Endocrine (2018) 59:338–343
DOI 10.1007/s12020-017-1351-0

ORIGINAL ARTICLE

Mineral metabolism abnormalities in patients with prostate cancer: a systematic case controlled study

Francesco Minisola[1] · Cristiana Cipriani[2] · Luciano Colangelo[2] · Mirella Cilli[2] · Alessandro Sciarra[1] · Magnus Von Heland[1] · Luciano Nieddu[3] · Emanuela Anastasi[4] · Roberto Pascone[5] · Valeria Fassino · Daniele Diacinti[6] · Flavia Longo[6] · Salvatore Minisola[2] · Jessica Pepe[2]

Received: 6 March 2017 / Accepted: 9 June 2017 / Published online: 28 June 2017

Abstract
Purpose Prostate cancer is the most common tumor in men. To the best of our knowledge a systematic assessment of bone and mineral abnormalities has not been performed in prostatic cancer patients consecutively enrolled.
Methods This study was therefore carried out to investigate changes of skeletal and mineral metabolism in patients with prostate cancer ($n = 69$). A population of patients with cancer of various origin was also investigated as a control group ($n = 53$), since a comparison with non-prostate cancer patients has not been previously reported.
Results In the prostatic cancer group, one patient had extremely high values of C-terminal Fibroblast Growth Factor 23, low values of tubular reabsorption of phosphate and very high values of bone alkaline phosphatase, suggesting the diagnosis of oncogenic osteomalacia. We found nine patients with primary hyperparathyroidism in the group of prostate cancer vs. only one in cancer patients group ($p < 0.026$). We stratified the population on the basis of Gleason score, prostate specific antigen and hormonal therapy. Using a generalized linear model with a logit link to predict the probability of developing primary hyperparathyroidism, only Gleason score, C-terminal fibroblast growth factor 23 and hormonal therapy had a significant effect ($p < 0.05$). Controlling for other covariates, a rise in fibroblast growth factor 23 increases the odds of developing primary hyperparathyroidism by 2% ($p = 0.017$), while patients with higher values of Gleason score have a much greater probability of developing primary hyperparathyroidism (log-odds = 3.6, $p < 0.01$). The probability decreases with higher values of Gleason score while on hormonal therapy; a further decrease was observed in patients on hormonal treatment and lower values of GS. Finally, lower grade of Gleason score without hormonal therapy have a significant protective factor ($p < 0.01$) decreasing the odds of developing primary hyperparathyroidism by 8%.
Conclusion We showed a remarkable prevalence of primary hyperparathyroidism in men with prostate cancer; the multivariate analysis demonstrates that higher aggressiveness of prostate cancer, as determined by Gleason score, is a significant predictor of increased risk of developing primary hyperparathyroidism.

Keywords Prostate cancer · Hypercalcemia · Hyperparathyroidism · Vitamin D · FGF23

Francesco Minisola and Cristiana Cipriani contributed equally to this work.

✉ Salvatore Minisola
salvatore.minisola@uniroma1.it

[1] Department of Gynecology-Obstetrics & Urology, Sapienza University of Rome, Rome, Italy

[2] Department of Internal Medicine and Medical Disciplines, Sapienza University of Rome, Rome, Italy

[3] Faculty of Economics, UNINT University, Via delle Sette Chiese 139, 00147 Rome, Italy

[4] Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy

[5] Department of Pediatrics and Infantile Neuropsychiatry, Sapienza University of Rome, Rome, Italy

[6] Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University of Rome, Rome, Italy

Introduction

Prostate cancer is the most common tumor in men. According to the World Cancer Research Fund International, more than

1.1 million cases of prostate cancer were recorded in 2012, accounting for around 8% of all new cancer cases and 15% in men [1]. It is mainly a disease of elderly subjects; therefore, considering the world's aging population, more and more often doctors will face this neoplasia.

A number of abnormalities of skeletal and mineral metabolism have been described in patients with prostate cancer. Indeed, skeletal complications are frequently encountered; bony metastases are predominantly of the blastic type even though some of them produce lytic lesions. Changes of serum calcium values (i.e., hypocalcemia and hypercalcemia) often parallel skeletal osteoblatic or osteolytic involvement, respectively.

