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Bone mineral density in Nigerian men on androgen deprivation therapy for advanced prostate cancer

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Abstract

Background: Cancer of the prostate (CaP) is the most frequently diagnosed non-cutaneous malignancy worldwide, and it is the second leading cause of death from cancer in men. In the developing world, majority of patients with CaP present in advanced stage and often times, androgen deprivation therapy (ADT) is the only treatment option available. ADT has been reported to increase the risk of osteopenia and osteoporosis in patients with CaP in studies done predominantly among the Caucasians. There is a dearth of report of the effect of ADT on CaP in the black population most especially Nigerian population despite our high incidence of CaP. The aim of this study was to determine the effect of advanced CaP and its treatment using ADT on bone mineral density (BMD) in our patients.

Results: The age of the patients ranged from 54 to 88 years (mean 70.15 ± 6.7) and 50 to 85 years (mean 68.92 ± 8.5) for the case and control groups, respectively. The mean BMD of the control group (0.26 ± 1.5) was significantly higher than the case group pre-ADT (− 0.78 ± 1.7) ($p = 0.044$). Post-ADT, the BMD was significantly lower (− 1.15 ± 1.7) than pre-ADT ($p = 0.001$) among the case group.

Conclusion: Advanced CaP was found to be associated with a decrease in BMD, and ADT was associated with a further decline in the BMD. Therefore, prevention and treatment of skeletal-related events is vital in management of patients with advanced CaP.

Keywords: Prostate cancer, Androgen deprivation therapy, Benign prostatic hyperplasia, Bone mineral density

1 Background

Cancer of the prostate (CaP) constitutes a significant cancer burden both locally and globally. In Nigeria, it is the most commonly diagnosed cancer among men and mostly present in the advanced stage when androgen deprivation therapy (ADT) is the mainstay of treatment. Currently, ADT is the cornerstone of therapy for locally advanced and metastatic CaP [1].

CaP is largely androgen-dependent and responds to endocrine therapy. ADT is an effective treatment modality which decreases the rate of disease progression, alleviates symptoms, and prolongs patients' survival [2]. ADT can be achieved through surgery (i.e., bilateral orchidectomy) or medical therapy (gonadotropin releasing hormone agonists, antagonists and antiandrogens).

Although ADT is effective in the management of advanced CaP, it can result in significant side effects. Hot flushes and decreased libido are some of the short-term side effects of ADT seen in these patients. The long-term consequences are potential decline in muscle mass and bone mineral density (BMD) with attendant skeletal-related events [3, 4]. The loss of BMD and increased risk of SRE's may have negative impact on the quality of life and overall patient survival [4, 5]. Furthermore, skeletal-related events (SREs) are negative predictors of overall

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survival in patients with CaP [4]. Therefore, maintenance of optimum bone health throughout the natural course of CaP is vital to maintaining the quality of life and also prolonging survival of these patients.

In view of this, many studies have brought into focus the need to predict and prevent the progression of osteoporosis in patients with CaP receiving ADT [3, 5, 6] Some authors have recommended that all patients with CaP should undergo baseline BMD measurement before initiating ADTs, and repeat BMD assessments should be performed every 6–12 months in patients with baseline osteopenia and osteoporosis and every 1–2 years in patients with a normal baseline BMD [6, 7] The majority of these studies were conducted in predominantly Caucasian population [5, 8–12]. Moreover, previous research among African-American populations has documented contradicting reports [13, 14]. Existing literature review revealed no previously documented study of the effects of treatment of CaP with ADT on BMD in the Nigerian population in spite of the high incidence [15] and mortality [16] of CaP among this population. In addition, measurement of BMD among patients with advanced CaP is not routinely done in our practice and therefore, this study aimed at evaluating the effect of advanced CaP and its treatment using ADT on the BMD of Nigerian men.

2 Methods

2.1 The patients

This was a prospective case–control study among men attending the urology clinic in a Teaching Hospital, in Lagos from July 2016 to June 2017. Two groups of men were recruited. Group 1, the case group, consisted of men with hormone-naive histologically confirmed adenocarcinoma of the prostate who have locally advanced or metastatic disease and group 2 were men with benign prostatic hyperplasia.

