

Prevalence and incidence of primary hyperparathyroidism in Bahrain: A retrospective study from one medical center

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Abstract

OBJECTIVES: Primary hyperparathyroidism (PHPT) is considered the third endocrine disorder worldwide. However, the incidence of PHPT is variable in different populations. Since there are no studies on PHPT performed in Bahrain or the surrounding Arab Middle Eastern countries, this study aimed to determine the prevalence and incidence of PHPT and its variants in Bahrain.

METHODS: A retrospective study was conducted over a 3-year period (2018-2020) at the Bahrain Defense Force Military Hospital. Patients' data with normal kidney function, age 14 years and older, and had related laboratory results (calcium, PTH, phosphorus, and vitamin D) were retrieved and analyzed for prevalence and incidence of hypercalcemia and PHPT according to age and sex.

RESULTS: Out of 9650 patients, 417 patients had corrected hypercalcemia. Of these, 240, 125, and 88 patients per 100,000 had classic, non-classic, or early/normocalcemic PHPT, respectively. These numbers resulted in a prevalence of PHPT of 274 per 100,000 in Bahrain. The age-adjusted incidence of all types of PHPT was 179 per 100,000/year. Overall, PHPT incidence, whether classic or not, significantly increased in the 50 years age group and above (OR 1.023 with 95% CI 1.013-1.033). Furthermore, hypercalcemia and non-classic PHPT were predominant in females than males. Lastly, vitamin D level was significantly less in classic PHPT than the non-classic variant.

CONCLUSION: The high prevalence and incidence of PHPT should alarm physicians and clinical practices in Bahrain and the Middle East region to investigate routinely for classic and non-classic PHPT to control and manage the complications that arise from PHPT. However, more epidemiological studies in the Middle East region are warranted to investigate the reasons behind the high incidence of PHPT.

INTRODUCTION

The parathyroid gland, located in 4 small glands posterior to the thyroid gland, is the gland that regulates calcium homeostasis by secreting parathyroid hormone (PTH). PTH has three prominent roles in calcium homeostasis. PTH a) stimulates bone resorption, and therefore, increasing serum calcium and phosphorus levels, b) stimulates hydroxylation of 25 hydroxy calciferol to 1,25-dihydroxy calciferol, vitamin D, in which vitamin D stimulates calcium intestinal absorption, and c) increases the reabsorption of calcium and excretion of phosphorus from the kidney tubules. This calcium homeostasis becomes imbalanced when PTH secretion is not normal. Of these, primary hyperparathyroidism (PHPT) which is a relatively common endocrine disorder that results in hypercalcemia. PHPT usually occurs due to benign parathyroid adenoma with a possible multiglandular disease, but also some risk factors are associated with the development of PHPT (Bilezikian *et al.* 2018).

The diagnosis of PHPT has been improved over the last five decades after introducing auto-analyzers for routine biochemical testing (Arya *et al.* 2021). Since then, the classic PHPT clinical phenotype has changed from overt bone and renal consequences to asymptomatic hypercalcemia (Silva *et al.* 2018). Furthermore, non-classic variants with hypercalcemia and normal PTH or normocalcemia with high PTH have emerged (Walker *et al.* 2018; Schini *et al.* 2020).

The incidence of PHPT has been shown to be variable in different populations. Some showed 2-4 per 10,000 adults, whereas others have reached 80-90 per 10,000 (Wermers *et al.* 1997; Clarke BL 2013; Yeh *et al.* 2013). Furthermore, the prevalence of PHPT tripled in women and men from 1995 to 2010 reaching 232.7 per 100,000 women, and 85.2 per 100,000 men (Yeh *et al.* 2013). Furthermore, PHPT incidence increased with age and was more frequent in females than males (Yeh *et al.* 2013).

During our clinical work, we observed the possibility of high PHPT cases in Bahrain. Furthermore, we did not find studies on PHPT that have been performed in Bahrain or the surrounding Arab Middle Eastern countries. Therefore, this study aimed to determine the prevalence and incidence of PHPT and its variants in Bahrain. Furthermore, since the complications of PHPT are mainly long term-effects due to bone resorption and hypercalcemia effect on the kidneys and the cardiovascular system, the present study should alarm physicians and clinical practices of the incidence rate of PHPT and the consequent complications that arise from it.

