Original Article

Prevalence of Preexisting Cardiovascular Diseases in Prostate Cancer Patients and Cardiac Risks of Hormonal Therapy

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Abstract

Background: Cardiovascular diseases (CVDs) are a prominent cause of mortality in prostate cancer patients. However, it has been reported that patients with preexisting CVDs are at greater risk. Literature on the magnitude of this problem in Saudi Arabia is lacking.

Objectives: To measure the prevalence of prostate cancer patients with preexisting CVDs in our population and to elucidate the possible risk factors of new cardiovascular events (CVEs) in patients who received androgen deprivation therapy (ADT).

Materials and Methods: This retrospective study included all patients newly diagnosed with prostate cancer at a tertiary hospital in the Eastern Province of Saudi Arabia from October 2008 to January 2019. The prevalence of preexisting cardiovascular diseases in these patients were determined. In addition, the incidence of new CVEs after initiating ADT was determined along with the risk factors for the same.

Results: The prevalence of preexisting CVD in our cohort was 16%. About 6% of the patients who received ADT had CVEs after a median follow-up of 39 months (IQR: 11-49 months). In the univariate analysis, hyperlipidemia ($P = 0.002$), stroke ($P = 0.001$), peripheral vascular disease ($P = <0.001$), cardiac patients with stents ($P = <0.001$), and cardiac patients without stent ($P = <0.001$) were significant risk factors of new CVEs after initiating ADT. However, in the multivariate regression analysis, only history of stroke and CVD (with or without stent) were found to be significant risk factors of new CVEs after initiating ADT ($P = 0.01$).

Conclusion: About one-fifth of the prostate cancer patients had preexisting CVDs. This study also found that luteinizing hormone-releasing hormone agonist could be a risk factor for new CVEs.

Keywords: Androgen deprivation therapy, cardiovascular disease, prevalence, hormonal therapy, prostate cancer, Saudi Arabia

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INTRODUCTION

Prostate cancer is the second most common cancer in males and the fifth leading cause of death worldwide.[1] In Saudi Arabia, a recent study reported the incidence and mortality rates of 2.5% and 1.4% respectively.[1] The second leading cause of mortality in prostate cancer patients is cardiovascular diseases (CVDs). Cancer survivors are at increased risk of CVDs compared with the general population owing to the modified lifestyle of cancer patients and the toxicities of cancer therapies.[2,3]

For over six decades, hormonal therapy (HT), which is the androgen deprivation therapy (ADT), has been the standard conventional treatment option for metastatic prostate cancer, and even for local prostate cancer in certain patients.[4,5] ADT in the form of luteinizing hormone-releasing hormone (LHRH) agonists and LHRH antagonists have replaced surgical castration and became the typical medical HT.[6,7] In early studies, LHRH antagonists were positioned as reducing the risk of CVDs compared with LHRH agonists.[8] However, contemporary trials conducted in Europe and North America have shown that no significant relations could be drawn to confirm the CVDs risk of LHRH agonists over LHRH antagonists.[3,9,10]

In Saudi Arabia, the prevalence of CVDs in prostate cancer is understudied, and the risk of cardiovascular events (CVEs) in patients treated with HT is also poorly investigated. The current study was conducted to determine the prevalence of preexisting CVDs in prostate cancer patients in a population from Saudi Arabia and elucidate the possible risk factors of CVEs in patients who had received ADT.

MATERIALS AND METHODS

Study design, setting, and patients

This retrospective study included all patients diagnosed with prostate cancer at King Fahad Specialist Hospital (KFSH), Dammam, from October 2008 to January 2019. KFSH is a tertiary hospital with specialized prostate cancer clinics that receives cases from throughout the Eastern Province of Saudi Arabia. The study was conducted after obtaining ethical approval from the Institutional Review Board of KFSH. All data were retrieved from the electronic medical records.

The prevalence of CVD among prostate cancer patients was calculated as the total number of patients with CVDs at the time of diagnosis over the total number of patients diagnosed with prostate cancers. To determine the incidence of new CVEs after initiating ADT, we included all patients with prostate cancer who were started on ADT for the first time during the study period and had completed a follow up of at least 1 year. Patients were excluded if they had a short follow up from the initiation of ADT (<1 year), had received ADT outside our center, or if the data in the medical records were insufficient.

Variables

The following variables were recorded at the time of the diagnosis of prostate cancer: age, body mass index (BMI), prostate-specific antigen levels, history of diabetes mellitus, hypertension, hyperlipidemia, and CVDs (which was defined as one of the following: stroke, deep vein thrombosis, peripheral vascular disease, and cardiac diseases with and without stent). In addition, data regarding any CVEs after the initiation of ADT were recorded. BMI was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25-29.9), and obese (>30). CVEs were defined as any CVDs that occurred after starting ADT.

