

URINARY CALCIUM IN CANCER- A PILOT STUDY

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ABSTRACT

Hypercalcemia is the most common life-threatening metabolic disorder associated with neoplastic diseases, occurring in an estimated upto 20% of all adults with cancer. Solid tumors, such as lung or breast cancers as well as certain hematologic malignancies (particularly multiple myeloma) are most frequently associated with hypercalcemia. Although the clinical importance of PTH (parathyroid hormone) and vitamin D and the resulting concentration of calcium in the serum are widely known, the role of urine calcium testing is not often discussed and is less obvious. This study was undertaken to get a direction towards simple, non invasive method of predicting prognosis of solid cancers by estimating urinary calcium in relation to urinary creatinine. Spot urine samples from 29 cancer patients and 28 healthy controls were obtained for the study. Spectrophotometric estimation of urinary calcium was carried out using O -Cresolphthalein complexone method. There was a significant difference in the median ratio of calcium in the urine samples of the cancer patients which was expressed in relation to urine creatinine. The cancer patients who were in advanced stages showed the ratio of urine calcium: urine creatinine more than 0.2 indicating hypercalcemia. Hence, urine calcium can be measured as a predictive marker in advanced stages of certain solid cancers.

Keywords: Urinary calcium, cancer, hypercalcemia, advanced stages, solid cancers.

INTRODUCTION

Calcium is the most widespread mineral in the body and one of the most essential one. It is required for muscle contraction and nerve signaling¹. Hence, the serum concentration of calcium has obvious significance. Almost all of the calcium in the body is stored in bone and the rest in the blood. Serum calcium also reflects parathyroid hormone (PTH) function and vitamin D status.

Hypercalcemia is the most common life-threatening metabolic disorder associated with neoplastic diseases, occurring in an estimated 10% to 20% of all adults with cancer. It also

occurs in children with cancer, but with much less frequency (approximately 0.5% -1%)²⁻⁴. Solid tumors, such as lung or breast cancers as well as certain hematologic malignancies (particularly multiple myeloma) are most frequently associated with hypercalcemia⁵.

Any disease causing increase in serum calcium can lead to increase in urine calcium (hypercalciuria). In addition to hyperparathyroidism, other diseases include, multiple myeloma (or any osteolytic neoplasm), osteoporosis, vitamin D overdose, renal tubular acidosis, hyperthyroidism, Paget's disease and Sarcoidosis. Drugs containing calcium (such as some antacids) and calcium

supplements can lead to direct increases in urine calcium. The diuretic spironolactone can also cause increases in urine calcium since it is given as a calcium salt and appears to decrease tubule reabsorption of calcium. Androgens such as nandrolone and treatment with growth hormone can also cause increases in urine calcium. Acetazolamide and systemic corticosteroids are also associated with increased calcium excretion^{6,7}.

Although the clinical importance of PTH and vitamin D and the resulting concentration of calcium in the serum are widely known, the role of urine calcium testing is not often discussed and is less obvious. Therefore, this study is undertaken to get a direction towards simple, non invasive method of measuring prediction of solid cancers.

MATERIAL AND METHODS

Spot urine samples from 29 cancer patients and 28 healthy controls were obtained for the study. Patients were suffering from a variety of cancers. While collecting the urine samples, care was taken to avoid the samples with the history of hypercalciuria due to other causes than cancer such as hyperparathyroidism, osteoporosis, vitamin D overdose, renal tubular acidosis, hyperthyroidism and Paget's disease. Informed consents from normal volunteers and cancer patients were taken before collecting the samples. Spectrophotometric estimation of urinary calcium was carried out using O -Cresolphthalein complexone method⁸. Although a 24-hour collection is the best, random urine calcium measurement can be performed and is expressed in relation to creatinine. Urine creatinine was estimated using Jaffe's method⁹.

Reference range: A normal reference interval for the urine calcium (mg/dL): urine creatinine (mg/dL) ratio is <0.14. Values exceeding 0.20 are found in patients with hypercalciuria.

Statistical analysis: Data was analyzed statistically using Kruskal Wallis and Mann Whitney tests. $P < 0.05$ was considered to be significant. Statistical software SPSS version 17 was used to analyze the data.

RESULTS

We recruited 28 normal subjects, 13 cancer with normal urinary calcium and 16 cancer with high urinary calcium (cancer*). There was a significant difference ($p=0.0005$) between normal, cancer and cancer* patients (**Table 1**). The median value for ratio of urinary calcium in normal group is

0.1967 and the inter quartile range is [0.0498-0.423]. The median value for ratio of urinary calcium in cancer* group is 0.8885 and the inter quartile range is [0.595-1.976]. The median value for ratio of urinary calcium in cancer group is 0.0296 and the inter quartile range is [0.009-0.097].

Table 1: Comparison between quartiles of normal, cancer and cancer*

Groups	Median	Inter quartile range
Normal (n=28)	0.1967	[0.0498 – 0.423]
Cancer (n=13)	0.0296	[0.009 – 0.097]
Cancer*(n=16)	0.8885	[0.595 -1.976]

*** Significant at the level of 0.0001

** Significant at the level of 0.001

DISCUSSION

Healthy kidneys are capable of filtering large amounts of calcium, which is subsequently reclaimed by tubular reabsorption. The kidneys are capable of increasing calcium excretion nearly fivefold to maintain homeostatic serum calcium concentrations. However, hypercalcemia may occur, when the concentration of calcium present in the extracellular fluid overwhelms the kidneys' compensatory mechanisms¹⁰.

The fundamental cause of cancer-induced hypercalcemia is increased bone resorption with calcium mobilization into the extracellular fluid and inadequate renal calcium clearance either due to osteolytic hypercalcemia or humoral hypercalcemia^{11,12}. The latter is caused by bone resorption mediated by circulating osteoclast-activating factors released from distant tumor cells. It is believed that hypercalcemia results from the release of factors by malignant cells that ultimately cause calcium reabsorption from bone. One such factor is a PTH-like protein known as parathyroid hormone-related protein or peptide (PTHrP) which is a primitive protein that appears to have important roles in calcium transport and developmental biology¹³⁻¹⁵. Increased blood levels of PTHrP have been found in patients with solid tumors who develop hypercalcemia. Circulating growth factors may also mediate hypercalcemia. Potential mediators include transforming growth factor-alpha and -beta, interleukin-1 and -6, and tumor necrosis factor (TNF)-alpha and -beta¹⁶.

The major clinical value of urine calcium is to guide the clinician in determining the cause as well as the best treatment options for patients who present with disease, related to inappropriate calcium metabolism. Primarily, urine testing is performed to supplement serum testing. Since urine calcium estimation involves

non-invasive method, this is preferred by the patients as well as the clinicians. Patients who were in advanced stages of their cancer have shown the higher ratio of urine calcium to urine creatinine. Hence, urine calcium level can also be measured as a predictive marker in advanced stages of certain solid cancers.

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