MATERIALS AND METHODS

Study Protocol and Design

A study protocol was submitted and approved by the Research & Research Ethics Committee at the Royal Services of Bahrain Defense Force (BDF) Military Hospital in January 2021. This study is a retrospective cohort conducted at the Royal Medical Services of BDF, whereby all patients' laboratory data record between January 1, 2018, till December 31, 2020 were retrieved.

Subjects and Laboratory Data

The inclusion criteria were set for patients 14 years old and above and have a normal kidney function (estimated GFR >60 ml/min). All subjects' records attending BDF hospital for calcium, phosphate, PTH and vitamin D during January 1, 2018 till December 31, 2020 were retrieved.

Data Collection

All the laboratory results and demographic data were obtained from electronic medical records using a data collection tabulation. Measured laboratory variables including PTH, calcium, phosphate, albumin, and vitamin D were retrieved.

Data Analysis

The incidence was defined as the number of new cases of PHPT per year divided by the number of outpatients and admitted to BDF for the that year. Furthermore, we performed a descriptive statistical analysis based on the skewness score of > 2. For laboratory data parameters with Skewness >2, results were expressed as median (interquartile range, IQR), otherwise data were expressed as mean (\pm SD). Categorical data were reported as percentages. To test for significance, ANOVA for means or the non-parametric Kruskal-Wallis test for medians was used to compare the quantitative variables among groups. To identify risk factors associated with the development of hypercalcemia and PHPT, a multinomial logistic regression model was applied with the adjustment for covariates such as age. The estimated effect was reported by adjusted odds ratios (ORs) with their 95% confidence intervals (95%

Tab. 1. Demographic characteristics of the study population

Parameter	Value	Percentage
Age	48.3 \pm 19.2	-
Sex	Males	58.9
	Females	41.1
Nationality	Bahraini	79.5
	Indian	4.7
	Pakistani	4.4
	Syrian	1.6
	Jordanian	1.5
	Bangladeshi	1.5
	Yemeni	1.0
	Sudanese	0.9
	British	0.5
	Philippines	0.4
	American	0.2
Others	3.6	

