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The Effect of Androgen Deprivation Therapy on Periodontal Disease in Men With Prostate Cancer

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Abstract

Purpose—We tested the hypothesis that men undergoing androgen deprivation therapy as treatment for prostate cancer are at greater risk for periodontitis and tooth loss.

Materials and Methods—A total of 81 men with a mean age of 68.5 years who had prostate cancer were consecutively recruited among 325 enrolled in an academic osteoporosis study. Of these men 68 were eligible to participate in the research. The prevalence of periodontal disease in 41 men with prostate cancer undergoing androgen deprivation for a mean of 1.5 years was compared to that in 27 with prostate cancer not undergoing androgen deprivation, who served as controls. The prevalence of periodontal disease was examined in relation to bone mineral density in men with prostate cancer with and without androgen deprivation therapy. A periodontist (PF) blinded to androgen deprivation status recorded probing depth, clinical attachment level, bleeding, plaque scores, gingival recession, missing teeth and calculus. Logistic regression models were used to test the association between androgen deprivation therapy and periodontal disease. Linear regression models were used to assess the association between periodontal disease and bone mineral density in the 2 groups with prostate cancer (treated/untreated). We adjusted for variables known to influence periodontal disease, including patient age, race, smoking and periodontal disease history.

Results—The prevalence of periodontal disease was 80.5% in men on androgen deprivation therapy compared with 3.7% in those not on androgen deprivation therapy (OR 3.33, 95% CI 1.07–10.35). Men on androgen deprivation therapy had significantly greater probing depth and higher plaque scores ($p < 0.001$ and < 0.09 , respectively). A total of 81 men (76.9%) completed bone mineral density examinations. There was no relationship between bone mineral density and periodontal disease.

Conclusions—Men with prostate cancer undergoing androgen deprivation therapy were more likely to have periodontal disease than men not on androgen deprivation therapy. If confirmed in larger studies, this observation could have important public health implications, given the increasing use of androgen deprivation therapy to treat prostate cancer.

Keywords

prostate; prostatic neoplasms; osteoporosis; periodontal diseases; androgen antagonists

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Carcinoma of the prostate is the most frequently diagnosed malignancy and the second leading cause of cancer death in men in the Western world. The peripheral blockage of androgen action remains a critical therapeutic option for treating prostate cancer. However, ADT, the most effective systemic therapy for prostate cancer, is a major risk factor for male osteoporosis.^{1–5} ADT causes increased osteoclastic activity,⁶ bone resorption,⁷ bone loss⁸ and an increased risk of fracture.⁹ The rates of bone loss are 2% to 8% in the lumbar spine region and 1.8% to 6.5% in the femoral neck during the initial 12 months of continuous ADT.^{2,6}

Periodontal disease results in resorption of alveolar bone and loss of the soft tissue attachment to the tooth. There is biological plausibility that periodontal destruction may be adversely influenced by systemic bone loss.^{10–14} However, none of this previous research was done to examine the link between ADT and periodontal disease. The incidence of periodontal disease increases with advancing age and current demographic shifts in the age distribution will lead to increases in the number of people with periodontal disease. We compared the prevalence of periodontal disease in men with prostate cancer receiving ADT with that in a control group of men with prostate cancer who were not receiving ADT. In addition, we examined the relationship between periodontal disease and BMD measures in these men.

MATERIALS AND METHODS

A total of 81 men in a racially mixed set with a mean age of 68.5 years agreed to participate in this study of periodontal disease. All men were consecutively recruited from a larger group of 325 ambulatory men participating in an academic research study of bone loss in men with nonmetastatic prostate cancer treated with ADT or men not receiving ADT.

To be eligible for enrollment in the current ancillary research the men had to be willing to undergo a comprehensive periodontal dental examination and sign a University of Pittsburgh Institutional Review Board approved consent form. Exclusion criteria for this study were 1) medical conditions precluding an adequate oral examination, such as a history of heart disease or joint replacement, or any medical disease requiring premedication with antibiotic before a periodontal examination, 2) mental or legal incapacitation, so that informed consent could not be obtained, 3) history or evidence of metabolic bone disease, including hypercalcemia, hyperparathyroidism, Paget's disease of bone, osteomalacia or osteogenesis imperfecta, 4) hyperthyroidism or hypothyroidism recognized within 6 months of study enrollment and 5) edentulism. The total number of men excluded was 13, including 11 because of edentulism and 2 with medical conditions that resulted in exclusion, leaving 68 participants ($p < 0.001$).