Hypophosphatemia has also been frequently reported [2, 3]; this could be related to an increased influx of phosphate into growing skeletal metastases or alternatively to vitamin D insufficiency, decreasing tubular reabsorption of phosphate owing to secondary hyperparathyroidism. In this context, clinical descriptions in which hypophosphatemia is related to increased production of fibroblast growth factor 23 (FGF23) by prostate cancer cells have been increasingly reported [4, 5]. FGF23 is synthesized in bone and then released into the circulation; it acts on the proximal tubules to determine, within hours, urinary phosphate excretion by reducing the expression of two sodium-dependent phosphate co-transporters (NPT2a and NTP2c). In addition, FGF23 reduces renal production of 1,25-dihydroxyvitamin D [1,25(OH)D] indirectly reducing calcium absorption [6].

Surprisingly, to the best of our knowledge a systematic assessment of bone and mineral abnormalities has not been performed in prostatic cancer patients consecutively enrolled. Furthermore, it is also important to know how these abnormalities are found in a population with non-prostate cancer.

This study was therefore carried out in order to investigate changes of skeletal and mineral metabolism in patients with prostate cancer. A population of patients with cancer of various origin was also investigated as a control group, since a comparison with non-prostate cancer patients has not been previously reported.

Patients and methods

During the period January 2014-May 2015, we consecutively enrolled 69 patients with prostate cancer followed at the Department of Gynecology-Obstetrics & Urology "Sapienza", Rome University (Group A). During the same period, 53 cancer patients followed at Department of Radiological Sciences, Oncology and Anatomical Pathology, were enrolled (Group B). Patients were admitted to this investigation based on their willingness to participate to the study; the baseline demographic parameters of those who denied their consent were not different from respective counterparts (data not shown).

The exclusion criteria were a known previous history of metabolic bone diseases (i.e., Paget's disease) or other disorders known to influence mineral metabolism (such as hyperthyroidism, monoclonal gammopathy of undetermined significance and so on). Furthermore, patients taking drugs affecting bone metabolism (for example, bisphosphonates, denosumab, steroids) or mimicking primary hyperparathyroidism (PHPT) (i.e., thiazide diuretics or lithium) were excluded; calcium supplements did not represent a criterion of exclusion, as well as cholecalciferol supplements in doses up to 800 I.U./day.

Each patient eligible for this investigation underwent an initial comprehensive health survey and physical examination. Metabolic investigation included a 3-h morning urinary collection, after 12-h overnight fasting, for measurement of phosphate (P) and creatinine (Cr). Midway this collection, a blood sample was taken for the measurement of serum ionized calcium (Ca^{++}), P, Cr, bone alkaline phosphatase (BALP), C-terminal crosslinking telopeptides of type I collagen (CTX), parathyroid hormone (PTH), calcidiol [25(OH)D], calcitriol [1,25$(OH)_2$D], carboxy-terminal FGF23, total and free prostate specific antigen (PSA). Furthermore, each patient in both arms underwent global bone scintiscan according to previously described procedure [7] to detect skeletal metastases. Patients with prostate cancer underwent biopsy of prostate tissue for determining Gleason score (GS) [8].

Body mass index (BMI) was calculated by the person's weight's in kilogram, divided by height in squares meter. Serum Ca^{++} (normal values, n. v.: 1.17–1.33 mmol/l) was determined using an ion-specific electrode (Nova 8; Nova Biochemical, Waltham, MA), under anaerobic conditions within 1 h of blood sampling. Serum and urinary levels of P and Cr were measured by means of a Cobas 6000 analyzer (Roche Diagnostics, Switzerland) (n. v.: serum p = 2.5–4.5 mg/dl, serum Cr = 0.7–1.2 mg/dl). Creatinine clearance was calculated using the formula of Cockcroft & Gault [9]. The tubular maximum rate of phosphate reabsorption in relation to GFR ($TmPO_4$/GFR) was calculated from a nomogram of Walton and Bijvoet [10]. Serum 25 (OH)vitamin D levels were measured using LIAISON 25-OH Vitamin D TOTAL Assay (DiaSorin USA, Stillwater, MN, USA), a competitive one-step backfill chemiluminescence assay with a measurement range of 4–150 ng/ml and functional sensitivity of 4.0 ng/ml or less. The intra-assay and inter-assay precision of this assay were 8.9 and 12.8%, respectively, with a reported cross-reactivity values of 100% for both 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3. Serum immunoreactive PTH 1–84 levels were measured by LIAISON (Diasorin, Stillwater,

