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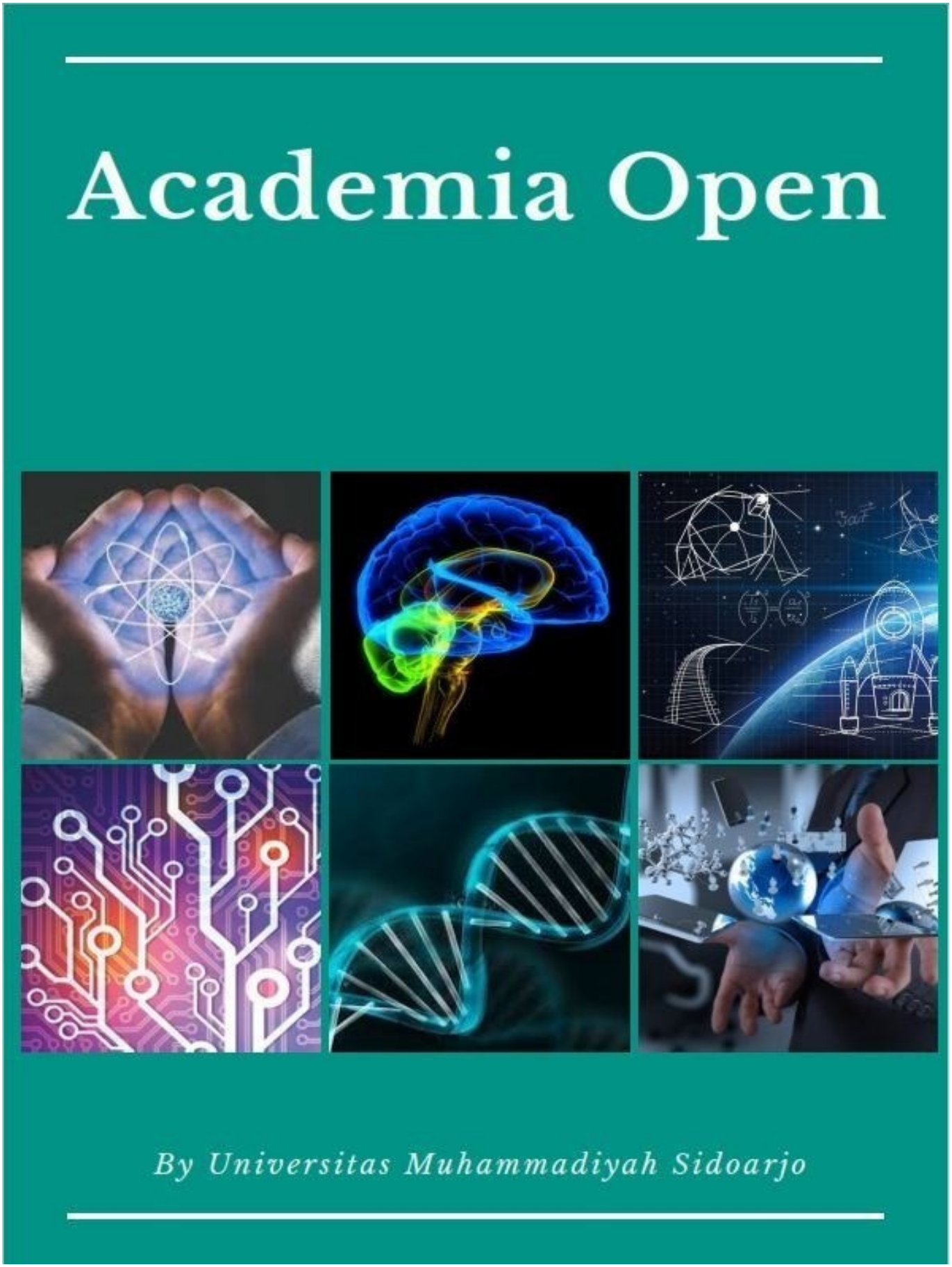

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Biochemical Profiles in Women with Parathyroid Carcinoma Under Chemotherapy

