The relationship between daily calcium intake and bone mineral density in men with prostate cancer

Jacques Planas, Juan Morote, Anna Orsola, Carlos Salvador, Enrique Trilla, Lluis Cecchini and Carles X. Raventós

Department of Urology, Vall d’Hebron Hospital, Autònoma University School of Medicine, Barcelona, Spain

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OBJECTIVE

To analyse the relationship between daily calcium intake (DCI) and bone mineral density (BMD) in patients with prostate cancer, and to assess if DCI is a risk factor for osteoporosis in this group of patients.

PATIENTS AND METHODS

DCI was assessed by a standard questionnaire answered by men with prostate cancer who had had bone densitometry. BMD was measured by dual-energy X-ray absorptiometry in the lumbar spine and different hip sites, in a cross-sectional study including 372 men with prostate cancer free of bone metastases, 71.5% (266) under androgen-deprivation therapy (ADT) and 28.5% (106) after radical prostatectomy (RP). Osteoporosis was defined according to the International Society for Clinical Densitometry official position (2005).

RESULTS

A DCI of <1000 mg, the National Institute of Health recommendation, was detected in 93% of the men, (93.5% under ADT and 91.5% after RP). Osteoporosis was identified in 49.2% (183) of the patients, 54.9% (146) under ADT and 34.9% (37) after RP. The mean DCI was 609.7 mg in men with osteoporosis and 682.8 mg in those without (P < 0.001); in men under ADT the mean DCI remained significantly lower in those with osteoporosis (615.5 vs 700.4 mg, P < 0.001). A multivariate analysis showed that DCI was an independent risk factor for osteoporosis, together with patient age, ADT and its duration.

CONCLUSIONS

DCI seems to be related to BMD; a low DCI was an independent risk factor for osteoporosis in men with prostate cancer. In the study population overall the DCI was inadequate. Urologists should recommend a DCI of >1000 mg in patients with prostate cancer, especially in those under ADT.

KEYWORDS
calcium intake, osteoporosis, prostate cancer, androgen deprivation therapy

INTRODUCTION

Prostate cancer is one of the most frequently diagnosed neoplasms in men, with >500 000 cases newly diagnosed every year, and with an increasing incidence [1]. The mainstay of treatment for men with metastatic disease is androgen-deprivation therapy (ADT). Currently, ADT is increasingly prescribed to men with no evidence of metastatic disease, e.g. those presenting with extraprostatic disease, in some receiving radiation therapy or in PSA relapse after local therapy [1]. Consequently, the group of otherwise apparently healthy men receiving ADT for many years is increasing. Therefore, long-term side-effects of ADT therapy are important in these patients. Loss of bone mineral content and consequent osteoporosis related to ADT has been widely reported [2–7]. The duration of ADT has been related to a higher rate of osteoporosis, reaching half in those patients undergoing ADT for >60 months [8], and being more severe during the first year [9]. Osteoporosis is important because it is a significant cause of bone fracture; about a third of all hip fractures occur in men, and mortality after a hip fracture is greater in men than in women. ADT for prostate cancer has been shown to increase the risk of fracture [10]. Defeulein and Resnick [11] suggested that skeletal fractures are negatively associated with overall survival in men with prostate cancer. Apart from hypogonadism secondary to ADT, other risk factors for osteoporosis include a low daily calcium intake (DCI), together with smoking, slim stature, alcohol consumption and decreased physical activity. The USA National Institutes of Health (NIH) recommended in 1994 an optimum DCI of 1000 mg in men aged 25–65 years, while men aged >65 years recommended to consume >1500 mg of calcium daily [12].

The aim of the present study was to evaluate the relationship between DCI and bone mineral density (BMD) in a group of patients with prostate cancer; a secondary aim was to evaluate whether DCI can act as a prognostic risk factor for osteoporosis, especially in patients under ADT.

PATIENTS AND METHODS

DCI was evaluated at the time of BMD assessment in a cross-sectional study including 372 men with prostate cancer who were free of bone metastases. The general characteristics of the study population are summarized in Table 1. A group of 106 patients (28.5%) with clinically localized prostate cancer had a radical prostatectomy (RP) and were free of biochemically progression at the time, with a mean (range) follow-up of 42.6 (6–79) months; 266 patients (71.5%) with clinically advanced disease but free of bone metastases were under ADT (LHRH agonist) with a mean treatment duration of 42.8 (12–98) months. Bone scintigraphy was used systematically when the serum PSA level was >10 ng/mL. Men with bone disorders or secondary causes of osteoporosis were excluded from the study.
BMD was measured at the lumbar spine (L2–L4) and four different hip sites (femoral neck, Ward’s triangle, trochanter and total hip) in all patients, using dual-energy X-ray absorptiometry with a Lunar DPX-IQ 4977 (GE Healthcare, USA) detector device. Dual-energy X-ray absorptiometry is normally used to measure the BMD and is recommended and approved by the USA Food and Drug Administration; it is not invasive and precise, with low radiation exposure and takes only 10 min. We followed the International Society for Clinical Densitometry official position 2005 criteria for the diagnosis of osteopenia and osteoporosis.

