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CALCIUM STATUS IN SUDANESE CANCER PATIENTS ATTENDING THE INSTITUTE OF NUCLEAR MEDICINE, MOLECULAR BIOLOGY AND ONCOLOGY.

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Abstract

Objective: The aim of this study was to study the incidence of hypercalcaemia together with the related biochemical parameters and anthropometric measurements in Sudanese cancer patients attending the Institute of Nuclear Medicine, Molecular Biology and Oncology (INMO), Gezira State, Sudan.

Methods, materials and study subjects: The study was a prospective study performed on 100 cancer patients (age ranging between 4- 70 years). The study period was from 15/4/2003 to1/9/2003. Another 100 persons (age and sex matched) were used as control group. The biochemical parameters measured in this study were serum calcium, serum inorganic phosphorus and serum albumin. Calcium, inorganic phosphorus and albumin were measured by Spectrophotometery. Anthropometrics measurements determined were weight and height. A questionnaire was filled in order to obtain information regarding: age, sex, residence, tribe and information about education, occupation, marital status and past medical history. Type of cancer, date of diagnosis, stage of cancer, treatment, and present complaints were recorded.

Results: Hypercalcaemia was detected in ten of the patients (10%). This is similar to the internationally published rates. The types of cancers associated with hypercalcaemia were cancer of the breast (20%), skin (20%), prostate (10%), bladder (10%), rectum (10%), unknown primary (10%) and hematological malignancies (20%).Mean serum calcium (9.48 ± 1.07 mg/dL) and inorganic phosphorus (4.45 ± 1.01 mg/dL) were higher in the cancer patients than the control group (9.03 ± 0.56, 4.13 ± 0.72 mg/dL respectively). However, the difference is statistically not significant. Serum albumin concentration was similar in the patients and control groups (4.97±0.63 and 4.93±0.41 g/dL respectively). The differences of weight and height were not significantly different in the two groups.

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Conclusion: It is concluded that the calcium, phosphorus and albumin levels among Sudanese individuals were similar to the internationally published levels. Hypercalcaemia is not a rare condition among cancer patients and should be checked whenever there is a symptom because it can lead to many serious complications.

Introduction

Calcium is the fifth most common element in the body. It is found mainly in the skeleton, with small amounts in soft tissues and extracellular fluid (1) Calcium plays important physiological roles; it is required for many general metabolic functions in the body. Such functions include absorption of vitamin B12, activation of the fat-splitting enzyme pancreatic lipase, and secretion of insulin. Calcium also occurs in cell membrane, where it governs how permeable the membrane is to nutrients. Many of these actions are only poorly understood. It is also essential for the functional integrity of nerve and muscle, where it has a major influence on the integrity of membranes. To carry out these various roles, ionic calcium must be available to the appropriate tissues in the proper concentration. As in the case for other essential constituents of the body, an endocrine control system has evolved that ordinarily keeps the plasma concentrations of ionized calcium within narrow limits. This is accomplished in the case of calcium by placing controls at the site of excretion (kidney), and by keeping a large store in the skeleton accessible for deposits or withdrawals depending upon peripheral demand. Intracellular concentration of ionized calcium is also strictly regulated in part by control of the exchange of the ion between the cell and its environment (2). The steady state content of calcium in the skeleton is a consequence of the net effect of bone resorption and new-bone formation. The calcium of bone is in a constant exchange with the calcium of the interstitial fluids. The rate of exchange is modifiable by drugs, hormones, vitamins and other factors that may influence the level of calcium in the interstitial fluids and also the forms in which the action is present (2)

The calcium intake varies from 200 to 2500 mg per day and in the United States the predominant source is dairy products. The skeleton contains more than 90% of the calcium of the body.(2) The main source for calcium in the human diet is milk (160 mg per 100g), cheese (120- 400mg/100g) smaller amounts of calcium are also found in cereals and seeds. Calcium may be added to flour e.g. calcium lactate was added to flour in United Kingdom. Sesame is a rich source, containing about 1200 mg/100g (2). Secondary sources of calcium include grains, egg yolk, legumes, nuts and green vegetables (3) Hormones modulate calcium homeostasis. Parathyroid hormone (PTH), which is the most important calcium