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Abstract

General Background: Parathyroid carcinoma is a rare endocrine malignancy characterized by excessive parathyroid hormone secretion and severe metabolic disruption. Specific Background: Although its biochemical profile is well documented, evidence describing how chemotherapy influences circulating calcium, phosphate, vitamin D metabolites, and trace elements—particularly among older women—remains limited. Knowledge Gap: Few studies systematically compare these biochemical alterations with healthy controls to determine the extent of treatment-associated metabolic derangement. Aims: This study evaluates and correlates key biochemical parameters in women with parathyroid carcinoma undergoing chemotherapy relative to age-matched healthy subjects. Results: Findings demonstrated significantly elevated serum calcium and parathyroid hormone, alongside reduced phosphate, 25(OH)D, 1,25(OH)2D, zinc, and iron in the patient group, indicating marked disruptions across mineral metabolism, vitamin D dynamics, and trace element homeostasis. Novelty: The study provides one of the first integrated biochemical assessments focused exclusively on chemotreated female patients, revealing a broader metabolic signature than previously recognized. Implications: These results highlight the importance of comprehensive biochemical monitoring to improve diagnostic accuracy, evaluate treatment response, and anticipate complications, thereby supporting more precise management strategies for parathyroid carcinoma.

Highlight :

- Elevated calcium and PTH are the key biochemical disturbances.
- Reduced phosphate and vitamin D indicate notable metabolic impairment.
- Trace element changes support the need for comprehensive biochemical evaluation..

Keywords : Parathyroid Carcinoma, Hypercalcemia, Parathyroid Hormone (PTH), Vitamin D Deficiency, Hypophosphatemia

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Introduction

Parathyroid carcinoma (PC) is a rare, but highly aggressive endocrine cancer affecting diagnosis and treatment. Despite being less than 1% of all cases of primary hyperparathyroidism (PHPT), it is clinically much more relevant due to the biochemical olay and the potentially fatal consequences it can cause [1]. It is unrelated to the more common hypersecretory form of parathyroid hormone (PTH), characterized by hypercalcemia, hypophosphatemia, and other renal and skeletal complications [2]. Although there exist significant biochemical and imaging advances, the disease is frequently overlooked or identified following extensive workup [3]. Epidemiologic studies have indicated that PC can occur sporadically or as part of a hereditary syndrome, such as hyperparathyroidism-jaw tumor (HPT-JT) syndrome associated with CDC73 mutations [4].

While the disease has been recognized globally, geographic differences in clinical presentation and course have been reported [5]. European and Asian single-center reports also reveal a high tendency to several surgical interventions following the diagnosis of the disease, and metastases to distant organs, especially to the lungs, have a significant effect on survival. HC is the most prevalent metabolic disorder linked with PC [6].

A serum calcium level above 3mmol/L (approx. 12mg/dL) is associated with malignancy. One such investigation reported that the median serum calcium was 3.675, with serum PTH significantly greater with phosphate insufficiency in patients with PC [7]. Patients with these symptoms were said to suffer from differing damages of hypercalcemia and then nephrolithiasis, painful bones, intolerable abdominal pains, and trauma damages of the nerves. Mildly elevated PTH values (which exclude other benign parathyroid disease -- arguably the most important differential in this hyperparathyroidism case) The literature estimates PTH to most commonly be in concentrations between 3 and 10 times the upper limit of normal [8].

PTH levels in some of the most recent studies of PC patients were elevated in nearly all cases, and levels above 500 pg/mL are considered very high. In malignant cases, there will be hormone overproduction that leads to the visible chemistry profile and clinical case [9]. The leading cause of hypophosphatemia is renal phosphate wasting from PTH. An example of a biochemical marker is serum phosphate levels <2.0 mg/dL which are common in PC patients. In this disease as a result of hypophosphatemia, the patient manifests a symptom, i.e., weakened bone and skeletal architecture [10]. This implies that metabolic derangement of vitamin D in PC. Over 80% of patients have low or subnormal 25-hydroxyvitamin D (25(OH)D) levels, which can worsen the severity of the disease and lead to metabolic bone disease [11].

