Cancer Investigation, 18(7), 664–669 (2000)

SPECIAL ARTICLES

A Medical Hypothesis: Phosphorus Balance and Prostate Cancer

Suman Kapur, Ph.D.

Director, Arogyadham
Deendayal Research Institute
New Delhi, India

ABSTRACT

Over the last three decades the mortality rate for prostatic carcinoma has steadily increased. Carcinoma of prostate (CaP), the most common malignancy in men, is also the second most common cause of cancer deaths in men. However, few epidemiologic studies have been done, and there are scant clues to the etiology/pathogenesis of CaP. As treatment failures for advanced carcinoma continue to frustrate clinicians, more emphasis has recently been focused on strategies to prevent invasive CaP. Prostatic hyperplasia is a universal phenomenon in aging men. Mechanism and signals causing this growth are not understood. Thus, prostatic diseases affect men over the age of 45 and increase in frequency with age so that by the eighth decade more than 90% of men have benign prostatic hyperplasia, of which some progress to CaP. Data from several studies support that higher levels of active metabolite of vitamin D, 1,25-$(OH)_2$-D, reduce the risk of prostatic hyperplasia and CaP. Men with high serum levels of 1,25-$(OH)_2$-D have a reduced risk of poorly differentiated and clinically advanced CaP. Receptor for vitamin D has been reported in both normal and cancer prostate cells. 1,25-$(OH)_2$-D inhibits proliferation and induces differentiation of normal and neoplastic cells. Hypercalcemic activity of 1,25-$(OH)_2$-D or its analogues, however, thwart their use for therapy in humans. 1,25-$(OH)_2$-D also has an established role in phosphorus homeostasis. Low dietary intake of phosphorus leads to an increase in serum concentration of 1,25-$(OH)_2$-D. In addition, dietary fructose reduces plasma phosphate levels by 30 to 50% for more than 3 hr due to a rapid shift of phosphate from extracellular to intracellular compartment. Fruit intake has been shown to be associated with reduced risk of CaP, particularly the advanced type. Put together, these observations support that dietary determinants of hypophosphatemia, leading to increased plasma levels of 1,25-$(OH)_2$-D, could reduce the risk of aging men to develop prostatic diseases, both benign prostatic hyperplasia and CaP.

PROSTATE CANCER: THE GLOBAL SCENARIO

Over the last three decades, despite aggressive efforts toward earlier detection and treatment, the mortality rate for prostatic carcinoma has steadily increased (1). Cancer of the prostate (CaP), the most common malignancy in men (1), is, after carcinoma of lung, the second most common cause of cancer death in men older than age 55. In the United States alone, over 100,000 new cases of CaP are diagnosed annually. Until recently, however, very few epidemiologic studies have been conducted, and there are scant clues as to the etiology and pathogenesis of CaP. There are striking differences in prostate cancer incidence rates among racial and ethnic groups, with African-American men displaying the highest incidence of prostate cancer in the world, whereas Japanese and Chinese men have the lowest rates (1). The identification of androgens as the major regulator of prostatic epithelial proliferation, both in normal prostate and in prostatic carcinoma, was originally hoped to offer a target for therapeutic intervention of advanced tumors (2–4). However, in practice, the concept of "total androgen ablation" therapy has found only limited success (3–5). As treatment failures for advanced carcinoma continue to frustrate clinicians, emphasis has recently been focused on possible strategies to prevent invasive prostatic carcinoma (6–8).

PROSTATIC HYPERPLASIA

Development of prostatic hyperplasia is a universal phenomenon in aging men. Prostate, which is the largest male accessory gland, weighs only a few grams at birth. At puberty it undergoes androgen-mediated growth and reaches the adult size of about 20 g by the age of 20. It remains stable in size for about 25 years, and during the fifth decade a second growth spurt is seen in most men. Regulating signals and mechanisms for this growth are not very well understood. Consequently, the disease affects men over the age of 45 and increases in frequency with age so that by the eighth decade more than 90% of men have benign prostatic hyperplasia (BPH), of whom some progress to CaP. The disorder is a major cause of morbidity in elderly men. The prostate surrounds the urethra, and any enlargement is a potential cause of urinary tract obstruction. Overall, about 10% of men at some stage or the other require prostatic surgery to relieve urinary tract constriction.