To evaluate DCI, patients answered a dietary questionnaire, at the time of BMD measurement, which included information about the patient’s daily diet (mainly about the intake of dairy products), and the responses were used to estimate DCI by multiplying the quantity of any product consumed by the calcium content of the product (e.g. 250 mL of milk × 1.2 mg calcium/mL of milk = 300 mg calcium). The questionnaire was validated by the Endocrinology and Nutrition Department of our institution.

For statistical analysis, the quantitative variables were expressed as the mean, SD and range. The nonparametric Mann–Whitney U-test was used to compare means. Logistic regression analysis was used to for the multivariate analysis. In all tests, \( P < 0.05 \) was taken to indicate statistical significance.

TABLE 1 The general characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>372</td>
</tr>
<tr>
<td>Mean (SD, range):</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>69.8 (7.2, 53–89)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>6.8 (2.4, 4–10)</td>
</tr>
<tr>
<td>Serum PSA at diagnosis, ng/mL</td>
<td>9.2 (74.3, 0.1–1320)</td>
</tr>
<tr>
<td>DCI, mg</td>
<td>645.3 (214.1, 200–1700)</td>
</tr>
</tbody>
</table>

TABLE 2 Characteristics according to ADT and DCI

<table>
<thead>
<tr>
<th>Mean (SD, range)</th>
<th>No ADT</th>
<th>ADT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>106</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>67 (54–80)</td>
<td>71 (53–89)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gleason score</td>
<td>6.3 (3–10)</td>
<td>7 (5–10)</td>
<td>0.001</td>
</tr>
<tr>
<td>PSA at diagnosis, ng/mL</td>
<td>7.8 (2.9–13.2)</td>
<td>89.3 (1.8–1320)</td>
<td>0.034</td>
</tr>
<tr>
<td>DCI, mg</td>
<td>639.7 (200–1500)</td>
<td>651.0 (200–1700)</td>
<td>0.333</td>
</tr>
</tbody>
</table>

TABLE 3 The mean (SD, range) DCI according to the BMD and ADT

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>No osteoporosis</th>
<th>Osteoporosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>189</td>
<td>682.8 (207.3, 200–1700)</td>
<td>609.7 (212.7, 100–1200)</td>
<td>0.001</td>
</tr>
<tr>
<td>With ADT</td>
<td>120</td>
<td>652.3 (225.4, 200–1500)</td>
<td>610.9 (226.1, 200–1300)</td>
<td>0.001</td>
</tr>
<tr>
<td>Without ADT</td>
<td>69</td>
<td>700.4 (195.1, 200–1700)</td>
<td>615.5 (208.1, 200–1300)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

TABLE 4 Analysis of predictive factors for osteoporosis by multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT (yes vs no)</td>
<td>2.103 (1.288–3.341)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.037 (1.006–1.069)</td>
<td>0.018</td>
</tr>
<tr>
<td>DCI, mg</td>
<td>0.998 (0.997–0.999)</td>
<td>0.001</td>
</tr>
<tr>
<td>ADT duration, months</td>
<td>1.318 (1.175–1.478)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

RESULTS

The analysis of age, Gleason score, serum PSA at the diagnosis of prostate cancer and the DCI at the BMD assessment according to hormonal treatment status are summarized in Table 2; 93% of the patients (346/372) had a calcium consumption below the NIH recommendation (2000 mg/day). This high rate of men with a low DCI was similar regardless of ADT status, at 91.5% (97/106) in those not treated with ADT and 93.6% (249/266) in those under ADT.

As expected, the rate of osteoporosis was significantly higher in patients under ADT (\( P \leq 0.001 \)); the overall rate of osteoporosis was 49.2% (183 men), whereas osteopenia was identified in 35.5% (132) and a normal BMD in 15.3% (57). In patients under ADT the rate of osteoporosis was 54.9% (146) while 30.8% of the patients (82) had osteopenia and 14.3% (38) a normal BMD. Interestingly, there was also a high rate of osteoporosis of 34.9% (37) in hormone-naive patients, with 47.2% (50) having osteopenia and 17.9% (19) a normal BMD.