Active 1,25-dihydroxyvitamin D [1,25(OH)2D] from the body is only mildly low or in the normal range, as the triad of calcium, phosphate and, kidney function is in a tenuous equilibrium. Treatment can paradoxically change PTH without worsening hypercalcemia, which has clinical significance especially in cases of Vitamin D insufficiency [12]. In PC, trace elements such as iron and zinc have received little attention, assumed to reflect different, specific chemical derangements. In PHPT, zinc metabolism is altered; urine excretion is increase and serum levels are mildly lower. Iron deficiency and anemia of chronic disease lead to PTH release and stimulation of bone resorption, an effect that is easily observed in some PC patients [13].

This reflects the need to explore those other factors that may contribute to the phenotype of the disease beyond calcium and phosphorus set-point cycles, PTH, or vitamin D. Clinical evaluations point out that filling in the pancreatic cancer diagnosis has never been easy [14]. They are diagnosed inappropriately as adenomas until they show aggressive growth, recurrence or metastasis. That some of these individuals have undergone multiple unsuccessful procedures. Other classifications focus on less common causes with intrathyroidal PC, uri-parathyromatosis and other family syndromic abnormalities as advanced polish case presentations [15].

However, the role of imaging and histology is often underrated and overshadowed by other biochemical markers of evaluation. We know surgery is and always has been the gold standard procedure even with its imperfections in treatment models, even with the reality of the extreme likelihood of recidivating. One will find a middle ground between the use of chemotherapy and the more sophisticated paradigms of molecular targeting [16]. Nonetheless, it should be remembered that biochemical markers play key roles in both managing recurrence issues and diagnosing early recurrence buffers. The objective of the present study is to investigate biochemical alterations occurring in women with PC following chemotherapy and compare them to the control group patients of similar age [17].

Materials and Methods

A. Study Design and Setting

This one-year case–control study was conducted at Al-Rifai General Hospital, situated in the Al-Rifai District of Dhi Qar Governorate, Iraq, to assess changes in biomarker patterns among women diagnosed with parathyroid carcinoma while undergoing chemotherapy, relative to a cohort of healthy controls matched for age.

B. Study Population

Two hundred women were included and randomly assigned into two groups of 100 each:

1. patients group: (n =100):Female patients 55-70 years old with histopathological and clinical diagnosis of parathyroid carcinoma who receiving chemotherapy.
2. Control group (n = 100): Age-matched healthy women aged between 55–70 years old and without a history of endocrine disease, malignancies or chronic diseases.

C. Inclusion and Exclusion Criteria

1. **Criteria for inclusion:** Female, between the ages of 55–70 years, diagnosed to have parathyroid carcinoma under chemotherapy (for the patient group) and apparently healthy with absence of systemic illness (for the control group).
2. **Exclusion criteria:** Previous chronic disease (diabetes mellitus, renal failure, cardiovascular disease, autoimmune diseases), history of parathyroid surgery, or use of vitamin/mineral supplements within the previous three months.

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3. **Ethical considerations**: the Local Ethics Committee of College of Medicine, University of Thi-Qar reviewed and approved the study protocol. Al-Rifai General Hospital Administrative consent. All participants provided written informed consent before data and sample collection.

4. **Sample Collection and Laboratory Analysis:** Under aseptic precautions, fasting venous blood samples were collected. The serum was separated by centrifugation, and was analysed immediately or stored at −20 °C until analysed in the laboratory. The biochemical parameters were determined as follows:

Serum calcium (mg/dL) and phosphate (mg/dL): Both were performed via automated colorimetric assays.

a. Parathyroid hormone (PTH, pg/mL),25-hydroxyvitamin D [25(OH)D, ng/mL],1,25-dihydroxyvitamin D [1,25(OH_2)D, pg/mL]: All quantitated with commercial ELISA kits (will be provided by manufacturer).

b. Zinc (µg/dL) and iron (µg/dL): Quantified by atomic absorption spectrophotometry; and standard quality control measures.

Statistical analysis Data are expressed as mean ± SD. Group differences were analyzed using an independent Student's t-test with a cutoff for significance of $p < 0.05$. Distribution was examined with the SPSS v. XX (IBM Corp, Armonk, NY, USA).

