



Study of Parathyroid hormone, Cortisol and Calcium in the Serum of Non- metastatic Prostate Cancer Patients Cohorts in Iraq

Jaleel Ibrahim Asaad

*Biotechnology Research Center, Al-Nahrin University, Baghdad, Iraq

Abstract : The causes of prostate cancer (PCa) are not well understood (1). There is an endogenous and exogenous factor that affects PCa incidence (2). Calcium (Ca) regarded as endogenous factor and it has been shown to be principle for increasing proliferation cell of the prostate (3). Parathyroid hormone (PTH) functions to increase calcium uptake in the elementary tract and to mobilize calcium from bone. Parathyroid hormone PTH is now understood to have mitogenic effects for prostate cancer cells (4). Cortisol is the active form of glucocorticoids, produced and secreted by the adrenal cortex (5). Results has showed there is no significant difference ($p > 0.05$) in calcium level between PCa patients and control respectively (8.89 ± 1.50 , 9.24 ± 0.34 mg/dl) and cortisol level in PCa patients with control respectively (325.08 ± 12.3 , 319.33 ± 15.1 nm/l). There is no significant differences ($p > 0.05$) in PTH level between PCa patients than control group respectively (56.62 ± 11.54 , 56.15 ± 10.12 pg /ml) Conclusion /these finding may be important to get new promising treatment or new biomarker for PCa. More studies should be achieved in Iraq.

Keywords; Prostate, cancer, PTH, Calcium, Cortisol.

Introduction

Prostate cancer (PCa) ranks the 10th among leading cancers in male in Iraqi (Iraqi Tumor Registry, 2009). There is 473 new cases which constitute 2.78 per/ 10^5 in 2011⁶, and it is the second leading death from cancer in USA⁷.

Many exogenous and endogenous factors affect prostate cancer incidence². Calcium (Ca) can activate or inhibit cellular signaling to get response like muscle contraction, synaptic transmission, cellular proliferation and apoptosis⁸. A high intake of calcium is considered to be cause of prostate cancer⁹. Prevention the entrance of the excess calcium flow in to cancer cells due to stimulation of mitochondria and cytoplasmic pathways stopped proapoptotic steps and made the cell immortal¹⁰. The calcium-sensing receptor (CaSR) plays a central role in calcium homeostasis and regulating parathyroid hormone (PTH) secretion and renal calcium excretion to normalize Ca¹¹. Parathyroid glands are four small glands located on the posterior side of the thyroid and regulate calcium serum (Tfelt-Hansen et al., 2003). Parathyroid hormone (PTH) implicated in bony metastases with (CaSR) by modulation of parathyroid hormone related peptide (PTHrP) secretion from cancer cells¹¹. Cancer-induced hypercalcemia (CIH) occurs in Lung cancer, breast cancer and myeloma while rarely occurs in patients with colorectal and prostate cancer¹². Hypocalcemia of severe degree is not common in patients with malignant disease¹³. There is inverse relationship between secondary PTH elevation and calcium level⁴. Elevated serum PTH in men associated with advanced prostate cancer¹⁴. Cortisol produced in humans from adrenal gland cortex by the zonafasciculata. Cortisol regulates many biological processes including metabolism, behavior,

growth and cellular apoptosis via glucocorticoid receptor GR activation⁵. Cortisol has mixed glucocorticoid and mineralocorticoid effects¹⁵. Cortisol affects mutant androgen receptors AR and made it responsive to low level of cortisone which converted to cortisol by 11 β -Hydroxysteroid dehydrogenase (11 β -HSD) type I, which would then drive the growth of prostate cancer that related with obesity cancer¹⁶. Studies on experimental animals have shown that corticosteroids could stimulate tumor growth and increased metastasis of pulmonary and mammary tumors¹³. Obese subjects have high level of serum cortisol as a result of increased rate of the synthesis due to systemic stress induced by obesity that lead to abnormal production of adipokines from adipose tissue and high level of tumor necrotic factor-alpha (TNF- α) in turn may activate tumor progression¹⁴.

Material and methods

Blood samples were collected from ten (10) prostate cancer patients from AL-AMAL general hospital in Iraq/Baghdad and ten (10) healthy subjects, age matched. Blood samples were centrifuged (2000 rpm for 10 minutes), the serum immediately stored in -20 C° until analysis. Serum calcium, parathyroid hormone and cortisol hormone measured by Cobas e 411 (GERMANY) using (ROSCHE) kits for detection according to the manufacturer's instructions.