Statistical analysis

Data analysis was conducted using SPSS version 27. A Chi-squared test and *t*-test were applied to compare the HT group and no HT group. Through univariate and multivariate regression analyses, the risk factors of CVEs were analyzed in patients who received HT after adjustments for confounders. A *P* value of <0.05 was considered significant.

RESULTS

A total of 394 patients were diagnosed with prostate cancer at our center during the study period, of which 219 met the inclusion criteria. Of these, 163 patients received ADT. The median age of patients at diagnosis was 69 years, and the median follow up was 47 months (IQR: 25.5–80 months). At presentation, 52% were metastatic. The prevalence of diabetes mellitus, hypertension, and hyperlipidemia were 50%, 54%, and 17%, respectively. The prevalence of preexisting CVDs was 16%. About 6% of the patients had CVEs after the initiation of ADT, with a median duration of 39 months (IQR: 11–49 months) [Table 1].

In the univariate analysis, hyperlipidemia ($P = 0.002$), stroke ($P = 0.001$), peripheral vascular disease ($P = <0.001$), cardiac patients with stents ($P = <0.001$), and cardiac patients without stent ($P = <0.001$) were significant risk factors for new CVEs after initiating ADT [Table 2]. However, in the multivariate regression analysis, only history of stroke and CVD (with or without stent) were significant risk factors of CVEs after initiating ADT ($P = 0.01$). When

Table 1: Descriptive data of all prostate cancer patients in the cohort (*N*=219)

Parameters	*n* (%)
Stage at diagnosis	
Localized	105 (47.9)
Metastatic	114 (52.1)
Median age (Years) (IQR)	69 (62–76)
Body mass index	
Underweight (<18.5)	14 (6.4)
Normal (18.5–24.9)	88 (40.2)
Overweight (25–29.9)	72 (32.9)
Obese (>30)	45 (20.5)
Median PSA levels (ng/mL) (IQR)	44 (45–204)
Chronic medical illness	178 (81.3)
Hypertension	118 (53.9)
Diabetes mellitus	110 (50.2)
Hyperlipidaemia	37 (16.9)
History of CVD	35 (16.0)
Stroke	4 (1.8)
Deep vein thrombosis	4 (1.8)
Peripheral vascular disease	1 (0.5)
Cardiac diseases with stent	19 (18.7)
Cardiac diseases without stent	8 (3.7)

PSA – Prostate specific antigen; CVD – Cardiovascular disease; IQR – Interquartile range

Table 2: Univariate analysis predicting the risk factors for cardiovascular events in patients started on androgen deprivation therapy for prostate cancer (*N*=163)

Variable	CVEs after ADT		*P*
	Yes, *n* (%)	No, *n* (%)	
Hypertension (*n*=159)			
Yes	4 (2.5)	80 (50.3)	0.40
No	6 (3.8)	69 (42.7)	
Diabetes mellitus (*n*=160)			
Yes	6 (3.8)	76 (47.5)	0.57
No	4 (2.5)	74 (46.3)	
Hyperlipidemia (*n*=161)			
Yes	5 (3.1)	20 (12.4)	0.002
No	5 (3.1)	131 (81.4)	
Body mass index (*n*=161)			
Underweight	-	13 (8.1)	0.556
Normal	5 (3.1)	57 (35.6)	
Overweight	4 (2.5)	47 (29.4)	
Obese	1 (0.6)	33 (20.6)	
CVD - stroke (*n*=161)			
Yes	2 (1.2)	3 (1.9)	0.001
No	8 (5)	148 (91.9)	
CVD - DVT (*n*=161)			
Yes	-	5 (3.1)	0.56
No	10 (6.2)	146 (90.7)	
CVD - PVD (*n*=161)			
Yes	1 (0.6)	-	<0.001
No	9 (5.6)	151 (93.8)	
CVD - with stent (*n*=161)			
Yes	5 (3.1)	11 (6.8)	<0.001
No	5 (3.1)	141 (87)	
CVD - without stent (*n*=161)			
Yes	2 (1.3)	5 (3.1)	0.013
No	8 (5)	145 (90.6)	

CVD – Cardiovascular disease; CVEs – Cardiovascular events; DVT – Deep vein thrombosis; PVD – Peripheral vascular disease; ADT – Androgen deprivation therapy

patients who received ADT were compared with those who did not, it was found that the patients who received ADT were significantly older ($P = 0.01$) and tended to have more comorbidities than patients not started on ADT.

DISCUSSION

This is the first study that has determined the prevalence of CVDs in prostate cancer patients from the Eastern Province of Saudi Arabia, where the rate of prostate cancer is high.[11] This study found that about one-fifth of the newly diagnosed prostate cancer patients had preexisting CVDs. In addition, the prevalence of some of the risk factors of CVD such as diabetes mellitus, hypertension, and hyperlipidemia were found to be high in this group of population. Finally, a history of cardiac disease with or without stent and history of stroke were found to be significant risk factors for developing CVEs after starting ADT in patients with prostate cancer.