The DCI was 639.7 mg in patients not under ADT and 651.0 mg in those under ADT (not significantly different). The analysis of DCI according to the presence or absence of osteoporosis and related to hormonal status is shown in Table 3. Patients with osteoporosis (183) had a significantly lower DCI (609.7 mg) than those with no osteoporosis (682.8 mg; \( P < 0.001 \)). The DCI remained significantly lower in osteoporotic patients regardless of their hormonal status. On multivariate analysis patient age (\( P < 0.01 \)), associated ADT (\( P < 0.003 \)), ADT duration (\( P < 0.001 \)) and DCI (\( P < 0.001 \)) were independent predictors for the risk of having osteoporosis (Table 4).

DISCUSSION

The current study emphasizes the low DCI in men with prostate cancer; up to 93% of the patients had a DCI of <1000 mg. According to the NIH recommendations, an optimum...
calcium intake should be ≥1000 mg/day in men aged 25–65 years and >1500 mg/day in men aged >65 years [12]. The report also establishes a relationship between DCI and BMD status. Moreover, a low DCI was an independent risk factor of osteoporosis. Another interesting finding was the high incidence of osteoporosis in hormone-naïve patients, at 34.9% of this group.

Inadequate intake of calcium and vitamin D leads to reduced calcium absorption, increased serum parathyroid hormone concentration, and bone loss [13]. The dietary intake of calcium decreases with age and a substantial proportion of the elderly take less than the recommended dietary allowance of 1000 mg/day [12]. Numerous publications indicate the importance of DCI and vitamin D intake as risk factors for developing osteoporosis in men. To our knowledge, the present study is the first to evaluate and quantify DCI in men with prostate cancer (treated with ADT or not), apart from detecting a statistical relationship with osteoporosis in these patients. Few studies have focused on the role of DCI as a risk factor for osteoporosis in men, especially in those with prostate cancer. Evaluating the low BMD in hormone-naïve patients with prostate cancer, Smith et al. [14] found that up to 88% of their patients had a DCI of <1000 mg. There was no significant association between BMD measured at any skeletal site and DCI. In a study to determine the cross-sectional demographic, anthropometric, historical, lifestyle and neuromuscular factors associated with BMD of the lumbar spine and proximal femur, 5995 men aged ≥65 years were recruited (The Osteoporotic Fractures in Men Study [15]). The authors found that the median DCI was 1138.5 mg. Men who reported higher dietary calcium intakes had a modestly higher hip BMD, but there was no apparent association with lumbar spine BMD. Vitamin D was not related to either hip or spine BMD. In a prospective study of 50 patients with prostate cancer who chose to have orchidectomy, Agarwal et al. [16] found that non-smokers, non-alcoholic patients, those with higher physical activity and patients with a body mass index of ≥25 kg/m² had a statistically significantly higher BMD. In that study, dietary calcium had a discernible but statistically insignificant effect on BMD. The present findings support that the DCI is important and has a statistically significant effect on the BMD in men with prostate cancer under ADT.

Vitamin D and calcium have had much attention for the treatment of osteoporosis, but few studies have focused on their use in men. Reports of vitamin D and calcium supplementation to address the loss of BMD, and studying the treatment of male osteoporosis, have shown positive effects. However, because of the study design, it is not clear how much of the benefit was due to vitamin D or calcium supplementation [7,13]. In a 2-year, randomized, double-blind study of 33 patients with at least one osteoporotic fracture, Ebeling et al. [17] concluded that calcium supplementation (500 mg/day) did not prevent subsequent osteoporotic fractures to a significant extent. Dawson-Hughes et al. [13] conducted a 3-year, placebo-controlled, double-blind study of 445 adult men and women. Using 700 IU of supplemental vitamin D and 500 mg of calcium they moderately reduced bone loss, measured at the femoral neck, spine and total body. More importantly, there was a significant decrease in the rate of symptomatic non-vertebral fractures, by half in women and men aged >65 years. That study strongly supported the benefit of calcium and vitamin D supplementation. Similarly, in another report, Peacock et al. [18] used a 750-mg calcium supplement vs placebo in 122 healthy men observed for 4 years in a randomized, double-blind, placebo-controlled trial. Fracture rates and withdrawal rates were similar among the groups, but calcium supplementation prevented bone loss and reduced high bone turnover significantly when compared with placebo. The control arms of two studies [7,19] consisting of vitamin D and calcium supplementation (500 mg/day) in addition to placebo, examined the role of bisphosphonates in the treatment of osteoporosis. Orwoll et al. [19] found only an increase in lumbar spine BMD but not in other sites in patients receiving calcium and vitamin D supplementation. Smith et al. [7] studying ADT-induced osteoporosis showed that calcium supplementation maintained femoral neck BMD, whereas it failed to prevent BMD loss at other sites.

In the present study the rate of osteoporosis was 34.9% in those men not under ADT; even though there was no control group, this finding suggests that men with prostate cancer might have a lower BMD than age-matched controls. This was previously reported in other studies but the mechanism is not clear [4,7,14,20]. It was suggested that an increase of serum interleukin-6 production by the prostate tumour would negatively affect patients, inducing the loss of bone mass [3]. This interesting issue has not been detailed completely, and more studies on molecular or genetic alterations on prostate cancer cells involved in bone dynamics are necessary.