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regulator. It is secreted from parathyroid glands in response to low unbound plasma calcium. PTH causes bone resorption and promotes calcium reabsorption in the renal tubules preventing loss in the urine (4). Vitamin D [1, 25-dihydroxycholecalciferol (1, 25, DHCC)], which is the third regulator, maintains intestinal calcium absorption. Calcitonin; a hypocalcaemic hormone, the effects of which are generally opposite to those of the parathyroid hormone. It is secreted from C-cell in thyroid gland in response to hypercalcaemia (2). In Bone, Calcitonin suppresses resorption of bone by inhibiting the activity of osteoclast, a cell type that "digests" bone matrix, releasing calcium and phosphorus in to blood. In the kidney, calcium and phosphorus are prevented from being lost in urine by reabsorption in the kidney tubules. Calcitonin inhibits tubular reabsorption of these two ions, leading to increased rates of their loss in urine.

There are two main mechanisms by which hypercalcaemia occur in cancer patients. Local osteolytic hypercalcaemia, which occurs with extensive bone metastases in multiple myeloma, breast cancer etc. although local destruction of the bone doesn't explain the hypercalcaemia completely, but apparently the tumors secrete some factors that stimulate locally osteoclasts bone resorption.

The other mechanism is seen in patients with cancer of lungs (squamous cell type), renal, ovary and bladder where these tumors secrete factors, which act systemically to cause bone resorption (5). One such factor is a PTH-like protein known as parathyroid hormone-related protein (PTHrP) or peptide (PTHrP) is a primitive protein that appears to have important roles in calcium transport and developmental biology. It shares partial amino acid sequence and conformation homology with normal PTH, binds with the same receptors on skeletal and renal target tissues, and affects calcium and phosphate homeostasis as does PTH.

Increased blood levels of PTHrP have been found in patients with solid tumors, but not in patients with haematological malignancies who develop hypercalcaemia. Circulating growth factors may also mediate hypercalcaemia. Potential mediator includes transforming growth factor (TGF) alpha and beta, interleukin-1 tumor necrosis factor (TNF) alpha and beta, and interleukin-6 (6)
Hypercalcaemia is the most common metabolic disorder in malignancy that requires emergency therapy when severe or symptomatic. In study from South Africa malignant tumors were the commonest cause of hypercalcaemia (38.4%) and accounted for the most severe cases of hypercalcaemia among the study population (22). It has been estimated that hypercalcaemia occurs in 10% to 20% of cancer patients at some time during the course of their disease (7).
The presence of hypercalcaemia was associated with increased frequency of distant metastases, bone metastases, and increased mortality (8).

No study has been conducted in Sudan to assess the hypercalcaemia in cancer patients in spite of its relevance to the management. The objective of the present work was to study the incidence of hypercalcaemia in Sudanese cancer patients attending INMO. This study was adopted to direct the attention of the treating doctors to the magnitude of this condition among their patients.

Methods, materials and study subjects

Hundred cancer patients attending INMO were the population of this study. These patients were chosen from old and new patients attending different clinics in the hospital.
There was no age, sex, disease, or treatment discrimination. Questionnaire was designed and filled for each patient. Another 100 matched persons from the community were also chosen to form the control group. Chemical reagents and kits used for determination of calcium and albumin were obtained from CRESCENT DIAGNOSTICS-Saudi Arabia. The chemicals used for preparation of standards were of the Analar grade. Deionised distilled water was used throughout the analysis.

Instruments:
Centrifugation as well as Spectrophotometery was used for determination of calcium, and albumin.

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Blood samples**:**
Blood samples were collected from each patient on presentation.

Questionnaire:
For each patient a questionnaire data form was filled in order to obtain information regarding: age, sex, residence, tribe and information about education, occupation, marital status and past medical history. Type of cancer, date of diagnosis, stage of cancer, treatment, and present complaints were also recorded. The levels of calcium and albumin of the study groups were determined.

Anthropometric measurements: -
Weight and height were measured. Readings were taken to the nearest 0.1 Kg and cm.