Statistical analysis

SPSS 20.0 programs used for least significant difference (LSD ≤ 0.05). Analysis of variance test (ANOVA) between sites and different studies parameters.

Results

There is slight reduction but not significant ($p > 0.05$) between serum calcium level of prostate cancer patients than healthy group respectively (8.89 ± 1.50 , 9.24 ± 0.34 mg/dl), (Table- 1).

There is slight elevation but not significant ($p > 0.05$) in serum cortisol level of prostate cancer patients than healthy group (325.08 ± 12.3 , 319.33 ± 15.1 nm/l) respectively. (Table- 1)

Table -1: levels of calcium, cortisol and parathyroid hormone in prostate cancer patients and control (Mean \pm SD)

Test	Prostate cancer	Control
serum calcium mg/dl	8.89 ± 1.50	9.24 ± 0.34
cortisol hormone nm/l	325.08 ± 12.3	319.33 ± 15.1
parathyroid hormone pg/ml	56.62 ± 11.54	56.15 ± 10.12

There is no significant difference reduction in serum parathyroid hormone level of prostate cancer patients compare to healthy group (56.62 ± 11.54 , 56.15 ± 10.12 pg/ml) respectively, ($p > 0.05$) (Table- 1).

Discussion

Although many experimental and clinical studies enrolled calcium and parathyroid hormone (PTH) in the development of prostate cancer, the epidemiologic data are sparse.

Calcium (Ca) homeostasis controls many cellular processes mediated signaling pathways including tumorigenesis (angiogenesis, tumors progression, invasion and metastasis) (8). Hypocalcaemia occur when total calcium level lower than (8.5 mg/dl)¹⁵. This study found a slight reduction in the serum level of Calcium in the prostate cancer (PCa) patients, and this finding may be related to the low serum albumin level that bound calcium¹⁵. And/or low level of vitamin D (Vit D) in the serum of prostate cancer (PCa) patients decrease the serum calcium level¹⁶.

In a prospective study in Sweden, no significant association between serum calcium and fatal prostate cancer was found. Although a significant positive association was found between albumin-adjusted serum

calcium and the risk of “aggressive prostate cancers”), Authors gave a conclusion of a time-dependent association between serum calcium and the risk of fatal prostate cancer¹⁷. As well bone metastases from prostate cancer are mainly blastic (bone-forming) and commonly cause increased serum levels of PTH, and subsequently hypocalcemia (calcium ions are transferred from serum into blasticbone⁴.

Cortisol considered as glucocorticoids family and its receptors (GR) closely related with androgen receptors (AR) and may have to substitute its action in case of castrated resistance prostate cancer (CRPC). Cortisol and (GR) has tumor suppresser action but less than production of androgen¹⁵. Ectopic adrenocorticotrophic hormone (ACTH) and/or corticotropin-releasing hormone (CRH) are associated with a growing list of tumors. (16). High level of cortisol in CRPC is worst prognosis (Scher et al., 2012). This study demonstrated that rising of cortisol level in PCa patients in early stages was not significantly palpable. Resistance exercise does not appear to compromise testosterone suppression, and acute elevations in serum GH and DHEA may partly underlie improvements observed in physical function. A study by Galvão <http://www.nature.com/pcan/journal/v11/n2/full/4500991a.html> - aff1 *et al*, the effect of 20 weeks resistance training on a range of serum hormones, in prostate cancer patients, revealed an increase in dehydroepiandrosterone (DHEA), following acute exercise (P<0.05)(18). Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTH-rP) has important role in osteoblastic bone disease that affects patients with prostate and urinary tract cancer¹³. The clinical significance of secondary hyperparathyroidism in prostate cancer has not been widely studied. PTH has role in regulating serum calcium, and it promotes the proliferation and migration of prostate cancer cells *in vitro* and *in vivo*¹⁹. PTH-rP related protein is an autocrine growth factor made by prostate and other cancer cells, which aids in their progression in bone²⁰. PTH-related protein (PTHrP) was originally identified as the peptide responsible for humoral hypercalcemia of malignancy²¹. PTHrP and PTH bind to the same receptor (PTH/PTHrP receptor) that is expressed in cancer cells²². Secondary hyperparathyroidism frequently occur in metastatic prostate cancer patients and enhanced by vitamin D deficiency, which is common in elderly males²³.