Results

A. Measuring Study Variables

The study sample consisted of 200 women aged 55-70 years, who were divided into two equal groups, of which 100 were patients without parathyroid carcinoma (age-matched controls) and 100 patients with a histopathologically confirmed parathyroid carcinoma who were on chemotherapy. To generate comparability, the groups were constructed to be as equivalent as possible, apart from health status; hence, study participants were free of chronic systemic illness [18].

A striking disparity was noted when blood biochemical markers and tests of the control group were compared with those of parathyroid cancer patients. Blood calcium (13.8 ± 1.2 versus 9.5 ± 0.5 mg/dL; $p < 0.001$) and PTH (520 ± 180 versus 45 ± 15 pg/mL; $p < 0.001$) were significantly higher in patients. Skeletal DMP1L in mice with insulin resistance reveals a selective reduction of phosphate studies of patient cohort show evidence of reduced serum phosphate as well ($p<0.001$, 1.9 ± 0.3 vs. 3.8 ± 0.4 mg/dL) [19]. There was uneven distribution of some vitamin D metabolites by group. Levels of 25(OH)D were lower in patients (18 ± 6 vs 30 ± 8 ng/mL; $p = 0.002$). As expected, 1,25($OH)_2$D was lower in patients than controls (30 ± 10 vs. 48 ± 12 pg/mL; $p = 0.010$), but less so than for 25(OH)D. Trace element analysis showed variation in zinc and iron levels [20]. Serum zinc concentration was less in patients than in controls (70 ± 12 vs. 95 ± 15 µg/dL; $p = 0.020$). Serum iron levels dropped in the patient group (65 ± 18 vs. 110 ± 25 µg/dL; $p = 0.015$). Chemotherapy and tumour progression appear to damage secondary metabolism and nutritional data were consistent with this [21] (Table 1).

Table 1. Biochemical Parameters in Female Patients with Parathyroid Carcinoma Under Chemotherapy Compared to Healthy Controls**.**

Parameter	Healthy Controls (n=100)Mean ± SD	Parathyroid Carcinoma Patients (n=100)Mean ± SD	p-value
Serum Calcium (mg/dL)	9.5 ± 0.5	13.8 ± 1.2	<0.001
Serum Phosphate (mg/dL)	3.8 ± 0.4	1.9 ± 0.3	<0.001
PTH (pg/mL)	45 ± 15	520 ± 180	<0.001
25(OH)D (ng/mL)	30 ± 8	18 ± 6	0.002
1,25($OH)_2$D (pg/mL)	48 ± 12	30 ± 10	0.010
Zinc (µg/dL)	95 ± 15	70 ± 12	0.020
Iron (µg/dL)	110 ± 25	65 ± 18	0.015

Notes:

1. Values are expressed as *Mean ± Standard Deviation*.
2. Both groups included only **female participants aged 55–70 years**.
3. None of the participants had a history of chronic diseases.
4. Significant differences ($p<0.05$) were observed in calcium, phosphate, PTH, vitamin D, zinc, and iron between patients and controls (Fig 1,2,3,4,5,6,7).

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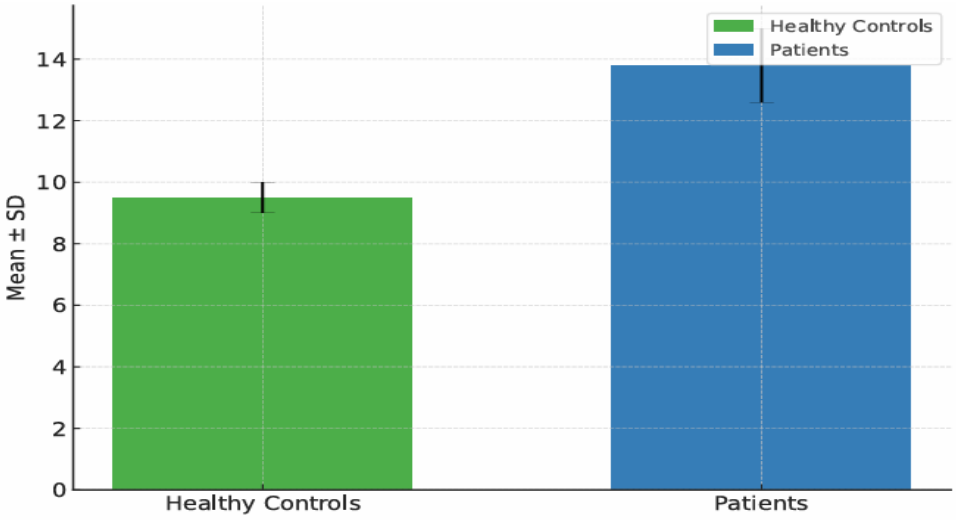