Results & discussion*:*

Among the study patients 72 (72%) belong to Gezira state. This fact could be explained by the area, which INMO drains. This has also been reflected among patients with hypercalcaemia where 8 (80%) of them belong to the same state. The mean age in the patients was found to be 45.49 ±15.56 years. The mean age in the control groups was found to be 39.91 ±13.38 years. The ratio of males: females were 2:3 (39:61) for the patients and control groups. This is in agreement with the INMO report for 2002 (9), which indicated the same finding. Among patients with hypercalcaemia the majority were females (60%). This reflects the above-mentioned distribution of sexes in patients group. This is in agreement with Vassilopoulou et al (8) who reported, the age at presentation of hypercalcaemic patients was comparable to the age of the overall group of patients that they studied. Seventy six percent of the patients came from rural areas; the same distribution has been noticed among patients with hypercalcaemia where the majority was rural residents (80%). High percentage of the patients (38%) was housewives. This also found in patients with hypercalcaemia (50% were housewives). The majority of the patients came from Northern and Central regions tribes (65%). X^2 test performed on this data indicates that tribe has significant effects on incidence of cancer ($P<0.000$). This has not been taken as conclusive evidence due to small sample size. Among patients with hypercalcaemia, Northern and Center regions again have the highest rate of hypercalcaemia incidence (60%). This reflects the above-mentioned distribution of the patients. Forty percent of the patients were literate. X^2 test performed on this group indicated that there is significantly high association between the education level and cancer ($P<0.000$). Among patients with hypercalcaemia 50% were literate. The majority of patients (80%) were married. Ninety percent of the patients with hypercalcaemia were married. The most common types of cancers that occurred among the study population were the Breast Cancer and hematological malignancy. (Table 1)

Table (1): Types of cancer among the study patients

Type of cancer	Patients	Patients with hypercalcaemia
Acute lymphoblastic leukemia	2	-
Acute myeloid leukemia	1	-
Breast cancer	32	2
Clymphocytic leukemia	2	-
Chronic myeloid leukemia	9	-
Bladder cancer	2	1
Cancer of the cervix	4	-
Cancer of the Larynx	2	-
Lung cancer	1	-

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Ovarian cancer	4	-
Prostate cancer	6	1
Cancer of the Rectum	2	1
Cancer of the Stomach	1	-
Hepatoblastoma	1	-
Hepatocellular carcinoma	1	-
Hodgkin's Disease	1	-
Cancer of the Hypopharynx	2	-
Cancer of the esophagus	2	-
Unknown primary	1	1
Multiple myeloma	2	1
Non-Hodgkin's lymphoma	8	1
Cancer of the nasopharynx	4	-
Polycythemia.	1	-
Renal cell carcinoma	1	-
Cancer of the anal canal	1	-
Cancer of the colon	1	-
Skin cancer	1	-
Testicular cancer	1	-
Malignant melanoma	2	2
Osteosarcoma	1	-
Total	100	10

This is in agreement with the INMO report for 2002. Warrell et al (6) found that ten to twenty percent from all cancer patients had hypercalcaemia. Solid tumors (such as lung or breast cancer) as well as certain haematological malignancies, particularly (multiple myeloma) are the most common cancers that are frequently associated with hypercalcaemia. Sixty percent of the patients studied were diagnosed with stage III &IV diseases, (Table2) which indicate that the majority of patients presented with advanced disease.

Table (2) Stage of cancer among the study patients.

Stage	Patients	Patients with hypercalcaemia
I	7	2
II	12	-
III	21	-
IV	39	6
Missing	21	2
Total	100	10

Among patients with hypercalcaemia(60%) had stage IV diseases. This indicates the strong association between advanced disease stages and increased incidence of hypercalcaemia. The overall incidence of advanced stage of disease among the study population is in agreement with the INMO report for 2002, and with Holland (5), who found that the high incidence of local osteolytic hypercalcaemia is associated with extensive bone metastases in multiple myeloma and breast cancer. Out of the study patients, (13%) were presented with significant past medical history. Among patients with hypercalcaemia 20% had past medical history. The only significant symptoms that occurred in patients were: nausea, vomiting and dizziness ($p < .000, .001, .000$ respectively). (Table3)

Table (3) Symptoms experienced by study patients.