Iddonet *al.*, and Pérez-Martínez *et al.* reported significantly higher PTH-rp expression in high-grade versus low-grade prostate cancers. Suggesting that an increased sensitivity of prostate cancers to PTH may contribute to bone metastasis^{24,25}.

This study show there is no detectable elevation in (PTH) in PCa patients for two reasons, the first; all the patients are newly diagnosed with prostate cancer and have no metastasis, and the second; most middle east population (patients and control) suffer from vitamin D insufficiency and this may affect the result^{26,27}.

Skinner & Schwartz <http://cebp.aacrjournals.org/content/18/11/2869.full> - aff-1 found that serum PTH and calcium were correlated significantly with free PSA. Their findings support the hypothesis that both variables (serum calcium and PTH) stimulate prostate growth in men.

Abbreviation

Calcium -sensing receptor /CaSR , parathyroid hormone related peptide/ PTHrP Prostate cancer /PCa, parathyroid hormone /PTH, Cancer-induced hypercalcemia /CIH Glucocorticoid receptor /GR, 11b-Hydroxysteroid dehydrogenase/ (11b-HSD), castrated resistance prostate cancer (CRPC), androgen receptor (AR)

References

1. Patel, AV.; Cheng, J.; Canzian, F.; Le Marchand, L.; Thun, MJ.; Berg, CD.; Buring, J.; Calle, EE.; Chanock, S.; Clavel-Chapelon, F.; Cox, DG.; Dorransoro, M.; Dossus, L.; Haiman, CA.; Hankinson, SE.; Henderson, BE.; Hoover, R.; Hunter, DJ.; Kaaks, R.; Kolonel, LN.; Kraft, P.; Linseisen, J.; Lund, E.; Manjer, J.; McCarty, C.; Peeters, PH.; Pike, MC.; Pollak, M.; Riboli, E.; Stram, DO.; Tjonneland, A.; Travis, R.C.; Trichopoulos, D.; Tumino, R.; Yeager, M.; Ziegler, RG and Feigelson, HS (2008) IGF-1, IGFBP-1, and IGFBP-3 polymorphisms predict circulating IGF levels but not breast cancer risk: findings from the Breast and Prostate Cancer Cohort Consortium (BPC3). *PLoS One* 3(7): e2578
2. Greenwald, P (2005) *Lifestyle and Medical Approaches to Cancer Prevention*. RRCR 166:1-15 Springer-Verlag