MN); the intra-assay and inter-assay coefficients of variation (CVs) were 8.1 and 10.2%, respectively. Serum 1,25 $[OH]_2D$ levels (n. v.: 19.9–67.0 pg/ml) were determined by RIA (IDS, Herlev, Denmark); intra-assay and inter-assay CVs were 9.3 and 9.6%, respectively, as previously described [11]. BALP concentrations were measured by an immune-enzymatic assay (Ostase BAP, IDS), whose intra-assay and inter-assay CVs were each less than 4.2%. Serum levels of CTX were determined by enzyme-linked immunosorbent assay (ELISA) (Serum CrossLaps ELISA, IDS). Intra-assay and inter-assay CVs were less than 2.2 and 7.7%, respectively. Plasma FGF23 levels, were measured by the second-generation ELISA (Immunotopics; Inc., San Clemente, CA, USA) that detects both the intact FGF23 and the C-terminal fragments. Intra-assay and inter-assay CVs were 8.0 and 7.0 at plasma concentrations of 25 and 300 RU/mL, respectively. All assays were carried out simultaneously in one batch, at the end of the study. Total and free PSA values were determined by Access Hybritech assays on automated instrumentation system (Beckman Coulter Inc., Fullerton, CA, USA; intra-assay and inter-assays CVs were 3.9 and 5.0, respectively.

Written informed consent was obtained from all participants. The protocol was approved by "Sapienza" University of Rome Ethics Committee.

Statistical analysis

We expressed basic variables by mean ± SD. The Shapiro–Wilk test and the *F* test were first used to prove normality and the equality of the variances in the two populations of patients, respectively. The null hypothesis of the equality of the two means was then tested, for each variable, through the two tailed Student's *T* test, when the *F* test turned out to be not significant and through the Satterthwaite's method when the *F* test was significant and Behrens–Fisher problem arose. To test for independence between dichotomous categorical variables and the presence of prostate cancer a Barnard's test was applied as a more powerful alternative to the Fisher's exact test [12]. Where necessary, continuous covariates have been transformed into dichotomous using standard thresholds. A multivariate analysis to determine the effect of all the covariates on the odds of developing PHPT has been performed via a generalized linear model with a logit link. A stepwise procedure to retain only the variables that had a significant influence on the model using Akaike Information Criterion has been carried out. Interaction effects of the covariates with GS have been considered in the model. All analyses have been performed using statistical package R 3.02. Test statistics with a *p*-value <0.05 have been considered significant.

Table 1 Demographic, prostate-related parameters and prevalence of skeletal metastases in prostate cancer patients and non-prostatic cancer population

	Patients with prostate cancer ($n=69$)	Patients with cancer ($n=53$)
Age (years)	70.6 ± 7.7	68.7 ± 8.8
Body Mass Index (kg/m^2)	26.8 ± 3.55	26.1 ± 3.2
Total PSA (ng/ml)	17.1 ± 50.5	1.4 ± 0.8[a]
Free PSA (ng/ml)	1.7 ± 3.7	0.3 ± 0.2[b]
Free/Total PSA ratio	0.20 ± 0.16	0.27 ± 0,12[b]
Gleason score low grade (*n*)	29	
Gleason score 3 + 4 or 4 + 3 (*n*)	20	
Gleason score high grade (*n*)	20	
Radical prostatectomy (*n*)	21	
Hormonal therapy (*n*)	30	
Radiotherapy (*n*)	16	
Skeletal metastases (*n*)	12	15

Note: Values are expressed as mean ± SD, where indicated
[a] $p<0.05$; [b] $p<0.01$ vs. prostatic cancer patients

Results

Table 1 shows main demographic parameters of the two populations studied. Group B included patients with neoplasia of urinary tract (18 patients), lung (16), gastrointestinal tract (13), oropharynx (3 patients) and of various origin (3). Gleason score values and treatments administered to prostatic cancer patients are also reported. Thirty-one patients of group A were studied while taking no treatment; some of those treated were receiving two or three therapies. Hormonal therapy was represented by luteinizing hormone-releasing hormone analogs, administered according to standard recommendations. An almost similar proportion of cancer patients (20 out of 53) was not receiving any therapy at the time of investigation. The number of patients with skeletal metastases was not significantly different between the two groups.