Symptoms	Patients	Control	Patients with hypercalcaemia	X^2 test
Nausea	23%	5%	40%	Significant

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Vomiting	16%	2%	40%	Significant
Constipation	25%	2.3%	40%	Not significant
General weakness	51%	5.3%	60%	Not significant
Muscle Aches	44%	4.2%	60%	Not significant
Dizziness	18%	1%	50%	Significant
Mental Dullness	1%	0%	10%	Not significant
Confusion	1%	0%	10%	Not significant.
Coma	0%	0%	0%	Not significant

This goes with the statement by Bajorunas (10), Mahon (11), Binns and Gurney (12), that patients with hypercalcaemia in malignancy (HCM) present with symptoms such as fatigue, mental dullness, weakness, anorexia or confusion, drowsiness or even coma. These symptoms were the most common symptoms among patients with hypercalcaemia. Chemotherapy was the most common treatment received by patients, radiotherapy came next in order. Almost the same distribution was noticed among hypercalcaemia patients. In this study, it was found that the difference between mean levels of serum calcium in patient (9.48±1.07) and control group (9.03±0.56) was statistically not significant (P<0.768). (Table 4)

Table (4): Biochemical parameters in the study population (Mean ± SD).

Variable	Patients (n=100)	Control group (n=100)	X^2 test
Serum calcium (mg/dL)	9.48±1.07	9.03±0.56	Not significant
Serum albumin(g/dL)	4.97±0.63	4.93±0.41	Not significant

The levels were normal for 87 patients and 99 respondents of the control group. The levels were low in three of respondents of the control, and also in three patients. The reference levels used were that of Hemphill and Gossman (13). The levels were high in one of the control group and 10 of the patients.

Hypercalcaemia usually is divided into two types: mild hypercalcaemia, which indicates, corrected total serum calcium < 12 mg/dl (< 6 mEq/L or 3.0 mmol/L), and moderate to severe hypercalcaemia which indicates corrected total serum calcium equal or >12 – 14 mg/dL (6-7 mEq/L or 3.0-3.5 mmol/L) (14, 20). According to this, there were 8 patients in the first group and two in the second group. In addition there was also one respondent from the control group who had mild hypercalcaemia. The incidence of hypercalcaemia among the patients of this study was found to be 10% and this is in agreement with Warrell et al, (6) who reported 10% to 20% incidence rate of hypercalcaemia among persons with cancer. Vassilopoulou et al (8) also reported a low incidence of hypercalcaemia among cancer patients. An update on hypercalcaemia in malignancy by Binns mentioned the same low incidence of around 10% (12). Twenty percent of the hypercalcaemic patients presented with cancer of the breast. In addition another 20% of them presented with multiple myeloma. Siddiqui et al (15) found that tumor – induced hypercalcaemia (TIH) occurred in 25% of patients who had multiple myeloma and hepatocellular carcinoma. In addition the author found this condition in 20% of the patients with cancer of the breast.

There were two breast cancer patients who had hypercalcaemia, both of them presented with metastatic disease. This goes well with the study performed by Toma et al (16), which studied tumor induced hypercalcaemia in metastatic breast cancer patients. The author found that tumor-induced hypercalcaemia (TIH) is a common condition in metastatic breast cancer affecting up to 30% of the patients, once or more during the course of disease. Serum calcium is known to fluctuate with factors like local osteolytic hypercalcaemia, which occurs with extensive bone metastases in multiple myeloma, breast cancer etc. Although local destruction of the bone does not explain the hypercalcaemia completely, apparently these tumors secrete some factors that stimulate locally osteoclast bone resorption. Also recalcification is

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delayed. The other mechanism is seen in patients with squamous cell lung cancer, renal, ovary and bladder cancers where these tumors secret factors, which act systemically to cause bone resorption. (5, 6, 17, 18). Calcium binds with albumin. This indicates that albumin is a good predictor of calcium level (19). Binns (12) recommends that allowances should be made for hypoalbuminaemia, which is commonly seen in cancer patients. Beers et al (21) found that symptoms of hypo-or hypercalcaemia are due to abnormalities in the ionized fraction of the plasma calcium concentration. However, the ionized total plasma calcium levels are rarely done routinely in clinical laboratories. The total plasma calcium is used to infer the ionized calcium fraction and is usually accurate except in the setting of hypoalbuminaemia. Since hypoalbuminaemia is not uncommon among patients with cancer, it is necessary to "correct" the total plasma calcium concentration for the percent of calcium that would have been measured if the albumin level were within normal range. The calculation is as follows: (normal albumin-patient's albumin) ×0.8 + patient's measured total calcium. There were four patients who had low level of albumin. By using the above-mentioned formula, their calcium levels were raised up and even one of them had marginal hypercalcaemic level.