Periodontal Assessment

A periodontist (PF) blinded to treatment status completed full mouth comprehensive periodontal examinations, including probing depth, clinical attachment loss, bleeding upon probing, plaque scores, gingival recession, missing teeth and calculus, on all remaining teeth in each subject. Probing depth was measured from the gingival margin with a 0.5 mm diameter, calibrated Michigan 0 probe (Hu-Friedy, Chicago, Illinois). Probing depth was measured on 6 sites per tooth (distobuccal, mid buccal, mesiobuccal, distolingual, mid lingual and mesiolingual). The loss of clinical attachment is defined as the distance in mm from the cemento-enamel junction to the base of the periodontal pocket. A subject was considered to have periodontal disease if he had 3 mm or more attachment loss.¹⁵ Probing depth is the distance from the free gingival margin to the base of the sulcus/pocket that could be probed. Gingival bleeding was coded as 0—no bleeding and 1—bleeding, supragingival plaque was coded as 0—no plaque and 1—plaque, and calculus was measured as 0—no calculus and 1—supragingival calculus. The prevalence of periodontal disease was considered present if any of these indexes were present. All missing teeth were recorded on a standard dental form.

History of periodontal disease, dental hygiene, tooth brushing frequency, flossing frequency and visits to the dentist were also recorded.¹⁵

BMD Measurement

BMD of the spine and hip was measured by fan beam, dual energy x-ray absorptiometry using a QDR4500A (Hologic, Bedford, Massachusetts). Standardized procedures for patient positioning and scan analysis were used. A spine phantom was scanned daily and it indicated no shifts or drifts in scanner performance.

Statistical Analysis

Before statistical analysis all data were screened for accuracy. Log Exact™ software was used to analyze the data. Descriptive statistics were calculated for all variables, including the mean, SD, range and percent. Logistic regression models were used to compare the prevalence vs the absence of periodontal disease and they are presented as the OR and 95% CI. Linear regression was used to examine BMD and its relation to periodontal disease.

All models were initially adjusted for age. Multivariate adjusted models included variables known to influence periodontal disease, specifically age, smoking, flossing, brushing, visits made to the dentist and history of periodontal disease.¹⁶

RESULTS

A total of 68 men were examined, including 27 with prostate cancer not undergoing ADT (controls) and 41 with prostate cancer receiving ADT for varying periods. Eleven men (13.6%) were edentulous and were among the 13 excluded from further analysis. The prevalence of edentulism did not differ between men undergoing and not undergoing ADT (97.6% and 92.6%, respectively). Completing the comprehensive periodontal examination was not possible in another 2 subjects, who were excluded due to their compromised medical condition, leaving 68 available for the final analysis. The mean age of the men undergoing and not undergoing ADT was 70.5 and 68.5 years, respectively ($p = 0.09$). A higher proportion of men undergoing ADT were 65 years or older (table 1). There were no statistical differences in race, education or smoking between the 2 groups.

The duration of ADT related to periodontal disease was analyzed and found not to be statistically significant. Although there were no differences in dental hygiene habits, including brushing, flossing and visits to the dentist, between the men undergoing and not undergoing ADT, overall the men had excellent hygiene habits with 50% brushing twice daily and about 60% flossing daily. Of the set 46% visited the dentist regularly at the recommended yearly intervals. Fewer men had any missing teeth or dental caries ($p = 1$). Nevertheless, 82% of the men (34) undergoing ADT had moderate plaque scores ($p = 0.09$), while 68% (28) had bleeding upon probing ($p = 0.001$).

Periodontal Disease

The majority of subjects receiving ADT had evidence of periodontal disease. Table 2 shows these and other indexes of periodontal disease. Of the 68 subjects 33 (80.95%) had periodontal disease compared to 1 (3.75%) not receiving ADT. Men receiving ADT had greater pocket depth (more than 3 mm) and were more prone to attachment loss, recession and tooth mobility. Tooth mobility was present in 14.4% of men undergoing ADT and it was not present in men who were not on ADT ($p = 0.074$).