Biochemical parameters in patients of the two groups are reported in Table 2. In the prostatic cancer group, a seventy-seven-old patient had extremely high values of C-terminal FGF23 (1400 RU/ml); in addition, he had low values of $TmPO_4$ together with very high values of bALP (122 µg/ml), suggesting the diagnosis of oncogenic osteomalacia. We found nine patients with PHPT in the group of prostate cancer vs. only one in cancer patients group ($p<0.026$ by Barnard test). The diagnosis of PHPT was based on confirmed elevated serum ionized calcium with elevated or unsuppressed serum PTH levels [13]. Two patients in group A and three patients in group B, were characterized by elevated serum Ca^{++} together with suppressed serum PTH values. Defining vitamin D insufficiency at a threshold

Table 2 Biochemical parameters of mineral metabolism in prostate cancer patients and non-prostatic cancer population

	Patients with prostate cancer ($n = 69$)	PATIENTS with cancer ($n = 53$)
s. ionized Ca (mmol/l)	1.29 ± 0.11	1.28 ± 0.14
s. P (mg/dl)	3.3 ± 0.6	3.4 ± 0.6
s. Cr (mg/dl)	1.09 ± 0.35	1.12 ± 0.67
s. bone ALP (μg/ml)	14.6 ± 15.4	18.0 ± 20.0
s. CTX (ng/ml)	0.57 ± 0.44	0.77 ± 0.48[a]
s. 25(OH)D (ng/ml)	20.2 ± 10.5	13.4 ± 7.9[b]
s. PTH (pg/ml)	47.7 ± 54.6	40.4 ± 25.7
s. $1,25(OH)_2D$ (pg/ml)	36.95 ± 14.11	41.43 ± 17.07
s. C-terminal FGF23 (RU/ml)	58.9 ± 166.7	63.0 ± 93.2
Estimated Cr. Clearance (ml/min)	73.3 ± 20.9	79.4 ± 36.2
$TmPO_4$/ GFR (mg/dl)	3.3 ± 0.7	3.1 ± 0.7

s. serum, *Ca* calcium, *P* phosphorus, *Cr* creatinine, *ALP* Alkaline phosphatase, *CTX* C-terminal crosslinking telopeptides of type I collagen, $TmPO_4$ tubular maximum rate of PO_4 reabsorption

Note: Values are expressed as mean ± SD, where indicated.

[a] $p < 0.05$; [b] $p < 0.01$ vs. prostatic cancer patients

of 30 ng/ml [14], we found a statistically significant ($p < 0.001$) higher prevalence in cancer patients (51 out of 52) vs. prostatic cancer patients (45 out of 69).

Concerning markers of skeletal turnover, bone alkaline phosphatase values were elevated in 12 patients with prostate cancer and in 15 patients of group B; levels C-terminal crosslinking telopeptides of type I collagen were raised in 16 and 23 patients, respectively.

We then stratified the population on the basis of Gleason score [≤ 7 (3 + 4) and ≥ 7(4 + 3)], PSA (< 4,0 ng/ml, between 4,0 and 10,0 and > 10,0) and HT (yes or no). Using a generalized linear model with a logit link to predict the probability of developing PHPT, only GS, C-terminal FGF23 and HT had a significant effect ($p < 0.05$). Controlling for other covariates, a rise in FGF23 increases the odds of developing PHPT by 2% (p-value = 0.017), while patients with higher values of GS have a much greater probability of developing PHPT (log-odds = 3.6, $p < 0.01$). The probability decreases with higher values of Gleason score while on hormonal therapy; a further decreases was observed in patients on hormonal treatment and lower values of GS. Finally, lower grade of Gleason score without hormonal therapy have a significant protective factor ($p < 0.01$) decreasing the odds of developing PHPT by 8%. In this last analysis, the patient with oncogenic osteomalacia was excluded, owing to the extremely high values of FGF23 (Fig. 1).

