DHEA-S were significantly higher in the control group than in the CAD group (P=0.048 P<0.0001 respectively). SHBG was higher in the CAD group than in the control group (p=0.007). -These significant differences were possibly because of the effects of age and diabetes on the serum levels of androgens.
Separham A ,2017(17)	Tabriz	Cross-sectional	Complete (≥50%) ST-Resolution	35 vs 13 Mean age: 54.9 vs 57.15 (p=0.58)	FT, ECG, Coronary angiography	-The serum levels of FT, was lower in patients with complete ST-resolution compared to those with incomplete ST-resolution (p=0.04). -A significant positive correlation was observed between the left ventricular function and serum levels of FT (r = +0.362).
Davoodi G , 2007(19)	Tehran	Cross-sectional	≥1 affected (≥50% stenosis) coronary vessels	388 vs 114 Mane age: 57 vs 52.9 (p<0.001)	TT, FT, DHEA-S, Coronary angiogram and Gensini score.	There was no significant correlation between FT, TT, DHEA-S and the presence or severity of CAD (p>0.1).
Ariabod V , 2019 (20)	Mashhad	Case-control	Myocardial infarction	30 vs 30 55.9 vs 56.5 (p =0.881).	Testosterone Normal range: 3 to 10 ng/L	-Serum levels of testosterone in CAD group were significantly lower than in control group (p=0.0001). -In CAD group, 21 (70%) patients had testosterone levels below the normal level while in control group all the men had normal level of testosterone.

TT: Total Testosterone; FT: Free Testosterone; DHEA-S: Dehydroepiandrosterone sulfate;
SHBG: Sex Hormone Binding Globulin; CAD: Coronary Artery Disease; EF: Ejection Fraction .