The present study has some limitations. It is a cross-over study, and we did not take into account the importance of other non-dietary factors such as body size, exercise levels, smoking or alcohol consumption, which might also be important for bone health and correlate with DCI. Also, a prospective use of a dietary diary questionnaire might have provided more accurate information on DCI. Nonetheless, the many patients included in the study, with the information on BMD measurements and DCI of these patients, strong support the validity of the findings.

In the present patients the low DCI could explain the high prevalence of osteoporosis; up to 93% of the patients had a DCI of <1000 mg, and therefore it seems reasonable to encourage those patients about to initiate ADT to follow Higano’s recommendations [5], to maintain a considerable daily intake of calcium (1000–1500 mg) and vitamin D (400–800 UI), and to stop smoking and consuming alcohol, or to take weight-bearing exercise regularly.

In conclusion, we report a significant relationship between a low DCI and the risk of osteoporosis in men with prostate cancer. The DCI was an independent risk factor for osteoporosis, with patient age, ADT and its duration. The present men with prostate cancer had a DCI well below that recommended and therefore we assume that the high prevalence of osteoporosis in the hormone-naïve patients could be related to the low DCI. We support the recommended optimum DCI of >1000 mg in patients with prostate cancer, and their BMD should be assessed especially before starting ADT, and monitored at intervals afterwards.

CONFLICT OF INTEREST
None declared.

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Correspondence: Jacques P. Morin, Urology Department, Vall d’Hebron University Hospital, P. Vall d’Hebron 119–129, 08035 Barcelona, Spain.

E-mail: jplanas@vhebron.net, 34021jpm@comil.es

Abbreviations: ADT, androgen deprivation therapy; DCI, daily calcium intake; BMD, bone mineral density; NIH, National Institutes of Health; RP, radical prostatectomy.

EDITORIAL COMMENT

These authors report an important study showing a low DCI in a large Southern European group of patients with non-metastatic prostate cancer, including both those not requiring and those on ADT. Their study also shows a very high incidence of osteoporosis and osteopenia in these men. DCI was significantly less in those with osteoporosis. It would have been interesting if they had included a group of age-matched controls to determine DCI in those without prostate cancer and its relationship to BMD in their population.

The high rates of osteoporosis and osteopenia are similar to those in our group of Northern European patients with either locally advanced or metastatic prostate cancer, studied immediately before starting ADT [1]. The BMD in these patients was 6.6% lower than in age-matched controls. The authors conclude that, especially in those about to start ADT, the baseline BMD should be measured and monitored afterwards. These recommendations were recently included in North American guidelines. The question arises as to how patients with prostate cancer should be treated, based on the results of such BMD measurements?

The authors mention that a dietary questionnaire was used to determine DCI, mainly by assessing the intake of dairy products. At first glance it might seem sensible to encourage patients with prostate cancer to increase their intake of dairy produce. However, in a large prospective study in patients with prostate cancer, and involving monitoring of fat intake with dietary diaries over a mean of 5.2 years, Meyer et al. [2] observed that mortality was three times greater in those in the highest tercile for fat consumption than in the lowest tercile. Furthermore, we recently reported that adopting a very low-fat diet decreased the PSA velocity in patients with progressive prostate cancer and good performance status [3]. Thus, caution should be adopted before advocating an increase in dairy produce in patients with prostate cancer.

It would now seem sensible to commence all osteopenic and osteoporotic patients on calcium and vitamin D supplements (CaVitD) at the time of starting ADT. This strategy might be sufficient for those who are osteopenic and not on ADT. However, in a prospective longitudinal study of 430 patients requiring ADT, we found that 164 (38%) were osteoporotic at presentation. These were treated with LHRH analogues plus CaVitD, and of those surviving for 2 years, over half had become osteoporotic [4]; thus, additional or
alternative therapy is required for this group. The authors rightly indicate that more patients are starting ADT at an earlier stage and are likely to continue with this for longer periods. An increase in the use of antiandrogens might be appropriate, as these maintain BMD [5], proceeding to LHRH analogues only in those with progression. Other alternatives could be i.m. oestrogens, which also maintain BMD [6], or possibly oestrogen patches.

For those with osteoporosis at presentation or subsequently developing it, then i.v. bisphosphonates have been shown to increase BMD [7], but the optimum dosing schedule is unclear. Oral bisphosphonates are poorly tolerated, with a high withdrawal rate in patients with cancer [8]. Clearly much more work still needs to be done in this area before evidence-based algorithms can be developed.

Nigel J. Parr
Department of Urology, Wirral Trust Hospital, Wirral, UK.

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