DIETARY PHOSPHORUS AND CIRCULATING 1,25-DIHYDROXY VITAMIN D_3

Close endocrine regulation of absorption and excretion of phosphorus maintains steady-state plasma phosphorus levels. Hence, intestine and kidney are the two major organs that determine the external balance and plasma concentration of phosphorus. Intestinal absorption of phosphorus occasionally floods the extracellular fluids, but kidneys maintain homeostasis by excreting the precise amount absorbed in excess of the body's need. The reabsorption of phosphorus in the renal tubules is controlled by a multitude of hormonal, metabolic, and dietary factors. Of these, parathyroid hormone (PTH) and dietary intake of phosphate are the major determinants of renal tubular phosphate reabsorption. Normally, 85–90% of filtered phosphate is reabsorbed in the kidneys. Several different factors are known to affect the tubular phosphate transport (9).

1,25-$(OH)_2$D, the active form of vitamin D, has a well-established role in phosphorus homeostasis. Renal synthesis of 1,25-$(OH)_2$D, from its endogenous precursor, 25-hydroxy-vitamin D_3, is catalyzed by 25-hydroxy-vitamin D_3-1α-hydroxylase (1-hydroxylase) (10–13), an enzyme that can be stimulated by PTH (14–20) and suppressed by 1,25-$(OH)_2$D (16,18,19), normal vitamin D status (20), and dietary intake of phosphorus (21), possibly through an effect on its plasma concentration (18,22). Restriction of dietary phosphorus induces an increase in the serum concentration of 1,25-$(OH)_2$D in normal men and women (23–26) and children with moderate renal insufficiency (27). Conversely, in patients with idiopathic hypercalciuria (28) or primary hyperthyroidism (29), supplementation of phosphorus induces a decrease in serum concentration of 1,25-$(OH)_2$D from supernormal to normal levels. Portale et al. (30) demonstrated that in healthy men, reduction and increase in the oral intake of phosphorus can induce rapidly occurring, large, inverse, and persisting changes in the serum concentrations of 1,25-$(OH)_2$D by increasing the production rate of the same in the renal cortical tissue. Studies, both in chick and rat (21), have shown that dietary phosphorus restriction increase the activity of 1-hydroxylase in the renal cortical tissue.

VITAMIN D AND PROSTATE EPITHELIAL CELL PROLIFERATION

Several different cell types are known to possess the functional vitamin D receptor and are responsive to the

actions of 1,25-$(OH)_2$D (31). Epidemiologic data suggest that vitamin D may play a role in the progression of prostate cancer. Schwartz and Hulka (32) proposed that the recognized risk factors of age and race in combination with vitamin D deficiency disease caused by lack of ultraviolet exposure are related to prostate cancer mortality. Recent findings have supported this hypothesis and suggest that about 6% of mortality from prostate cancer in the United States could be related to ultraviolet exposure (33). In the United States, prostate cancer mortality rates exhibit a marked north-south gradient, with higher rates observed in the north (32,33). This gradient correlates well with ambient levels of ultraviolet radiation. Vitamin D has potent antitumor properties, and studies have suggested that vitamin D metabolites and analogues may be modifiers of the growth of various cancers (31,34–39). Data from several different in vitro animal, genetic, epidemiologic, and geographic studies support the view that higher levels of 1,25-$(OH)_2$D reduce the risk of prostatic hyperplasia and CaP. Recent studies have shown that typically higher levels of 1,25-$(OH)_2$D inhibit cellular proliferation and induce differentiation of both normal and neoplastic prostate cells in vitro (40–43). Moreover, limited in vivo studies in rodents also support antitumor potency of 1,25-$(OH)_2$D analogues against prostate cancer (39,44). Older men having high circulating 1,25-$(OH)_2$D have been shown to have a reduced risk of poorly differentiated and clinically advanced prostate cancer (45,46). The hypercalcemic activity of 1,25-$(OH)_2$D or its analogues, however, prevents their use as a therapeutic agent in humans.