Men with other cancers apart from CaP, fracture/deformity of the intermediate phalange of the middle finger of the non-dominant hand, and those on therapy with anti-resorptive agents were excluded.

2.2 Bone mineral density testing

BMD of the patients was assessed using accuDEXA device from Lone Oak Medical Technologies. It is a bone densitometer that estimates BMD of the intermediate phalange of the middle finger of the non-dominant hand. It is a self-contained, table-top unit, employing Dual Energy X-ray Absorptiometry (DEXA) technology. After the finger is scanned, results are generated in less than 1 min. This BMD value is a relative indicator of bone density elsewhere in the body, and the accuDEXA's BMD estimates can be used as an aid to the physician in determining fracture risk.

BMD was checked at the point of diagnosis before commencement of androgen deprivation therapy and at 3 months post-ADT. The BMD of the control group was also measured. A *T* score of 0 means BMD of the patient was equal to the norm for a healthy young adult of the same sex and race, which is the standard norm on the calibrated accuDEXA equipment. Differences between BMD of the patient and that of the established norm were measured in units called standard deviations (SDs). The more the standard deviations below 0 indicated as negative numbers, the lower the BMD of the patient and the higher the risk of fracture occurrence. A T –score > -1 is considered normal or healthy. A *T* score between -1 and -2.5 indicates that patient has low bone mass (osteopenia). A *T* score of -2.5 or lower indicates that patient has osteoporosis. The greater the negative number, the more severe the osteoporosis.

Samples for baseline serum PSA were also taken pre- and post-ADT.

2.3 Data collection and statistical analysis

The data obtained from the patients were entered into Statistical Package for Social Sciences (SPSS) version 22 for analysis. Univariate analysis of categorical variables; race and clinical stage was done using frequency tables while continuous variables including age, and bone mineral density were expressed as mean ± standard deviation (SD). Test of association between categorical variables was done using Pearson Chi-square. Comparison of mean BMD of the control and case group was done using independent *t* test. Comparison of the mean BMD pre- and post-ADT was done using paired *t* test. Wilcoxon rank value and McNemar test were used as appropriate. Results were displayed using appropriate graphical presentations. For all statistical tests, p value < 0.05 was considered as statistically significant.

3 Results

3.1 Patient characteristics

One hundred and fifty-four patients were enrolled in the study, 77 in each group. The age of patients ranged from 54 to 88 (mean = 70) years among the case group and 50–85 (mean = 69) among the control group ($p = 0.283$). The mean Gleason score was 8. The median PSA pre- and post-ADT was 346 and 9 ng/ml, respectively. Majority (91%) had bilateral orchidectomy as the method of ADT.

3.2 BMD results

The BMD categories based on the T score were analysed for the control and the case group. In the control group, 55 patients (71.4%) had normal BMD (*T* score -1 or more), 19 patients (24.7%) had osteopenia (*T* score between -1 and -2.5) while 3 patients (3.9%) had

osteoporosis (*T* score − 2.5 or lower). In the case group, pre-ADT, 43 patients (55.8%) had normal BMD (*T* score − 1 or more), 23 patients (29.9%) had osteopenia (*T* score between − 1 and − 2.5) while 11 patients (14.3%) had osteoporosis (*T* score − 2.5 or lower). Using Fischer's exact test for categorical tables, there was a statistical significance between the BMD categories of the two groups. ($p=0.039$). Correlation between age and BMD value showed worsening BMD with increasing age in case and control group; *p* value of 0.012 and 0.004, respectively.

The range of the BMD of case group (pre-ADT) was − 4.825 to 3.069, while that of the control group was − 3.565 to 3.543. The mean BMD of the case group (pre-ADT) was much lower than that of the control group, − 0.78 ± 1.7 and 0.26 ± 1.5, respectively. There was statistically significant difference in the mean BMD of the case and control groups (t = 2.027; $p=0.044$) (Table 1).