The findings of this study are comparable with those in recent studies from other countries. A prospective study from Canada that included about 2500 patients with prostate cancer with a mean age of 68 years reported that about 22% had preexisting CVDs.[3] Similarly, a retrospective study from the United Kingdom that included >20,000 newly diagnosed patients with prostate cancer reported the prevalence of existing CVDs to be 19%.[12] This percentage is higher than the prevalence in the general population. For example, in a community-based study conducted in Saudi Arabia between 1995–2000, 542 of 7646 (6.6%) males aged 30–70 years were found to have an existing CVD (3.9% and 9.3% for those aged 30–39 years and 60–70 years, respectively).[13] Another recent population-based study in Saudi Arabia by Alhabib *et al.* showed the prevalence of CVD in the age group 35–70 years was 5.5%: 6.6%, 13.3%, 8.7% for males aged 50–59 years, 60–70 years, and 50–70 years, respectively.[14]

CVDs in patients with prostate cancer could be explained by the prevalence of CVD risk factors such as obesity, diabetes mellitus, hypertension, hyperlipidemia, smoking, and physical inactivity.[14,15] In addition, both prostate cancer and CVDs are more prevalent in older patients, and thus the incidence increased with increasing age, with the risk for both significantly increasing in patients aged >50 years.[16,17] In our cohort, the median age at diagnosis was 69 years. The majority of the patients had hypertension (54%) and diabetes mellitus (50%), while about one-sixth (17%) had hyperlipidemia. In addition, more than half of the patients had a BMI of ≥25 kg/m^2 at diagnosis. However, we did not have adequate data about their physical activity and smoking status, which could be unreported risk factors. Moreover, the prevalence of CVD risk factors in patients

aged >40 years are primarily hypertension, diabetes mellitus, and being overweight.[18] Alhabib *et al*. studied the risk factors of CVDs and chronic diseases in a general Saudi population and found that in males aged >35 years, the prevalence of hypertension was 33%, diabetes mellitus was 28%, and hyperlipidemia was 31%. Moreover, almost all of them (90%) had a BMI of ≥25 kg/m^2.[14] However, in a Canadian study, the majority of the patients with prostate cancer were found to be hyperlipidemic (46%) and hypertensive (45%), while a minority were diabetic (16%).[3]

In the current study, about 6% of the patients who received ADT developed CVEs, with a median follow up of 39 months. In addition, prostate cancer patients with a history of stroke or cardiac diseases were at significantly higher risk for CVEs after initiating ADT. A meta-analysis of observational studies found that ADT increases the risk of CVEs in patients with prostate cancer by 10% compared with those with no ADT; however, owing to the study design, confounding effects could not be excluded.[19] In the trial from Canada, a positive association was found between a plan to use ADT and baseline cardiovascular risk factors, but this association was not maintained in multivariate analysis, indicating that the association was related to confounders.[3] From the cardiovascular risk factors in our cohort, only history of stroke and cardiac disease were significant for developing new CVEs after the initiation of ADT. A systemic review and meta-analysis of six observational studies has shown that the risk of stroke increases by 20% in patients with prostate cancer who were started on ADT over a median follow up of 3.9 years.[20]

Strengths and limitations

Our study has several limitations, including the retrospective nature of the study that inherits its bias. In addition, the data were from a single tertiary center, which limits its generalizability. Despite controlling for many potential risk factors, all confounders could not be controlled due to insufficient data, including smoking status and physical inactivity. In addition, systemic treatment is now considered as the standard of care for initial treatment along with ADT in patients diagnosed with metastatic prostate cancer, and this could contribute to CVD but was not adjusted for in this study. Nonetheless, to the best of our knowledge, this is the first study from Saudi Arabia that has assessed the CVD profile in patients with prostate cancer. The result of this study emphasizes the importance of patients' education and considering a pathway for CVD prevention in high-risk groups, especially for patients with history of stroke and CVD, when planning to initiate ADT. Additional multicenter, multiregional studies with larger sample sizes should be conducted to develop prevention methodologies for such risk factors.

CONCLUSION

About one-fifth of newly diagnosed prostate cancer patients from the Eastern Province of Saudi Arabia had preexisting CVDs. Prostate cancer patients who received ADT were older with a predominance of chronic medical illnesses that might carry more risk toward future CVEs. A history of stroke and cardiac diseases were significant risk factors for CVEs if patients receive ADT.

Ethical considerations

The study was approved by the Institutional Review Board (Ref. No: URO0312-2020; date: March 16, 2020), King Fahad Specialist Hospital, Dammam, Saudi Arabia. The requirement for informed consent was waived owing to the retrospective study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by three independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: A.M.A, H.A.S, M.A.M, A.A.F, and A.A.M; Methodology: A.M.A, H.A.S, M.A.M, A.A.F, and A.A.M; Data analysis: A.M.A and A.A.M; Writing–original draft preparation: A.M.A and A.A.M; Writing – review and editing: A.A.M; Supervision: A.A.M.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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