1,25-$(OH)_2$D exerts its activities by binding the vitamin D receptor (31), which is a nuclear hormone receptor. Miller et al. (47) reported a ubiquitous presence of vitamin D receptor in seven different prostatic carcinoma cell lines. Peehl et al. (40) found that BPH epithelial cells and prostate tissue extracts also contain comparable receptors. Evidence for a role of 1,25-$(OH)_2$D also comes from the fact that genetic polymorphism of the vitamin D receptor gene, which may correlate with activity of the receptor, also predict the risk of prostate cancer (48–50). If circulating 1,25-$(OH)_2$D confers these benefits, adequate intake of vitamin D or its production in the skin through sunlight exposure should help prevent prostate cancer. As stated earlier, some geographic evidence does suggest that sunlight may be beneficial (32). However, ecologic, case control, and cohort studies consistently find higher intakes of dairy products, the major dietary source of vitamin D, associated with an enhanced risk of prostate cancer (51). This apparent paradox may be resolved by considering two aspects: 1,25-$(OH)_2$D may be more relevant than its precursor 25-(OH) D for biologic action and dairy products are also a major source of calcium, which lowers the levels of circulating 1,25-$(OH)_2$D. Activity of renal 1-hydroxylase is stimulated by low serum calcium levels (52,53), which would lead to increased formation of 1,25-$(OH)_2$D in the kidneys.

HYPOPHOSPHATEMIA AND PROSTATE CANCER: A HYPOTHESIS

Reduction in circulating phosphate increases 1,25-$(OH)_2$D serum levels appreciably (54,55). However, as phosphorus is generally abundant in most diets and is well absorbed intestinally, dietary-induced hypophosphatemia is rare. Thus, as such, dietary intake may not directly effect 1,25-$(OH)_2$D levels. At the same time it is noteworthy that dietary fructose reduces plasma phosphate levels by 30 to 50% for more than 3 hr due to the rapid shift of phosphate from the extracellular to the intracellular compartment (56,57). This hypophosphatemia occurs because fructose is very rapidly phosphorylated in the liver, catalyzed by the enzyme fructokinase (58), which bypasses the phosphofructokinase regulatory step in glycolysis (59).

In a study conducted jointly by a team of scientists in the United States and Sweden, fructose consumption (from both fruit and nonfruit sources) has in fact been shown to reduce the risk of prostate cancer, particularly the advanced disease. As already mentioned, another dimension to phosphorus homeostasis is related to dietary intake of calcium. The same study reports that both dietary and supplementary calcium is associated with higher risk of extraprostatic, metastatic, and fatal prostate cancer. Calcium is known to bind phosphorus, thereby reducing its bioavailability and leading to increase in circulating PTH levels. This in turn decreases circulating 1,25-$(OH)_2$D levels, which increases the risk of developing prostate related maladies, both BPH and CaP.

Put together, these studies provide indirect support for an influence of dietary determinants of serum 1,25-$(OH)_2$D levels on prostatic carcinogenesis. Given the morbidity and mortality caused by CaP worldwide, this hypothesis warrants further investigation.

DISTRIBUTION AND BALANCE OF BODY PHOSPHORUS

Phosphorus is an essential element of living matter. It is found in every cell of the body and is a major constituent of the skeletal system, a central part of energy transfer in cellular biochemical reactions, and an important component of membranes and other cell structures. Thus,

maintenance of phosphorus balance with serum inorganic phosphate concentration within normal range is critical for the normal function of the organism. As already stated above, the intestine is the only organ through which exogenous phosphate is added to the body and the kidney is the only organ through which excess phosphate is excreted. Thus, regulation of phosphate fluxes in these two organs is most important in the regulation of phosphorus balance. Processes that disturb the regulatory system responsible for the maintenance of phosphorus balance are known to cause significant clinical problems.