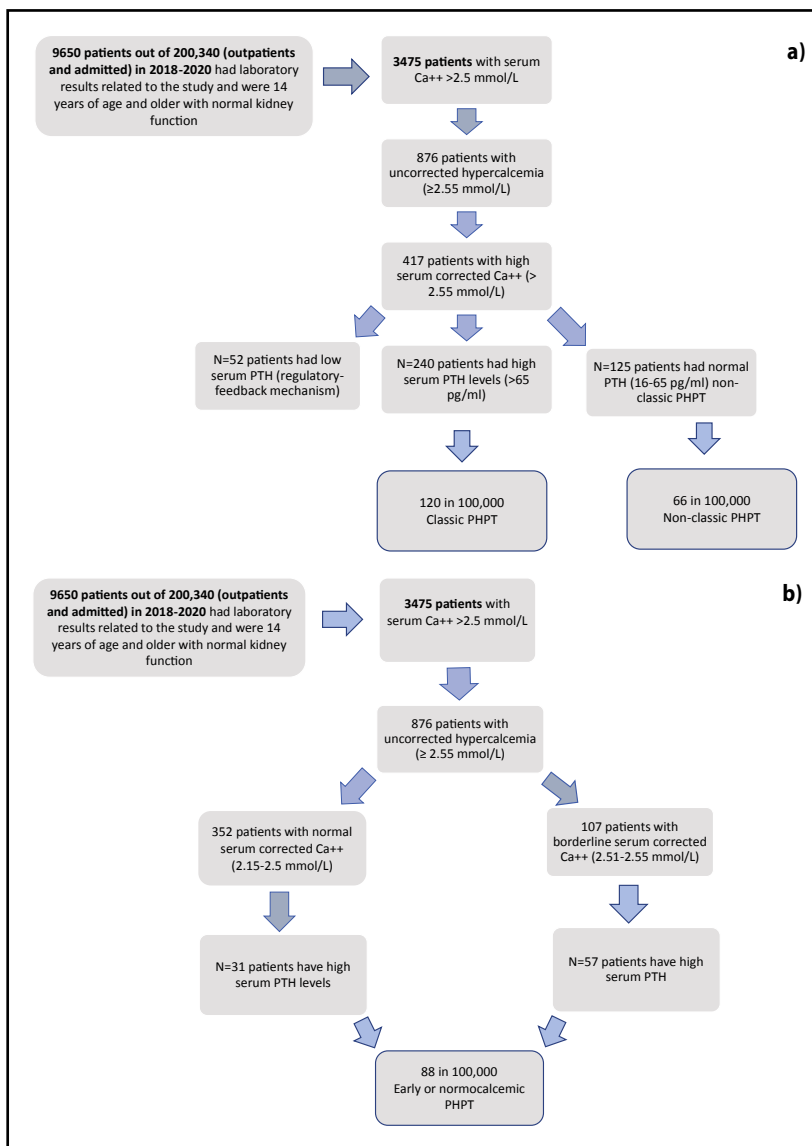


Fig. 1. Flow chart of how the study was performed. Patients were selected, categorized according of their hypercalcemia (a) or normocalcemia/ borderline serum calcium level (b), followed by their classification to classic PHPT, non-classic PHPT, or early/normocalcemic PHPT.

CI). A p-value of < 0.05 was considered to be statistically significant. All analyses were performed using SPSS 25 statistical package.

RESULT

Study population with hypercalcemia and prevalence of PHPT

During the 3-year period (2018-2020), 200,340 patients were either visited the outpatient clinic or admitted BDF hospital and have laboratory data in their names. Of these, 9650 patients with normal kidney function, age 14 years and older had related laboratory results (calcium, PTH, phosphorus, and vitamin D) were retrieved. The mean age of these patients was $48.3 (\pm 19.2)$ years old, and 58.9% were males and 41.1% were females. Most of the patients (79.5%) were Bahrainis (Table 1).

Within 9650 patients, 3475 patients had serum calcium level $> 2.5 \text{ mmol/L}$ and 876 patients had

uncorrected serum calcium levels of $> 2.5 \text{ mmol/L}$ (Fig 1a). Following correcting serum calcium values with albumin, 417 patients had high serum calcium concentrations. Of these, 240 patients had high PTH levels within 6 months period, indicating that these patients had classic PHPT. Furthermore, 125 patients were hypercalcemic but with normal PTH values within 6 months period implying that these patients had a non-classic PHPT. The last group of hypercalcemic patients (12.5%) had low PTH values suggesting a negative feedback for hypercalcemia.

From the 876 patients with uncorrected hypercalcemia, 352 patient's calcium were corrected to be normal, and 107 patient's calcium levels were on the upper high borderline (Fig 1b). Of these, 88 patients with normal or high borderline corrected serum calcium level had high PTH within 6 months period suggesting either early or normocalcemic PHPT (Fig. 1b). Therefore, the overall prevalence in Bahrain during 2018-2020 was 274 in 100,000 (Fig.1a &1b).