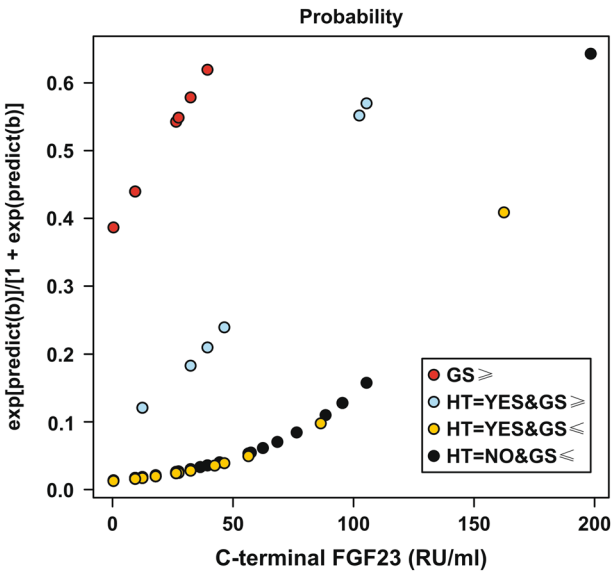

Fig. 1 Probability of developing primary hyperparathyroidism as a function of circulating fibroblast growth factor 23, taking into consideration values of Gleason score [≤ 7 (3 + 4) and ≥ 7(4 + 3)] and hormonal therapy

Discussion

In this study, we demonstrated that patients with prostate cancer are characterized by protean derangements of mineral metabolism. To the best of our knowledge, for the first time we showed that prostatic cancer patients have a high prevalence of coexistent primary hyperparathyroidism. This is not due to the fact that both diseases tend to be more prevalent with advancing age, since in an age-matched population of patients with cancers of various origin, the number of patients with PHPT was significantly lower. In addition, PHPT is more prevalent in postmenopausal females [15] thus reinforcing our findings in a male population.

Another important observation was the high prevalence of vitamin D insufficiency found in both populations, even though almost all patients in group B had calcidiol levels lower than 30 ng/ml. This finding can be explained by limited outdoor activities, especially in more fragile cancer population. Low levels of vitamin D should be corrected to reach sufficiency, since compensatory secondary hyperpathyroidism increases bone turnover thus favoring seeding of cancer cells [16]. Indeed, Schwartz demonstrated that suppression of PTH in advanced prostate cancer may reduce morbidity and mortality [17]. In this context, it is important to remember that some [18] but not all [19] authorities report a beneficial effect of vitamin D on prostate cancer prevention and treatment.

Recently, FGF23 has been an issue of intensive investigation. Besides its critical role in phosphate homeostasis [20], a number of in vitro studies have shown its role in prostate cancer tumorigenesis. For example, Feng and coworkers showed that FGF23 can act as an autocrine, paracrine and/or endocrine growth factor thus promoting prostate cancer progression [21]. Furthermore, Kim and associates showed that genetic variations in FGF23 are linked to prostate cancer risk [22]. We found one prostatic cancer patient with extremely high values of FGF23, who had massive skeletal involvement and low threshold of phosphate tubular reabsorption, despite marked hypophosphatemia. This biochemical constellation defines the clinical picture of oncogenic osteomalacia, which has been previously occasionally described in prostatic cancer patients [4, 5]. We cannot draw any definitive conclusion about prevalence of this syndrome in prostatic neoplasia, due to the relatively limited number of patients studied; however, in prostatic cancer patients with reduced tubular phosphate reabsorption in the presence of hypophosphatemia, this possibility should be kept in mind.