The human body contains approximately 600 to 700 g (17 moles) of phosphorus. About 85 to 87% of this is combined with calcium in the bone and teeth. About 10% of total phosphorus is combined with proteins, lipids, carbohydrates, and other macromolecules and resides in the soft tissues intracellularly. Intracellular phosphorus is organic phosphate and present as an integral constituent of phospholipids, nucleic acids, and phosphoproteins essential for maintenance of cellular integrity and metabolic functions. About 10% of total phosphorus exists in the inorganic state and is widely distributed in various chemical compounds. The amount of inorganic phosphate in the cell is small but is very critical for cell function as this is the only form used for the synthesis of ATP. Animal studies have shown that approximately 3 g of the stored bone phosphorus is exchangeable with the extracellular fluids. In pathologic conditions, a substantial amount of phosphorus may leave the skeleton, leading to demineralization or loss of whole bone mineral. Severe phosphorus depletion results in net release of phosphorus and calcium from bone regardless of the need for calcium in the extracellular fluids.

Over the first 20 years of life, the phosphorus balance is continuously positive, with an average of 2–3 mmol/day. From the fourth to fifth decade of life, the external balance in normal healthy subjects becomes negative, with an average loss of approximately 1 mmol phosphorus/day due to involutional bone loss. It is customarily expected that in healthy adults, the external balance of phosphorus must be zero when averaged over an appropriate period of time. Based on the data presented herein, I propose just the opposite, viz. a negative phosphorus balance in men after the second decade of their life.

DIETARY REQUIREMENTS AND SOURCES

Phosphorus is present in nearly all foods. Consequently, a dietary deficiency is not known to occur in humans. Dietary phosphate, ranging from 32 to 64 mmol/day (nearly 1.5 g), is in both inorganic and organic forms. Major portions of the organic forms are also hydrolyzed to inorganic phosphate and primarily absorbed in the duodenum and jejunum. Ileum and colon can also absorb smaller amounts of phosphate. When dietary phosphate supply is low, fecal phosphorus also decreases proportionately. Endogenous sources of phosphorus are saliva; the gastric, intestinal, and pancreatic secretions; and debris of enterocytes. A portion of endogenous phosphate is absorbed, and nearly 100–300 mg is excreted daily in the feces. Fecal phosphorus is both in inorganic and organic forms. Urinary phosphate excretion also decreases in response to dietary restriction of phosphorus.

PLASMA LEVELS OF PHOSPHORUS AND ITS REGULATION

The normal levels of phosphorus in plasma range between 2.5 and 4.8 mg/dl. The levels are 25–50% higher in growing children. The mechanism by which phosphate enters or exits cells has only recently been elucidated. Na^+-P^i cotransporter has been cloned and characterized. Once inside the cytosol, the phosphate anion participates in various phosphorylation reactions in the cytosol and is also transported into the mitochondria or exits the cell across the basolateral membrane. Activity of Na^+-P^i cotransporter is regulated by the intracellular concentrations of cyclic AMP. Several physiologic mechanisms are known to affect the transport of phosphate across the cell membranes. These cause gains or losses of phosphate by the cells with reciprocal changes in the plasma phosphate levels. Because inorganic phosphate ion concentrations in the intracellular and extracellular compartments are in equilibrium, the shifts of inorganic phosphate across cell membranes lead to a shift in the concentration of intracellular organic phosphate compounds such as glucose-6-phosphate, ATP, and phosphocreatine. Agents like insulin, glucose, fructose, and changes in blood pH cause a transfer of phosphate from the plasma to cells and lead to a transient fall in the plasma phosphate concentration. This hypothesis focuses on the possible role of this transient hypophosphatemia resulting from various stimuli. Several lines of evidence support the assumption that this may reduce the risk of elderly men to develop BPH and/or CaP.

CONCLUSION

A rather simple way to monitor phosphate balance of the body is to monitor the urinary phosphate excretion.

First, accurate estimations of inorganic and organic phosphate was done by Fiske and SubbaRow (60) in 1925. Reduced excretion of phosphorus would indicate a low serum phosphate level. It seems logical that a daily and/or periodic monitoring of urinary phosphate, using the single-reagent single-step Fiske-SubbaRow method, could help men regulate their dietary phosphate intake and consciously maintain a negative balance for it on a day to day basis. In addition, voluntary intake of fructose would then trigger a transient hypophosphatemia, leading to increased plasma 1,25-$(OH)_2$D and decreased prostate cell proliferation. Indeed, in a recent study, Giovannucci et al. (61) found that increased fruit consumption and decreased intake of calcium does reduce the risk of advanced prostate cancer.