3. Sun ,Y.; Selvaraj ,S.; Varma ,A.; Derry .S.; Sahnoun ,A and Singh, B. (2013) Increase in Serum Ca²/Mg² Ratio Promotes Proliferation of Prostate Cancer Cells by Activating TRPM7 Channels. *the journal of biological chemistry*, 288(1) : 255–263
4. Schwartz ,G (2008).Prostate Cancer, Serum Parathyroid Hormone, and the Progression of Skeletal Metastases. *Cancer Epidemiol Biomarkers Prev* ,17(3): 478-483.
5. Volden ,P and Conzen ,S (2013) The influence of glucocorticoid signaling on tumor progression. *Brain, Behavior, and Immunity* ,30 : 26–31.
6. Iraq cancer registry (2011) .Iraq cancer board .minister of health, Iraq.
7. Lee, A and Dong, X (2015).Driver or passenger - roles of the glucocorticoid receptor in castration resistance prostate cancers. *Receptors & Clinical Investigation* . 2: e431. doi: 10.14800/rci.431.
8. Monteith , G.; McAndrew ,D.; Faddy, H and Thomson ,S (2007) Calcium and cancer:targeting Ca²⁺ transport. *Nature reviews | cancer*, 7:519-530|
9. Daniyal ,M.; Siddiqui ,Z.; Akram ,M.; Asif, HM .;Sultana Sabira and Khan A (2014) Epidemiology, Etiology, Diagnosis and Treatment of Prostate Cancer. *Asian pacific Journal of Cancer Prevention*, 15 (22): 9575-9578
10. Dubois ,C.; Abeeel ,F and Prevarskaya ,N(2012)Targeting apoptosis by the remodelling of calcium-transporting proteins in cancerogenesis. *FEBS Journal*, (280) : 5500–5510
11. Feng ,J.; Xu, X.; Li, B.; Brown, E.; Farris ,A.; Sun, S-Y and Yang ,J (2014) Prostate cancer metastatic to bone has higher expression of the calcium-sensing receptor (CaSR) than primary prostate cancer. *Receptors & Clinical Investigation* , 1: e270.
12. Lumachi ,F.; Brunello , A.; Roma ,A and Basso, U (2009) Cancer-induced Hypercalcemia. *Anticancer research*, 29: 1551-1556
13. Rasmuson ,T.; Ljungberg, Bo.; Grankvis, K.; Jacobsen, J and Olsson, T (2001) Increased Serum Cortisol Levels are Associated with High Tumor Grade in Patients with Renal Cell Carcinoma. *ActaOncologica* , 40(1): 83- 87.
14. Tandon, PK and Rivvi, AA(2005) Hypocalcemia and parathyroid function in metastatic prostate cancer. *EndocrPract* ,11:254 –258.
15. Montgomery, B.; Cheng ,H.; Drechsler ,J and Mostaghel,E (2014) Glucocorticoids and prostate cancer treatment: friend or foe?. *Asian Journal of Andrology* , 16: 354–358
16. Huss ,L.; Butt ,S.; Almquist ,S.; Malm ,J and Manjer ,J (2014). Serum levels of vitamin D, parathyroid hormone and calcium in relation to survival following breast cancer. *Cancer Causes Control*, 25:1131–1140
17. Hemelrijck ,V.; Hermans, R.; Michaelsson,K, Melvin, J.; GarmoH and Hammar, N, (2012)Serum calcium and incident and fatal prostate cancer in the Swedish AMORIS study. *Cancer Causes and Control*,23:1349–58.
18. Galvão, D A.; Nosaka ,K.; Taaffe ,D R .; Peake, J.; Spry, N.; Suzuk, K.; Yamaya,<http://www.nature.com/pcan/journal/v11/n2/full/4500991a.html> - aff7 K.; McGuigan, M.; Kristjanson,<http://www.nature.com/pcan/journal/v11/n2/full/4500991a.html> - aff8 L J and Newton ,RU(2008) Endocrine and immune responses to resistance training in prostate cancer patients. *Prostate Cancer and Prostatic Diseases*, 11:160–165.
19. Jemal, A.; Siegel, R.; Ward, E.; Murray, T.; Xu, J and Thun, MJ(2007)Cancer statistics, *Cancer J Clin*,57:43–66.
20. Deftos, L.; Barken, I.; Burton, DW.; Hoffman ,RM and Geller, J(2005) Direct evidence that PTHrP expression promotes prostate cancer progression in bone. *BiochemBiophy Res Commun* ,327:468–72
21. Asadi ,F and Kukreja ,S(2005) Parathyroid hormone-related protein in prostate cancer. *Crit Rev Eukaryot Gene Expr* ,15:15–28.
22. Berruti ,A.; Cook ,R.; Saad ,F.; Buttigliero ,C.; Lipton ,A.; Tampellini ,M.; Lee, K.; Coleman ,R and Smith ,M (2012) Prognostic Role of Serum Parathyroid Hormone Levels in AdvancedProstate Cancer Patients Undergoing Zoledronic Acid Administration. *The Oncologist* ,17:645–652
23. Mosekilde, L (2005)Vitamin D and the elderly. *ClinEndocrinol(Oxf)* ,62:265–281
24. Iddon, J.; Bundred, NJ and Hoyland,J(2009) Expression of PTH-r Pr and its receptor in bone metastases from PCa. *J Pathol*,91:170–4) .
25. Pérez-Martínez,FC.;Alonso, V and Sarasa, JL(2007)Immunohistochemical analysis of low-grade and high-grade PCa. *J ClinPathol*,60:290–4.

26. Skinner, H.G and Schwartz<http://cebp.aacrjournals.org/content/18/11/2869.full> - aff-1 G. (2009) The Relation of Serum Parathyroid Hormone and Serum Calcium to Serum Levels of Prostate-Specific Antigen: A Population-Based Study. *Cancer Epidemiol Biomarkers Prev*, 18(11):2869–73
27. Pettifor JM (2004) Nutritional rickets: deficiency of vitamin D, calcium, or both? *Am J Clin Nutr* 80:1725-1729.