Figure 1. Serum Calcium (mg/dL) levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

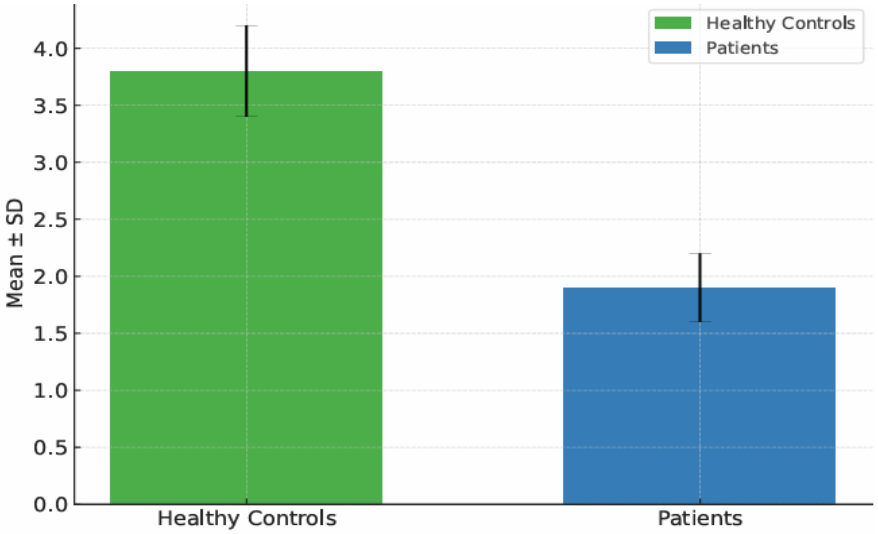

Figure 2. Serum Phosphate (mg/dL) levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

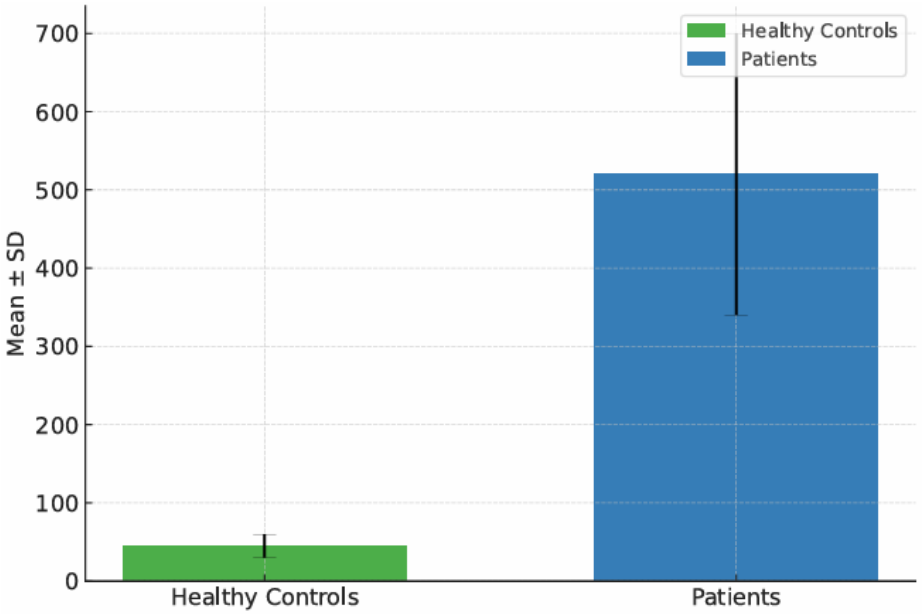

Figure 3. Serum Parathyroid Hormone (PTH, pg/mL) concentrations in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

