Phosphorus balance and prostate cancer

Suman Kapur

Molecular Biology, New Drug Discovery Research, Ranbaxy Research Laboratory, New Delhi 110020, India

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 (BPH), of which some progress to Carcinoma of Prostate (CaP). CaP, the most common malignancy in men, is also the second most common cause of death in men. Over the last three decades the mortality rate for CaP has steadily increased. There, however, are scant clues to the aetiology/pathogenesis of CaP. As treatment failures of advanced carcinoma continue to frustrate clinicians, emphasis has recently been focused on possible preventive strategies. Several studies support the view that higher levels of 1,25-(OH)2D, the active metabolite of vitamin D, reduce the risk of BPH and CaP. Men with high serum levels of 1,25-(OH)2D have a reduced risk of poorly differentiated and clinically advanced CaP. Hypercalcemic activity of 1,25-(OH)2D or its analogues, however, threat their use for therapy in humans. Incidentally, a low dietary intake of phosphorus has been reported to increase serum levels of 1, 25-(OH)2D. In addition, dietary fructose reduces plasma phosphate levels by 30 to 50% for more than 3 hr. Fruit intake has, indeed, been shown to be associated with reduced risk of CaP, particularly the advanced type. These observations, taken together, support that dietary determinants of hypophosphatemia, leading to increased plasma levels of 1, 25-(OH)2D, could reduce the risk of ageing men to develop prostatic diseases, both BPH and/or carcinoma of Prostate.

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 increased1. Cancer of the prostate (CaP), the most common malignancy in men1, is, after carcinoma of lung, the second most common cause of cancer death in men older than age 55. In the US alone, over 100,000 new cases of CaP are diagnosed annually. Over the last three decades, many epidemiological studies have been conducted and there are scant clues as to the aetiology 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 rates1. 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 or advanced tumours2,3,4. However, in practice, the concept of "total androgen ablation" therapy has found only limited success3,4,5. As treatment failures for advanced carcinoma continue to frustrate clinicians, emphasis has recently been focused on possible strategies to prevent invasive prostatic carcinoma3,4,5.

Prostatic hyperplasia

Development of prostatic hyperplasia is an almost universal phenomenon in ageing 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 20g 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 majority of 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 D3

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.

1,25-(OH)_2D, the active form of vitamin D, has a well-established role in phosphorus homeostasis. Renal synthesis of 1,25-(OH)_2D, from its endogenous precursor, 25-hydroxy-vitamin D_3, is catalysed by 25-hydroxy-vitamin D_3-1α-hydroxylase (1-hydroxylase). This enzyme is stimulated by PTH and suppressed by 1,25-(OH)_2D and normal vitamin D status and dietary intake of phosphorus, possibly through an effect on plasma phosphorus concentration. Restriction of dietary phosphorus induces an increase in the serum concentration of 1,25-(OH)_2D in normal men and women and children with moderate renal insufficiency. Conversely, in patients with idiopathic hypercalciuria or primary hyperthyroidism, supplementation of phosphorus induces a decrease in serum concentration of 1,25-(OH)_2D from supernormal to normal levels. Fortale et al. 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)_2D by increasing the production rate of the same in the renal cortical tissue. Studies, both in chick and rat, 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 (VDR) and are responsive to the actions of 1,25-(OH)_2D. Epidemiological data suggest that vitamin D may play a role in the progression of prostate cancer. Schwartz and Hulka have proposed that the recognised risk factors of age and race in combination with vitamin D deficiency disease caused by lack of UV exposure, are related to prostate cancer mortality. Recent findings have supported this hypothesis and suggest that about 6% of the mortality from prostate cancer in USA could be related to UV exposure. In the United States, prostate cancer mortality rates exhibit a marked north-south gradient, with higher rates observed in the north. This gradient correlates well with ambient levels of UV 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. Data from several different in vitro animal, genetic, epidemiological and geographical studies support the view that higher levels of 1,25-(OH)_2D reduce the risk of prostate hyperplasia and CaP. Recent studies have shown that typically higher levels of 1,25-(OH)_2D inhibit cellular proliferation and induce differentiation of both, normal and neoplastic prostate cells in vitro. Moreover, limited, in vivo, studies in rodents also support antitumor potency of 1,25-(OH)_2D analogues against prostate cancer. Older men having high circulating 1,25-(OH)_2D have been shown to have a reduced risk of poorly differentiated and clinically advanced prostate cancer. The hypercalcemic activity of 1,25-(OH)_2D or its analogues, however, prevents their use as a therapeutic agent in humans.

1,25-(OH)_2D exerts its activities by binding the VDR, which is a nuclear hormone receptor. Miller et al. reported a ubiquitous presence of VDR in seven different prostatic carcinoma cell lines. Peehl et al. found that BPH epithelial cells and prostate tissue extracts also contain comparable receptors. Evidence for a role of 1,25-(OH)_2D 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. If circulating 1,25-(OH)_2D 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. However, ecological, 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. This apparent paradox may be resolved by considering two aspects: 1) 1,25-(OH)_2D may be more relevant than its precursor 25-(OH)_2D for biological action and 2) dairy products are also a major source of calcium which lowers the levels of circulating 1,25-(OH)_2D. Activity of renal 1-hydroxylase is stimulated by low serum calcium levels, which would lead to increased formation of 1,25-(OH)_2D in the kidneys.
Hypophosphatemia and prostate cancer: A hypothesis

Reduction in circulating phosphate increases 1,25-(OH)_2D serum levels appreciably. However, as phosphorus is generally abundant in most diets and is well absorbed intestinally, diet-induced hypophosphatemia is rare. Thus, such dietary intake may not directly affect 1,25-(OH)_2D 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. This hypophosphatemia occurs because fructose is very rapidly phosphorylated in the liver, catalysed by the enzyme fructokinase, which by-passes the phosphofructokinase regulatory step in glycolysis.

In a study, conducted jointly by a team of scientists in USA and Sweden, fructose consumption (from both fruit and non-fruit 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 are 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)_2D levels which have been shown to increase 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)_2D levels on prostate carcinogenesis. Given the morbidity and mortality caused by CaP world-wide, this hypothesis warrants further investigation.

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 co-transporter has been cloned and characterised. 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 cotransporter is regulated by the intracellular concentrations of cyclic AMP (cAMP). Several physiological 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. Since inorganic phosphate ion concentrations in the intracellular and extracellular compartments are in equilibrium, the shifts of inorganic phosphate across cell membranes leads to a shift in the concentration of intracellular organic phosphate compounds such as glucose-6-phosphate, ATP and phosphocreatine. Agents like insulin, glucose and 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 evidences support the assumption that this may reduce the risk of elderly men to develop BPH and/or carcinoma of the prostate.

Conclusion

A rather simple way to monitor phosphate balance of the body is to monitor the urinary phosphate excretion. The first accurate estimations of inorganic and organic phosphates were done by Fiske and SubbaRow 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 to this, voluntary intake of fructose would then trigger a transient hypophosphatemia leading to increased plasma 1,25-(OH)_2D and decreased prostate cell proliferation. Indeed in a recent study Giovanniucci et al. found that increased fruit consumption and decreased intake of calcium does reduce the risk of advanced prostate cancer.

Acknowledgement

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

References