Conclusions

Most of the study patients (72%) lived in the Gezira State. The ratio of male: female of study groups was approximately 2:3 (39:61). The rural areas residents were more than urban residents in patients group. Although the available data do not permit drawing a conclusion this fact could indicate more predisposition of rural residents to cancer . In this study group the majority of the patients came from Northern and Central regions tribes. The most common types of cancers that occurred among the studied population were breast cancer and hematological malignancies. In this study 60% of patients were diagnosed as stage III &IV diseases, which indicate that the majority of the patients presented with advanced stages of disease.

In this study (10%) of cancer patients had hypercalcaemia. Solid tumors (breast cancer) as well as certain haematological malignancies, particularly (multiple myeloma) are cancers that frequently associated with hypercalcaemia. This rate is similar to the internationally published rates of hypercalcaemia in cancer patients.

References:

1. Burtis C A., and Ashwood E R., 2001. Tietz Fundamentals of Clinical Chemistry. 5th edition, Saunder Company, USA, page797-804.
2- Sukkar M.Y. Human Nutrition, for medical studies and allied health sciences.First edition, 1982, page 28-29.
3- Williams S R, 2001. Basic Nutrition and Diet Therapy. 11th edition. Mosby, Page 114-117.
4- Cantaraw A and Trumper M, 1962. Clinical Biochemistry.6th edition, Saunders Company, Philadelphia, pages 216-246.
5- Holland JF.1993. Cancer medicine. Third edition by Lea and Febiger, USA, pages 2291-2292.
6- Warrell RP, 1992. Etiology and current management of cancer-related hypercalcaemia. Oncology 6 (10): 37-43; pages 47-50.
7- Djulbegovi'c B and Sullivan DM, 1997. Decision making in oncology, evidence-based management. First edition, Churchill Livingstone, USA, page 437-445
8- Vassilopoulou R et al.1993. Incidence of Hypercalcemia in Patients with Malignancy referred to a Comprehensive Cancer Center. International Journal of the American Cancer Society, No.4, Volume11, P 1309-1312.
9- Gezira Radiotherapy Hospital. Institute of Nuclear Medicine, Molecular biology and Oncology. Annual Report 2001.
10- Bajorunas DR, 1990. Clinical manifestation of cancer-related Hypercalcaemia. Semin Oncol. 17(2 Suppl 5): 16-25.
11- Mahon SM, 1989. Signs and symptoms associated with malignancy-induced hypercalcaemia. Cancer Nurs 12(3): 153-60.

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12- Binns A and Gurney, 1998. Update on hypercalcaemia in malignancy. Palliative care. www.medicine.net.au.

13- Hemphill RR and Gossman W. Hypercalcaemia. Medicine Jorurnal, January 2002, Volume3, Number1.

14- Suki WN et al, 1970: Acute treatment of hypercalcaemia with furosemide. N Engl J Med 283(16): 836-40.

15- Siuddiqui I et al, 2002. Tumor-induced hypercalcaemia: predictor of early mortality. J. Pak. Med. Assoc. Aug; 52(8): 361-4.

16- Toma S N et al. 1998. Tumor induced hypercalcaemia in metastatic breast cancer: treatment and predictive factors. European society for medical Oncology, Archived Abstracts. No: 139, pages 1-2.

17- Horiuchi N et al. 1987. Similarity of synthetic peptide from human tumor to parathyroid hormone in vivo and in vitro. Science 1987, 238 (4833): 1566-8.

18- Sura LJ et al, 1987. Aparathyroid hormone-related protein implicated in malignant hypercalcaemia: cloning and expression. Science 1987, 237(4817): 893-6.

19- Ganong WF, 1999. Review of medical physiology. 19th edition. Appleton and Lange, Stamford, P365-377.

20- Ritch SH, 1990. Treatment of cancer-related hypercalcaemia. Semin Oncol 17(2Suppl5): 26-33.

21- Beers MH and Berkow R, 1999. The Merck manual of diagnosis and therapy.17th edition, Whitehouse Station, NJ: Merck Research Laboratories.

22- Diamond TH et al, 1987. Hypercalcaemia in the Johannesburg Hospital. Differential diagnosis and physician awareness of primary hyperparathyroidism. S Afr Med J. 1987 Jul 18; 72(2):113-5.