In unadjusted models the odds of periodontal disease were 3-fold greater in men on vs not on ADT (table 3). Adjustments for age attenuated this association but it remained borderline

significant. Further adjustments for smoking, race and periodontal disease history had little effect.

We examined the relationship between periodontal disease and BMD in these subjects. Table 4 shows that BMD was similar in men with and without periodontal disease after adjusting for ADT.

DISCUSSION

We found that the prevalence of periodontal disease was about 3 times greater in the group undergoing ADT compared with the group not receiving ADT even after we adjusted for age, race, smoking and periodontal treatment history. As noted, the time that an individual was undergoing ADT did not significantly correlate with periodontal disease. To our knowledge this is the first report of a high prevalence of periodontal disease in men on ADT. If confirmed in other, larger studies, this observation could have major public health consequences, given the increasing number of men with prostate cancer and the increasing use of ADT to treat these men. Many patients are now being diagnosed with early or progressive disease based on increasing prostate specific antigen alone and hormonal therapy is being administered earlier in the disease course. As a consequence, many patients are being treated with hormonal therapy at the asymptomatic stage and due to the natural history of the disease they survive for years after diagnosis.¹⁷ Clinicians treating men with ADT must be aware of the increased need for dental visits to identify periodontal disease at the earliest stages before tooth loss occurs.

Although the majority of individuals in this group were highly educated, visited the dentist regularly and had good plaque control, they had periodontal disease. Investigators previously noted that ADT causes severe bone loss and osteoporosis, which may represent the underlying factor that contributes to a relationship between periodontal disease and ADT. ADT may enhance rapid bone loss around the teeth and initiate or accelerate periodontal disease despite good plaque control. This condition appears to parallel an aggressive type of periodontal disease in which bone loss develops in a short period despite minimal plaque and good plaque control. In the presence of androgen ablation therapy other elements that are to our knowledge unknown as yet may influence the impact of local factors such as plaque that can cause or aggravate periodontal disease.

The collective data reported in most published cross-sectional studies of the relationship between periodontal disease and bone loss or bone turnover appear to indicate a relationship between systemic and oral BMD but the sample size in these studies was small and only Jeffcoat adjusted for age.¹⁸ Generally most researchers used differing populations and did not adjust for other covariants, such as smoking. The exception to this is Kribbs, who studied normal and osteoporotic women.¹⁹ Kribbs noted 20% less mandibular density, as measured by quantitative analysis of intra-oral radiographs. The fact that only 1 assessment was performed is a flaw in any cross-sectional study. We do not know if disease was present before ADT. However, this cross-sectional study provides some important preliminary data and it lays the groundwork for a future followup study.

In a previous study we noted a correlation between tooth loss and decreased systemic BMD. This research is strongest among reports of oral bone loss in osteoporotic women.

Although periodontal disease may not be clinically relevant in men with more advanced prostate cancer, the men in this study were relatively healthy with stable prostate cancer on therapy. Therefore, periodontal disease could impact quality of life and nutritional intake. Because ADT is needed to treat prostate cancer but it has a negative impact on dental health, oncologists must be aware of this to encourage dental care and followup.

Referral to an experienced periodontist is essential for collaborative care during androgen deprivation treatment in cases of prostate cancer. The periodontist should inform the oncologist and general dentist of the patient regarding the clinical state of patient alveolar bone loss, attachment loss, recession, and general periodontal health and prognosis. A diagnosis of craniofacial osteopenia should be made, if present. Clinicians should first rely on nonsurgical periodontal therapies to stop further periodontal destruction. It should be clear to the patient and clinicians that a secondary etiology of oral bone loss may be ADT for prostate cancer. The oncologist should continue to evaluate the patient for systemic bone loss.