In the case group, pre-ADT, 43 patients (55.8%) had normal BMD (*T* score > − 1), 23 patients (29.9%) had osteopenia (*T* score between − 1 and − 2.5) while 11 patients (14.3%) had osteoporosis (*T* score − 2.5 or lower). Following ADT, the BMD was assessed again at 3 months post-ADT; it showed a decreasing trend. The number of patients who had normal BMD pre-ADT had reduced to 31 (40.3%), the number with osteopenia had increased to 27 (35.1%) while the number of those with osteoporosis had increased to 19 patients (24.7%). Using McNemar test, there was a statistically significant difference, $p=0.043$ (Table 2).

The range of BMD of pre-ADT and at 3 months post-ADT was − 4.825 to 3.069 and − 4.189 to 3.509, respectively. The mean BMD was higher at diagnosis compared to at 3 months post-ADT, − 0.78 ± 1.7 and − 1.15 ± 1.7, respectively. Using paired *t* test, there was statistically significant difference between the mean values ($p=0.001$) (Fig. 1).

Table 2 Comparison of BMD pre- and post-ADT among men with advanced prostate cancer

	Pre-ADT (*N* = 77)	3-month post-ADT (*N* = 77)	*p* value
BMD *T* score			0.001
Mean ± SD	− 0.78 ± 1.7	− 1.15 ± 1.7	
Range	− 4.825, 3.069	− 4.189, 3.509	
BMD group			
Normal (> − 1)	43 (55.8)	31 (40.3)	0.043
Osteopenia (− 1 to − 2.5)	23 (29.9)	27 (35.1)	
Osteoporosis (< − 2.5)	11 (14.3)	19 (24.7)	
PSA			< 0.001
Median (Q1, Q3)	345.9 (65.4, 1399.2)	9.38 (1.6, 29.8)	
Range	17.0, 7865.0	1.6, 578.8	

4 Discussion

The incidence rate of CaP is increasing globally. In a hospital-based study done in the nineties, the incidence of CaP was put at 127/100,000 [17]. However, a more recent community-based study reported that the prevalence rate may be higher than that reported in hospital-based

Table 1 Patients characteristics, Gleason score, BMD categories of case and control groups, the mean BMD, decreasing trend of BMD pre- and post-ADT

	Cases (*n* = 77)	Control *n* (77)	Total	Statistics
Age groups (years)				
51–60	11 (14.3)	13 (16.9)	24 (15.6)	$p=0.283$
61–70	32 (41.6)	32 (41.6)	64 (41.6)	
71–80	28 (36.4)	27 (35.1)	55 (35.1)	
81–90	6 (7.8)	5 (6.5)	11 (6.5)	
Mean ± SD	70.15 ± 6.7	68.92 ± 8.5		
BMI				$p=0.578$
< 18.5	4 (5.2)	3 (3.9)	7 (4.5)	
18.5–24.9	48 (62.3)	56 (72.7)	104 (67.5)	
25.0–29.9	19 (24.7)	13 (16.9)	32 (20.8)	
≥ 30.0	6 (7.8)	5 (6.5)	11 (7.1)	
BMD group				
Normal (> − 1)	43 (55.8)	55 (71.4)	98 (63.6)	
Osteopenia (− 1 to − 2.5)	23 (29.9)	19 (24.7)	42 (27.3)	$p=0.039$
Osteoporosis (< − 2.5)	11 (14.3)	3 (3.9)	14 (9.1)	
Mean BMD *T* score	− 0.78 ± 1.7	0.26 ± 1.5		$p=0.044$