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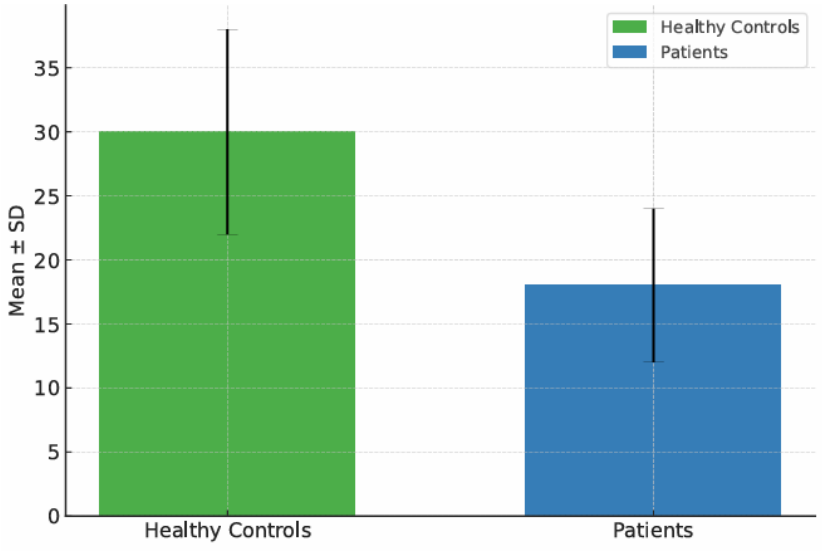

Figure 4. Serum 25-Hydroxyvitamin D [25(OH)D, ng/mL] levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

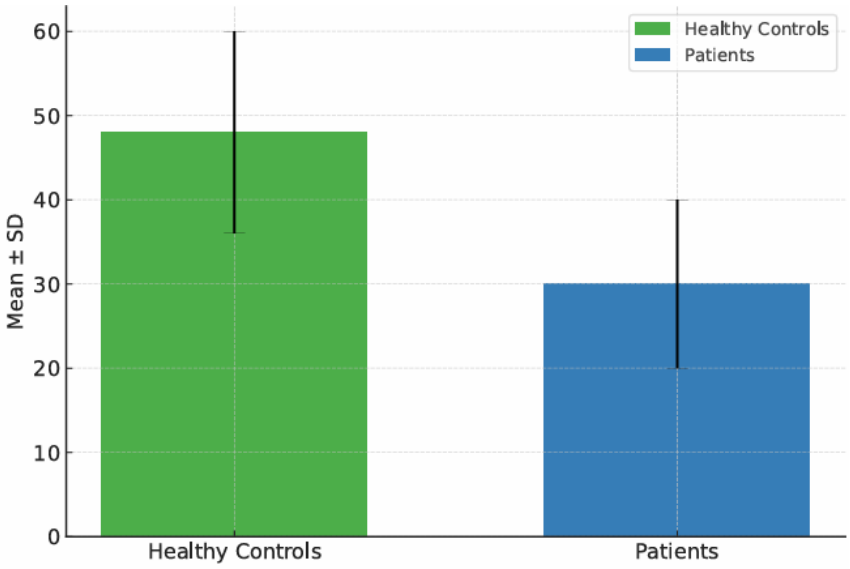

Figure 5. Serum 1,25-Dihydroxyvitamin D [1,25(OH)2D, pg/mL] levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