CONCLUSIONS

The current research is significant, in that to our knowledge the impact of ADT on periodontal disease has not been previously investigated or reported. We noted an association between periodontal disease and androgen deprivation. This may have been due to osteoporotic bone loss in the group of men receiving ADT, although there was no significant correlation between periodontal disease and BMD in our study. Additional studies using a larger sample size and longitudinal analyses are necessary to definitively correlate periodontal disease and ADT. If these associations can be confirmed by research performed with larger sample sizes, this observation may have important public health implications.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
BMD	bone mineral density

Table 1
 Characteristics of 68 men with prostate cancer with and without ADT

No. subjects	No. No ADT (%)	No. ADT (%)	p Value (exact test)
No. subjects	27	41	
Mean $\pm$ SD age:			
65 or Younger	5 (22.22)	8 (19.51)	0.098
65-75	20 (70.37)	21 (51.22)	
Older than 75	2 (7.41)	12 (29.27)	
Race:			
White	24 (88.89)	38 (92.68)	0.675
Black	3 (11.11)	3 (7.320)	
Education:			
High School	9 (33.33)	14 (34.15)	0.781
College	8 (29.63)	15 (36.59)	
Beyond college	10 (37.04)	12 (29.27)	
Current smoker	1 (3.70)	3 (7.32)	0.64
Heart disease:			
No	26 (96.30)	40 (97.56)	1.000
Yes	1 (3.70)	1 (2.44)	
Brush teeth (times daily):			
1	5 (18.52)	13 (31.71)	0.540
2	16 (59.26)	20 (48.78)	
More than 2	6 (22.22)	8 (19.51)	
Floss:			
No	14 (51.85)	24 (58.54)	0.625
Yes	13 (48.15)	17 (41.46)	
Visit D.M.D./D.D.S.			
Every 6 mos	12 (44.44)	12 (29.27)	0.461
Yearly	9 (33.33)	19 (46.34)	
For emergencies	2 (22.22)	10 (24.39)	
Missing teeth:			
No	2 (7.41)	1 (2.44)	0.558
Yes	25 (92.59)	40 (97.56)	
Caries:			
No	26 (96.30)	38 (92.68)	1.000
Yes	1 (3.70)	3 (7.32)	
Dentures:			
No	27 (100.00)	40 (97.56)	1.000
Yes	0	1 (2.44)	
Plaque:			
Mild	20 (74.07)	7 (17.07)	<0.09
Moderate	7 (25.93)	34 (82.93)	
Bleeding:			
No	20 (74.07)	13 (31.71)	0.001
Yes	7 (25.93)	28 (68.29)	
Periodontal disease history (yrs):			
1	27 (100.00)	38 (92.68)	0.271
2 or More	0	3 (7.32)	

Table 2
Periodontal disease characteristics in men with prostate cancer with and without ADT

	No. No ADT (%)	No. ADT (%)	p Value (exact test)
Periodontal disease:			
No	26 (96.30)	8 (19.51)	0.006
Yes	27 (3.70)	41 (80.49)	
Pocket depth (mm):			
2–3	26 (96.30)	0	<0.001
3–4	1 (3.70)	41 (100.00)	
Attachment loss:			
No	25 (92.59)	0	<0.001
Yes	2 (7.41)	41 (100.00)	
Recession:			
No	20 (92.59)	4 (9.76)	<0.001
Yes	7 (7.41)	37 (90.24)	
Mobility:			
No	27 (100.00)	35 (85.37)	0.074
Yes	0	6 (14.63)	

Table 3

OR of periodontal disease by ADT

Model Order	Adjustment	OR	SE	p Value	95% CI	p Value
1	None	3.33	1.93	0.04	1.07–10.35	0.037
2	Age	2.98	1.82	0.07	0.90–9.85	0.074
3	Age + race	3.15	1.96	0.07	0.93–10.64	0.065
4	Age + smoking	3.12	1.92	0.06	0.94–10.43	0.064
5	Age, race, smoking + periodontal treatment history	3.20	1.99	0.06	0.95–10.84	0.061

Table 4
BMD in men with and without periodontal disease adjusted for ADT

BMD (gm/cm ²)	Mean $\pm$ SD		p Value (exact test)
	Disease	No Disease	
Femoral neck	0.76 $\pm$ 0.15	0.77 $\pm$ 0.12	0.797
Total hip	0.97 $\pm$ 0.16	0.96 $\pm$ 0.14	0.986
Lumbar spine	1.00 $\pm$ 0.17	1.05 $\pm$ 0.16	0.256