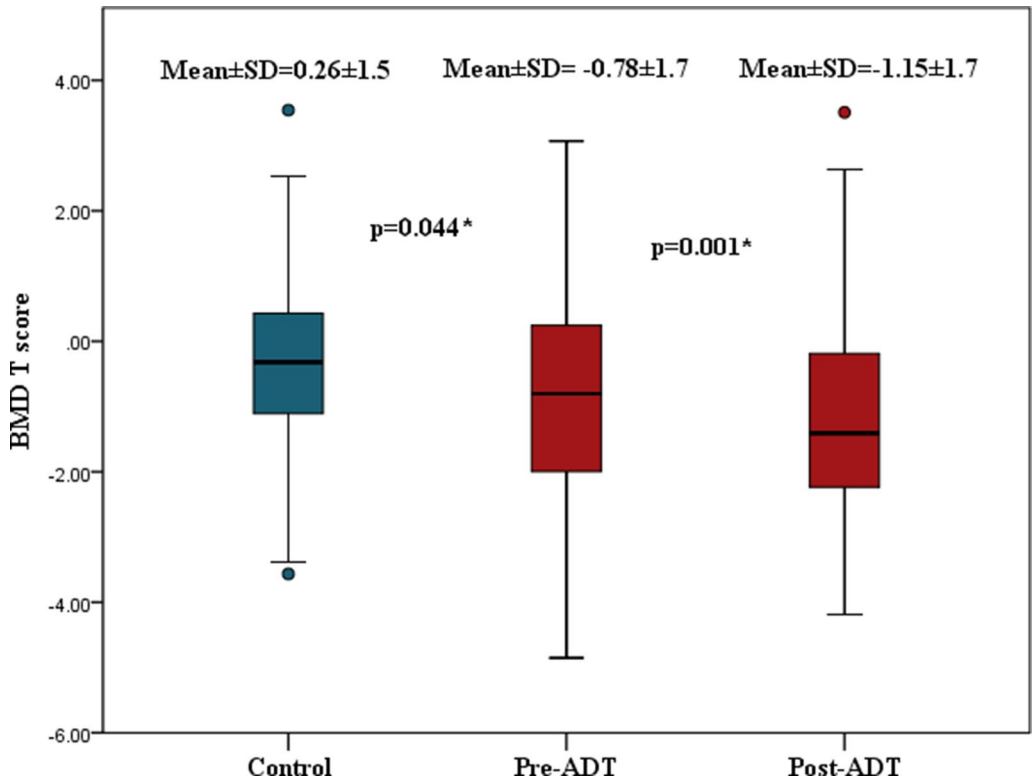

Fig. 1 Box plot comparing the mean BMD of the control and case group (pre- and post-ADT)

studies [18]. The Global trends and prostate cancer review 2018 put the incidence of CaP in Nigeria at 9.7% [19].

The similarity in the age of the case and control groups and the absence of statistically significant difference in these age groups ($p=0.283$) validate the rationale for using BPH patients as controls. This essentially eliminated the effects of age on the BMD of the two groups, as age is a confounding variable known to affect BMD [20, 21]. However with increasing age, there was statistically worsening *T* score in the case and control groups. In this study, we found out that men with CaP had significantly lower BMD as compared with controls (those without CaP). This validates the fact that CaP is associated with worse BMD, in addition, treatment with ADT further worsens the BMD in these patients. There was significant resolution in the symptoms the patients presented with following ADT, and therefore worsening of BMD cannot be attributed to disease progression or increase in osteoclasts activity. The high prevalence of low BMD in hormone-naïve patients with CaP has been reported in other studies [11, 20, 22]. However, there have been differences in the results due to inter-ethnic variations. The mean BMD of the control group determined from this study was 0.26 ± 1.5. Majority (71.4%) had normal BMD, and few (24.7%) had osteopenia while 3.9% had osteoporosis. This is similar to what was reported in healthy Jamaican men within same age group. It was, however, higher than that reported in a similar Caucasian healthy control group by Kwon et al. [20] despite the fact that both studies were conducted on the same age groups. Racial differences among our study populations may explain the reason for the higher BMD in our control group. Harris [23] reported that young healthy African-Americans have approximately 10% greater mean BMD compared to young healthy Caucasians. Similarly, the results of Tobago bone health study showed that BMD was 10–20% higher in Afro-Caribbean males than in United States non-Hispanic black and white males [13].

Furthermore, Adewole [24] and colleagues carried out a prospective study in Nigerian black women measuring their BMD. The local *T* scores obtained were compared with the *T* scores obtained using the African-American normative database; they found out that the BMD of the local young healthy normal female Nigerian is higher than that of the African-American female. In many studies involving assessment of BMD, Africans are generally under-represented; in addition, the factor that determines BMD in persons of African descent as compared to Caucasians is not fully known

yet. Some of the factors attributed to this difference include lifestyle factors, genetic differences, peak bone mass acquisition and bone geometry [25].