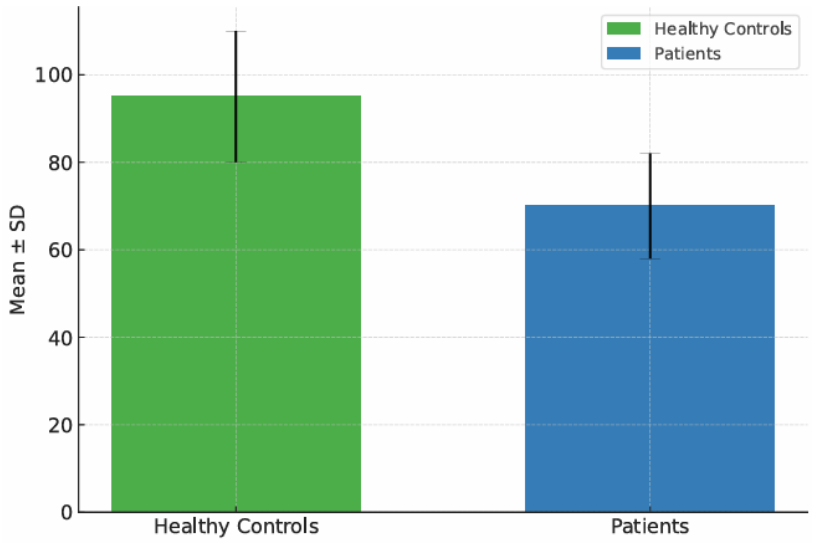

Figure 6. Serum Zinc (µg/dL) levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls.

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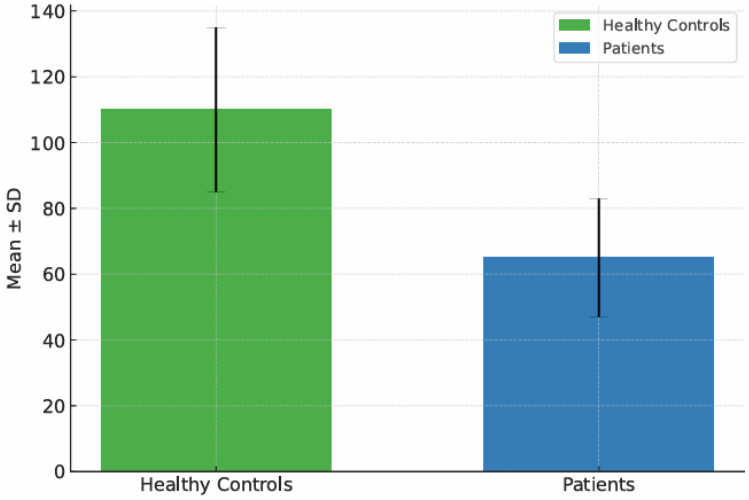

Figure 7. Serum Iron (µg/dL) levels in female patients with parathyroid carcinoma under chemotherapy compared to healthy controls

Discussion

This study investigated biochemical changes in women aged 55-70 years with parathyroid carcinoma (PC) on chemotherapy and gender-matched controls without chronic conditions [22]. Results also further showed that patients suffering from PC had broad metabolic derangements with substantial increases in serum calcium and parathyroid hormone (PTH) as well as large reductions of serum phosphate and 25-OH vitamin D and alterations of trace elements such as Zn and Fe. The findings are also consistent with the literature, indicating that aldosterone-producing adenomas (APA) represent an uncommon but malignant form of endocrine neoplasm with unique biochemical features [23].

Prostate cancer (PC) is characterized by hypercalcemia (HC), which may represent the most frequently seen biochemical abnormality in PC patients. Patients with PC had significantly higher calcium levels (13.8 ± 1.2 mg/dL) compared with controls (9.5 ± 0.5 mg/dL) ($P < 0.001$); therefore, our investigation consisted of a total of 15 patients with PC and 51 controls [24]. These data are in line with previous studies indicating that hypercalcemia is an almost inescapable aspect of parathyroid malignancy. As the mechanism of disease has been characterized previously, because a large efflux of PHT from malignant parathyroid cells results in hypercalcemia [25]. The amount of PTH was six times higher in group PC (520 ± 180 pg/mL vs 45 ± 15 pg/mL, $p < 0.001$). Recall that parathyroid carcinoma is characterized by hypercalcemia determined as result of high PTH. Using this approach, we found superphysiological levels that were comparable to those described in earlier series in which PTH is continuously elevated more than ten times over the normal upper limit of normal, a property that is often found in neoplasms [26].