ACKNOWLEDGMENT

I am grateful to Mr. S. P. K Gupta for his encouragement, critical comments, and meaningful suggestions on the manuscript.

Address reprint request to: Suman Kapur, Ph.D., Director, Arogyadham, Deendayal Research Institute, 7-E, Swami Ram Tirth Nagar, Jhandewalan Extension, New Delhi–110053, India.

REFERENCES

1. Boring CC, Squires TS, Tong T, et al: Cancer statistics, 1994. 1994 CA Cancer J Clin 44:7–42, 1944.
2. Huggins C, Hodges CV: Studies on prostatic cancer: effects of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1: 293–297, 1941.
3. Kozlowski JM, Ellis WJ, Grayhack JT: Advanced prostatic carcinoma: early versus late endocrine therapy. Urol Clin North Am 18:15–24, 1991.
4. McConnell JD: Physiologic basis of endocrine therapy for prostatic cancer. Urol Clin North Am 18:1–13, 1991.
5. Crawford ED, Nabors WL: Total androgen ablation: American experience. Urol Clin North Am 18:55–63, 1991.
6. Crawford ED, Fair WR, Kelloff GJ, et al: Chemoprevention of prostate cancer: guidelines for possible intervention strategies. J Cell Biochem 16H (Suppl):140–145, 1993.
7. Brawley OW, Thompson IM: Chemoprevention of prostate cancer. Urology 43:594–599, 1994.
8. Greenwald P, Kramer B, Weed D: Expanding horizons in breast and prostate cancer prevention and early detection. J Cancer Educ 8:91–107, 1993.
9. Kapur S, Gupta SPK: Dr. Yellapragada SubbaRow (1895–1948): the man and the method. Indian J Exp Biol 36:1079–87, 1998.
10. Fraser DR, Kodicek E: Unique biosynthesis by kidney of biologically active vitamin D metabolite. Nature (Lond) 228:764–766, 1970.
11. Gray RW, Boyle I, Deluca, HF: Vitamin D metabolism: the role of kidney tissue. Science 172:1232–1234, 1971.
12. Gray RW, Omdahl JL, Ghazarian JG, et al: 25-Hydroxycholecalciferol–1α-hydroxylase: Subcellular location and properties. J Biol Chem 247:7528–7532, 1972.
13. Midgett RJ, Speilvogel AM, Coburn JW, et al: Studies on calciferol metabolism. VI. The renal production of the biologically active form of vitamin D, 1,25-dihydroxy- chole-calciferol. J Clin Endocrinol Metab 36:1153–1161, 1973.
14. Garabedian M, Holick MF, Deluca HF, et al: Control of 25-hydroxy-cholecalciferol metabolism by parathyroid glands. Proc Natl Acad Sci USA 69:1673–1676, 1972.
15. Fraser DR, Kodicek E: Regulation of 25-hydroxycholecalciferol–1α-hydroxylase activity in kidney by parathyroid hormone. Nat New Biol 241:163–166, 1973.
16. Henry HL, Midgett RJ, Norman AW: Regulation of 25-hydroxyvitamin D hydroxylase in vivo. J Biol Chem 249:7584–7592, 1974.
17. Booth BE, Tsai HC, Morris RC Jr: Vitamin D. Status regulates 25-hydroxyvitamin D–1α-hydroxylase and its responsiveness to parathyroid hormone in the chick. J Clin Invest 75:155–161, 1985.
18. Henry HL: Regulation of the hydroxylation of 25-hydroxyvitamin D in vivo and in primary cultures of chick kidney cells. J Biol Chem 254:2722–2729, 1979.
19. Tanaka Y, Deluca HF: Rat renal 25-hydroxyvitamin D, 1- and 24-hydroxylases: their in vivo regulation. Am J Physiol 246: E168–E173, 1984.
20. Booth BE, Tsai HC, Morris RC Jr: Vitamin D status regulates 25-hydroxy-vitamin D–1α-hydroxylase and its responsiveness to parathyroid hormone in the chick. J Clin Invest 75:155–161, 1985.
21. Baxter LA, Deluca HF: Stimulation of 25-hydroxyvitamin D 125α-hydroxylase by phosphate depletion. J Biol Chem 251: 3158–3161, 1976.
22. Tanaka Y, Deluca HF: The control of 25-hydrovitamin D metabolism by inorganic phosphorus. Arch Biochem Biophys 154:566–574, 1973.
23. Gray RW, Wilz DR, Caldas AE, et al: The importance of phosphate in regulating plasma 1.25-$(OH)_2$-vitamin D levels in human studies in healthy subjects, in calcium-stone formers and in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 51:998–1001, 1977.
24. Insogna KI, Broadus AE, Gertner JM: Imapired phosphorus conservation and 1,25-di-hydroxyvitamin D generation during phosphorus deprivation in familial hypo-phosphatemic rickets. J Clin Invest 71:1562–1569, 1983.
25. Lurkin EG, Kumar R, Heath H: Hyper-phosphatemic tumoral calcinosis: effects of phosphate depletion on vitamin D metabolism and of acute hypocalcemia on parathyroid hormone secretion and action. J Clin Endocrinol Metab 56:1319–1322, 1983.
26. Maierhofer WJ, Gray RW Lemann Jr J: Phosphate deprivation increases serum 1,25-$(OH)_2$-vitamin D concentrations in healthy men. Kidney Int 25:571–575, 1984.
27. Portale AA, Booth BE, Halloran BP, et al: Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest 6:1580–1589, 1984.
28. Van Den Berg C J, Kumar R, Wilson DM, et al: Orthophosphate therapy decreases urinary calcium excretion and serum 1,25-dihydroxyvitamin D concentrations in idiopathic hypercalcemia. J Clin Endocrinol Metab 51:998–1001, 1980.
29. Broadus AE, Magee JS, Mallette LE, et al: A detailed evaluation