In our study, based on the available *T* score categories, there was a decreasing trend in the BMD pre-ADT compared to post-ADT. The number of patients with advanced CaP who had normal BMD pre-ADT reduced from 43 (55.8%) to 31 (40.3%). The number of patients with osteoporosis also increased from 11 (14.3%) pre-ADT to 19 (24.7%) 3 months post-ADT. The mean BMD pre- and post-ADT was statistically significantly ($p < 0.001$).

Other researchers have also documented worsening osteopenia and osteoporosis following ADT in patients with CaP, irrespective of race or ethnic group [26–29]. All these reinforce the fact that androgen deprivation therapy negatively affects bone mineral density. Some have suggested that men of African descent may be more immune against to skeletal-related complications which occur with the use of ADT [4].

The state of hypogonadism induced by ADT in patients with advanced prostate cancer is quite grave. There is an accelerated rate of bone resorption and increased risk of bone fractures. In addition, the risk of fractures following ADT has been shown to be higher with bilateral orchidectomy compared to GnRH agonists. In older men, the normal rate of loss of BMD is approximately 0.5 to 1.0% per year; with bilateral orchidectomy, the rate of loss in BMD is estimated at approximately 8–10% over the first 1 to 2 years [30], whereas the rate of BMD loss with GnRH is 3–7% per year [31]. More than 90% of the patients in our practice still opts for orchiectomy due to lack of affordability of GnRH agonists.

A significant number of the patients in urological practice in our environment have advanced CaP and when they develop skeletal-related events, this often result in their hospitalization with its attendant economic consequence. Groot et al. [32] reported that SREs double the annual treatment-related costs in patients with advanced prostate cancer. Therefore, maintenance of the optimum bone health throughout the course of the disease is important.

The main limitation in this study is that the accuDEXA machine used does not generate *T* scores based on normative data from black Africans; rather it generates *T* scores based on Caucasian males' normative data.

We utilized peripheral accuDEXA machine for assessment of BMD. BMD is most commonly measured using DEXA assessment of the hip or lumbar spine. However, it is expensive, not portable and not universally available. Studies have shown that results obtained with the use of peripheral accuDEXA can be used to diagnose osteopenia/osteoporosis when DEXA assessment of the hip is not available [33].

To the best of our knowledge, this is the first report of the effect of ADT on BMD of Nigerian patients with prostate cancer. Due to the fact that most of our patients present with advanced disease with the widespread use of ADT, we would recommend a further prospective study in the same subgroups of patients to validate the efficacy of peripheral DEXA by comparing with DEXA assessment of the hip. In addition, all patients with CaP and commenced on ADT should undergo a baseline BMD measurement, which is to be repeated serially during the course of treatment. Furthermore, CaP patients with baseline osteopenia and osteoporosis on ADT should be considered for pharmacologic interventions with use of calcium, vitamin D and anti-resorptive agents. This is to significantly reduce the risks of skeletal-related events which are negative predictors of overall survival.

5 Conclusion

CaP is associated with a decrease in the BMD, and ADT is associated with a further decline in the BMD of Nigerian patients with CaP. It is therefore necessary to bear this in mind and possibly make provision for prevention and treatment of skeletal-related events in patients receiving ADT for advanced CaP.

Abbreviations

CaP: cancer of the prostate; BMD: bone mineral density; ADT: androgen deprivation therapy; DEXA: dual energy X-ray absorptiometry; WHO: World Health Organization; GnRH: gonadotropin releasing hormone; PSA: prostate-specific antigen.

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Authors' contributions

OOO was involved in protocol/project development, data collection and management, data analysis, and manuscript writing/editing. SOI was involved in protocol/project development and manuscript writing/editing. EAJ contributed to protocol/project development, data Analysis, and manuscript writing/editing. OAA was involved in protocol/project development, data analysis, and manuscript writing/editing. AAA contributed to protocol/project development and manuscript writing/editing. OAO contributed to protocol/project development and manuscript writing/editing. All authors read and approved the final manuscript.

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Availability of data and materials

Datasets obtained and analysed in the current study are available upon request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee (Health Research and Ethics Committee, Lagos State University Teaching

Hospital, Ikeja, Lagos. Reg no. NHREC04/04/2008. www.nhrec.net. Ref No.: LREC/10/06/638) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Informed consent
Written informed consent was obtained from all individual participants included in the study.

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