Serum phosphate was significantly lower in patients with PC (1.9 ± 0.3mg/dL) than controls (3.8 ± 0.4mg/dL; $p<0.001$). PC relates to hypophosphatemia due to increased renal phosphate wasting associated with PTH production restraining renal phosphate reabsorption. Phosphate deficiency contributes to the pathogenesis of demineralized bone and to congenital skeletal dysplasia's that impact the most afflicted PS population [27]. Similarly, several metabolites of vitamin D were also highly altered in the PC group. Blood 25-hydroxyvitamin D [25(OH)D] levels were significantly lower in patients than in controls (18 ± 6 vs. 30 ± 8 ng/mL; $P = 0.002$). Men with PC had lower bioactive 1,25(OH)2D (1,25-dihydroxyvitamin D) levels compared with controls (30 ± 10 pg/mL vs. 48 ± 12 pg/mL, $p = 0.010$). Vitamin D deficiency, which further aggravates skeletal-related abnormalities as well as metabolic disorders, also characterizes excess PC patients [28].

Progression of carcinogenesis resulted in a large degree of change in the heat maps of trace element concentrations, including zinc and iron. Results: Serum levels of zinc were lower in the PC group (70 ± 12 µg/dL) than in controls (95 ± 15 µg/dL, $p = 0.020$). Specimens from PC patients showed reduced iron mg/dL (65 ± 18 vs 110 ± 25; $p = 0.015$) compared to controls [29]. These data suggest that some trace element imbalance, particularly deficiencies in zinc and iron, may be associated with developing PC disease [30]. Zinc deficiency affects some metabolic pathways, while iron deficiency stimulates the secretion of PTH, which inhibits the function of osteoblasts and enhances bone resorption [31].

Together, these results delineate an actionable biochemical signature of PC with immediate translational applications for diagnosis, therapeutic selection, and monitoring. This can help with the diagnosis, as PCA with chronic secondary hyperparathyroidism has a very different biochemical profile (high calcium, high PTH, low phosphate and low vitamin D metabolites). These biomarkers may assist in differentiating PC from adenomas and other causes of hyperparathyroidism (PHPT) [32].

The second reason is the availability of new therapeutic options that can be used to treat vitamin D, zinc and iron deficiency in patients with PC which can possibly improve the overall care of the patients. Vitamin D supplements are also effective for various diseases pertaining to bones and help improve global metabolism [33]. While lower levels of zinc and iron are widespread problems experienced by these PC patients the prospect of dietary supplementation as an approach to combating the effect of such restriction in affecting response to chemotherapy is virtually impossible. Due to a lack of underlying systemic chronic comorbidities in the older women, changes in biochemistry can be more precisely attributed to cancer. This advantage minimizes the risk of confounders interfering with interpretation of biochemical change and so, it is very useful for disease diagnosis and follow-up in this population [34].

The findings are in line with some other regional studies on parathyroid carcinoma. The biochemical profile of this cohort of patients parallels those reported for patients with PC in the rest of Asia (intrapthyroidal carcinoma or synchronous parathyromatosis are more common in western populations) [35]. These findings are broadly generalizable, consistent across most major subsets of males, and can be translated to inform global therapeutic use of biomarkers for the diagnosis and management of PC. Study limitations include genetic analysis. For parathyroid carcinoma, alterations in many of the genes, notably CDC73, are associated with the disease [36]. Additional investigation incorporating genetic profiling, better imaging modalities, and extended follow-up may identify the pathophysiologic pathway by which PC confers distant sequellae [37].

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Conclusion and Recommendations

We provide the first evidence for profound biochemical derangements in the context of parathyroid cancer in women receiving chemotherapy. PC has unique biochemical features such as increased calcium and PTH whereas phosphate, vitamin D metabolites, and trace elements are reduced. These findings may help in the diagnosis and follow-up of PC as well as perhaps starting new possibilities for treatment should vitamin D, zinc and iron insufficiencies appear to be determining factors linked to greater ovarian production of androgens among those patients. In a large multicenter cohort, using these exciting new developments in genetic profiling and imaging we could further validate the current findings and study how these tools can be employed to optimize the management of parathyroid carcinoma.

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