of oral phosphate therapy in selected patients with primary hyperparathyroidism. J Clin Endocrinol Metab 56:953–961, 1983.
30. Portale AA, Halloran BP, Murphy MM, et al: Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in human. J Clin Invest 77:7–12, 1986.
31. Reichel H, Koeffler P, Norman AW: The role of the vitamin D endocrine system in health and disease. N Engl J Med 320:980–991, 1989.
32. Schwartz GG, Hulka BS: Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 10:1307–1311, 1990.
33. Hanchette CI, Schwartz GG: Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. Cancer (Phila.) 70:2861–2869, 1992.
34. Binderup L, Brahmm E: Effects of a novel vitamin D analogue MC903 on cell proliferation and differentiation in vitro and on calcium metabolism in vivo. Biochem Pharmacol 37:889–895, 1988.
35. Colston K, Berger V, Coombes RC: Possible role for vitamin D in controlling breast cancer cell proliferation. Lancet 1:188–191, 1989.
36. Skowronski RJ, Peehl DM, Feldman D: Vitamin D and prostate cancer; 1,25-dihydroxy-vitamin D receptors & actions in human prostate cancer cell lines. Endocrinology 132:1952–1960, 1993.
37. Fan FS, Yu WCY: 1,25-dihydroxyvitamin D suppresses cell growth, DNA synthesis and phosphorylation of retinoblastoma protein in a breast cancer cell line. Cancer Invest 13:280–286, 1995.
38. James SY, Mackay AG, Colston KW: Vitamin D derivatives in combination with 9-cis retinoic acid promote active cell death in breast cancer cells. J Mol Endocrinol 14:391–394, 1995.
39. Lucia MS, Anzano MA, Slayter MV, et al: Chemopreventive activity of tamoxifen, N-(4-hydroxyphenyl) retinamide, and the vitamin D analogue Ro24–5531 for androgen-promoted carcinomas of the rat seminal vesicle and prostate. Cancer Res 55:5621–5627, 1995.
40. Peehl DM, Skowronski RJ, Leung GK, et al: Anti-proliferative effects of 1,25-dihydroxy-vitamn D on primary cultures of human prostatic cells. Cancer Res 54:805–810, 1994.
41. Miller GJ, Stapleton GE, Hedlund TE, et al: Vitamin D receptor expression, 24-hydroxylase activity and inhibition of growth by 1,25-dihydroxyvitamin D in seven human prostatic carcinoma cell lines. Clin Cancer Res 1:997–1003, 1995.
42. Hsieh TC, Ng CY, Mallouh C, et al: Regulation of growth, PSA/PAP and androgen receptor expression by 1,25-dihydroxy vitamin D in antidrogen-dependent LNCaP cells. Biochem Biophys Res Commun 223:141–146, 1996.
43. Esquenet M, Swinnen JV, Heyns W, et al: Control of LNCaP proliferation and differentiation: actions and interactions of androgens, 1α,25-dihydroxycholecalciferol, all-transretinoic acid, 9-cisretinoic acid and phenylacetate. Prostate 28:182–194, 1996.
44. Schwartz GG, Hill CC, Oeler TA, et al: 1,25-Dihydroxy-16-ene-23-yne vitamin D and prostate cancer cell proliferation in vivo. Urology 46:365–369, 1995.