Given the significant increased prevalence of primary hyperpathyroidism in patients with prostatic cancer, when compared with a population of non prostatic cancer patients, we investigated potential predictive factors of developing this endocrine disorder. We found that a rise in FGF23 values increases the probability of developing PHPT and that patients with higher values of GS have a much greater probability of developing this glandular disorder. The probability decreases with higher values of Gleason score while on hormonal therapy and a further decrease was observed in patients on hormonal treatment and lower values of GS. Finally, lower grade of Gleason score without hormonal therapy have a significant protective factor. We hypothesize that in patients with higher disease activity (as documented by higher values of Gleason score and greater skeletal involvement) there is a trend towards reduced serum calcium values owing to a greater influx of calcium in bone driven by metastases of osteoblastic type. Hypocalcemia, in addition exacerbated by vitamin D deficiency, stimulates PTH secretion, followed by a compensatory increase of FGF23 secretion, both systemically but more importantly locally, i.e., at the level of prostatic cancer cells. This last further causes a progression of the disease, thus creating a vicious circle. Paradoxically, hormonal therapy may have a protective effect at the various stages of disease, due to its negative effects on skeletal balance thus promoting efflux of calcium from bone [23]. Interestingly, these concepts have been partly postulated by Emmenegger and co-workers [24].

Conclusion

This is the first study in which patients with prostatic cancer have been extensively studied as far as mineral metabolism abnormalities are concerned. Most importantly a comparison with cancer patients of various origin has been simultaneously performed. We demonstrated that patients with prostate cancer constitute a heterogeneous population; therefore, they should be individually investigated since are characterized by various derangements of mineral metabolism. In particular, we showed a remarkable prevalence of PHPT in men with prostate cancer. The determination of FGF23, should be considered a useful biochemical tool in the evaluation of these patients owing to its predictive value and local autocrine regulation of the tumor progression. However, we should also be aware of the limitations of our investigation mainly deriving from its cross-sectional nature. Longitudinal studies should better clarify the causative relationship between FGF23 and primary hyperparathyroidism.

Funding This work was supported by public fund ("Sapienza" Rome University, Bando Ricerca Scientifica, 2015).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. World Cancer Research Fund International (2016), http://www.wcrf.org. Accessed 26 Dec 2016