45. Corder EH, Guess HA, Hulka BS, et al: Vitamin D and prostate cancer: a pre-diagnostic study with stored sera. Cancer Epidemiol Biomark Prev 2:467–472, 1993.
46. Gann PH, Ma J, Hennekens CH, et al: Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epideminol Biomark Prev 5:121–126, 1996.
47. Miller GJ, Stapleton GE, Hedlund TE, et al: Vitamin D receptor expression, 24-hydroxylase activity and inhibition of growth by 1α, 25-dihydroxy-vitamin D in seven human prostatic carcinoma cell lines. Clin Cancer Res 1:997–1003, 1995.
48. Taylor JA, Hirvonen A, Watson M, et al: Association of prostate cancer with vitamn D receptor gene polymorphism. Cancer Res 56:4108–4110, 1996.
49. Ingles SA, Ross RK, Yu MC, et al: Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J Natl Cancer Inst 89:166–170, 1997.
50. Morrison NA, Qi JC, Tokita A, et al: Prediction of bone density from vitamin D receptor alleles. Nature (Lond) 367:284–287, 1994.
51. Giovannucci E: Epidemiologic characteristics of prostate cancer. Cancer (Phila.) 75:1766–1777, 1995.
52. Hollick MF, Krane SM, Potts JT: Calcium, phosphorus, and bone metabolism: calcium regulating hormones. In: Harrison's Principles of Internal Medicine, 12th ed., edited by JD Wilson, E Braunwald, KJ Isselbacher, et al., New York, McGraw-Hill, 1991, pp. 1888–1902.
53. Avioli LV: Calcium and phosphorus. In: Modern Nutrition in Health and disease, 7th ed., edited by ME Shils, VR Young, Philadelphia: Lea & Febiger, 1988, pp. 142–158.
54. Portale AA, Halloran BP, Morris RC: Physiologic regulation of the serum concentration of 1,25-$(OH)_2$D by phosphorus in normal men. J Clin Invest 83:1494–1499, 1989.
55. Turner RT: Mammalian 25-hydroxyvitamin D-1α-hydroxylase: measurement and regulation. In: Vitamin D, edited by R Kumar, Hingham, MA, Martinus Nijhoff Publishing, 1984, pp. 175–196.
56. Hallfrisch J, Ellwood K, Michaelis OE, et al: Plasma fructose, uric acid, and inorganic phosphorus responses of hyper-insulinaemic men fed fructose. J Am Coll Nutr 5:61–68, 1986.
57. Israel KD, Michaelis OE, Reiser S, et al: Serum uric acid, inorganic phosphorus, and glutamic-oxalacetic transaminase and blood pressure in carbohydrate-sensitive adults consuming three different levels of sucrose. Ann Nutr Metab 27:425–435, 1983.
58. Woods HF, Eggleston LV, Krebs HA: The cause of hepatic accumulation of fructose-1-phosphate on fructose loading. Biochem J 119:501–510, 1970.
59. Mayes PA: Intermediary metabolism of fructose. Am J Clin Nutr 58 (Suppl):754S–765S, 1993.
60. Fiske CH, SubbaRow Y: The calorimetric determination of phosphorus. J Biol Chem 66:375–400, 1925.
61. Giovannucci E, Rimm EB, Wolk A, et al: Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 58:442–447, 1988.