2. R.C. Pelger, A.N.G.A. Lycklama, S.E. Papapoulos, N.A. Hamdy, Severe hypophosphatemic osteomalacia in hormone-refractory prostate cancer metastatic to the skeleton: natural history and pitfalls in management. Bone **36**(1), 1–5 (2005). doi:10.1016/j.bone.2004.09.017
3. S. Minisola, G. Perugia, A. Scarda, L. Scarnecchia, D. Tuzzolo, W. Rossi, G. Mazzuoli, Biochemical picture accompanying sclerotic bone metastases of prostatic origin. Br. J. Urol. **60**(5), 443–446 (1987)
4. C.L. Cotant, P.S. Rao, Elevated fibroblast growth factor 23 in a patient with metastatic prostate cancer and hypophosphatemia. Am. J. Kidney Dis. **50**(6), 1033–1036 (2007). doi:10.1053/j.ajkd.2007.07.031
5. M.P. Mak, V.T. da Costa e Silva, R.M. Martin, A.M. Lerario, L. Yu, P.M. Hoff, G. de Castro Jr., Advanced prostate cancer as a cause of oncogenic osteomalacia: an underdiagnosed condition. Supp. Care Cancer **20**(9), 2195–2197 (2012). doi:10.1007/s00520-012-1474-z
6. M.C. Hu, K. Shiizaki, M. Kuro-o, O.W. Moe, Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu. Rev. Physiol. **75**, 503–533 (2013). doi:10.1146/annurev-physiol-030212-183727
7. V. Carnevale, F. Dicembrino, V. Frusciante, I. Chiodini, S. Minisola, A. Scillitani, Different patterns of global and regional skeletal uptake of 99mTc-methylene diphosphonate with age: relevance to the pathogenesis of bone loss. J. Nucl. Med. **41**(9), 1478–1483 (2000)
8. P.M. Pierorazio, P.C. Walsh, A.W. Partin, J.I. Epstein, Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. **111**(5), 753–760 (2013). doi:10.1111/j.1464-410X.2012.11611.x
9. D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine. Nephron **16**(1), 31–41 (1976)
10. R.J. Walton, O.L. Bijvoet, Nomogram for derivation of renal threshold phosphate concentration. Lancet **2**(7929), 309–310 (1975)
11. C. Cipriani, E. Romagnoli, A. Scillitani, I. Chiodini, R. Clerico, V. Carnevale, M.L. Mascia, C. Battista, R. Viti, M. Pileri, C. Eller-Vainicher, S. Minisola, Effect of a single oral dose of 600,000 IU of cholecalciferol on serum calciotropic hormones in young subjects with vitamin D deficiency: a prospective intervention study. J. Clin. Endocrinol. Metab. **95**(10), 4771–4777 (2010). doi:10.1210/jc.2010-0502
12. G.A. Barnard, Significance tests for 2 X 2 tables. Biometrika **34** (1–2), 123–138 (1947)
13. S. Minisola, J. Pepe, S. Piemonte, C. Cipriani, The diagnosis and management of hypercalcaemia. BMJ **350**, h2723 (2015). doi:10.1136/bmj.h2723
14. E. Romagnoli, J. Pepe, S. Piemonte, C. Cipriani, S. Minisola, Management of endocrine disease: value and limitations of assessing vitamin D nutritional status and advised levels of vitamin D supplementation. Eur. J. Endocrinol. **169**(4), R59–69 (2013). doi:10.1530/EJE-13-0435
15. S. Minisola, J. Pepe, A. Scillitani, C. Cipriani, Explaining geographical variation in the presentation of primary hyperparathyroidism. Lancet Diabetes Endocrinol. **4**(8), 641–643 (2016). doi:10.1016/S2213-8587(16)00076-0
16. D. Santini, F. Pantano, B. Vincenzi, G. Tonini, F. Bertoldo, The role of bone microenvironment, vitamin D and calcium. Recent Results Cancer Res. **192**, 33–64 (2012). doi:10.1007/978-3-642-21892-7_2
17. G.G. Schwartz, Prostate cancer, serum parathyroid hormone, and the progression of skeletal metastases. Cancer Epidemiol. Prevention Biomarkers **17**(3), 478–483 (2008). doi:10.1158/1055-9965.EPI-07-2747
18. I.M. Shui, L.A. Mucci, P. Kraft, R.M. Tamimi, S. Lindstrom, K.L. Penney, K. Nimptsch, B.W. Hollis, N. Dupre, E.A. Platz, M.J. Stampfer, E. Giovannucci, Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: a prospective nested case-control study. J. Natl Cancer Inst. **104**(9), 690–699 (2012). doi:10.1093/jnci/djs189
19. I.M. Shui, A.M. Mondul, S. Lindstrom, K.K. Tsilidis, R.C. Travis, T. Gerke, D. Albanes, L.A. Mucci, E. Giovannucci, P. Kraft, Breast, prostate cancer cohort consortium, G.: circulating vitamin D, vitamin D-related genetic variation, and risk of fatal prostate cancer in the national cancer institute breast and prostate cancer cohort consortium. Cancer **121**(12), 1949–1956 (2015). doi:10.1002/cncr.29320
20. A. Bian, C. Xing, M.C. Hu, Alpha Klotho and phosphate homeostasis. J. Endocrinol. Invest. **37**(11), 1121–1126 (2014). doi:10.1007/s40618-014-0158-6
21. S. Feng, J. Wang, Y. Zhang, C.J. Creighton, M. Ittmann, FGF23 promotes prostate cancer progression. Oncotarget **6**(19), 17291–17301 (2015). doi:10.18632/oncotarget.4174
22. H.J. Kim, K.H. Kim, J. Lee, J.J. Oh, H.S. Cheong, E.L. Wong, B. S. Yang, S.S. Byun, S.C. Myung, Single nucleotide polymorphisms in fibroblast growth factor 23 gene, FGF23, are associated with prostate cancer risk. BJU Int. **114**(2), 303–310 (2014). doi:10.1111/bju.12396
23. V.B. Shahinian, Y.F. Kuo, J.L. Freeman, J.S. Goodwin, Risk of fracture after androgen deprivation for prostate cancer. N. Engl. J. Med. **352**(2), 154–164 (2005). doi:10.1056/NEJMoa041943
24. E.K. Lee, M.C. Martinez, K. Blakely, K.D. Santos, V.C. Hoang, A. Chow, U. Emmenegger, FGF23: mediator of poor prognosis in a sizeable subgroup of patients with castration-resistant prostate cancer presenting with severe hypophosphatemia? Med. Hypotheses **83**(4), 482–487 (2014). doi:10.1016/j.mehy.2014.08.005