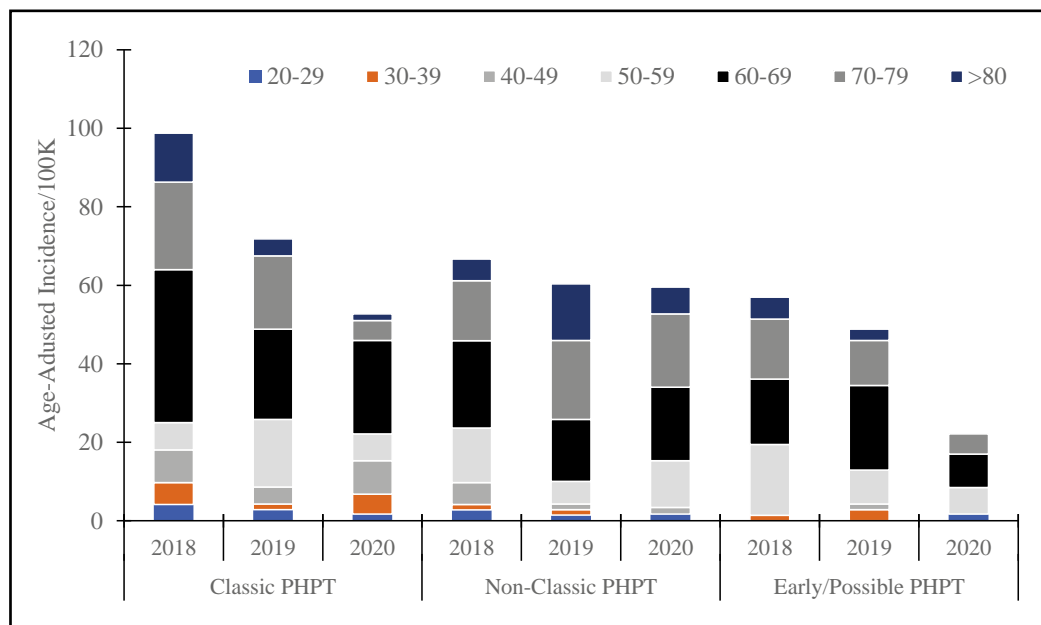


Fig. 2. Age adjusted incidence per 100,000 classified according to their PHPT status per each year.

Age-adjusted incidence of PHPT in relation to age and gender

The age-adjusted incidence per 100,000 of all types of PHPT, classic, non-classic, and early or normocalcemic PHPT in 2018, 2019 and 2020 were 222, 182, and 134, respectively, averaging into 179 per 100,000 (Fig. 2). Overall, the incidence of PHPT, whether classic or not, significantly increased in the 50 years age group and above (OR 1.023 with 95% CI 1.013-1.033). Furthermore, it was clear that the highest incidence-age of PHPT was between 60-69 years followed by 70-79 years and then 50- 59 years (Fig. 2). However, the maximum incidence of PHPT and in both sexes, was in the sixth decade. Besides, no PHPT cases in either sex was observed below the age of 20 years.

Hypercalcemia and PHPT in males and females

Most of the patients with hypercalcemia (93.8%) were Bahrainis. The incidence of hypercalcemia significantly increased with age (OR 1.034 with 95% CI 1.023-1.45 (Table 2). Furthermore, the incidence of hypercalcemia is more often to occur in females than males (Table 2). Following categorizing the subjects according to their serum calcium status, normocalcemic subjects were

younger than hypercalcemic subjects and even patients with the upper borderline calcium level (Table 3). These hypercalcemic subjects were categorized to classic and non-classic PHPT according to age and sex (Fig. 3a). In normocalcemia patients, high PTH/Early PHPT was more pronounced in the 50-59 years age male group, whereas it was more apparent in the 60-69 years age females. Furthermore, the percent of women with non-classic PHPT were significantly higher than men with non-classic PHPT ($p<0.01$). On the other hand, the frequency of classic PHPT was similar in both sexes.

Serum vitamin D and Phosphorous levels in hypercalcemia and PHPT

Vitamin D and phosphorus serum levels did not significantly change in patients with different calcium status (Table 4). In classic PHPT, however, vitamin D level was significantly less than in non-classic PHPT or regulated hypercalcemia ($p<0.05$). Furthermore, serum vitamin D levels did not significantly differ between males or females in any of the calcium status. On the other hand, serum phosphorus level was significantly higher in classic PHPT ($p<0.001$) more than in non-classic PHPT or regulated hypercalcemia (Table 4).

Tab. 2. Univariate analysis of age and gender of calcemic condition

Parameter	Calcemic Categorization	OR	CI 95%	P value
Age	Normocalcemia	Ref	Ref	Ref
	Borderline	1.016	1.002-1.030	<0.05
	Hypercalcemia	1.034	1.023-1.045	<0.001
Gender* (M to F)	Normocalcemia	Ref	Ref	Ref
	Borderline	0.745	0.478-1.161	n.s.
	Hypercalcemia	0.596	0.429-0.827	<0.01

*Adjusted with age

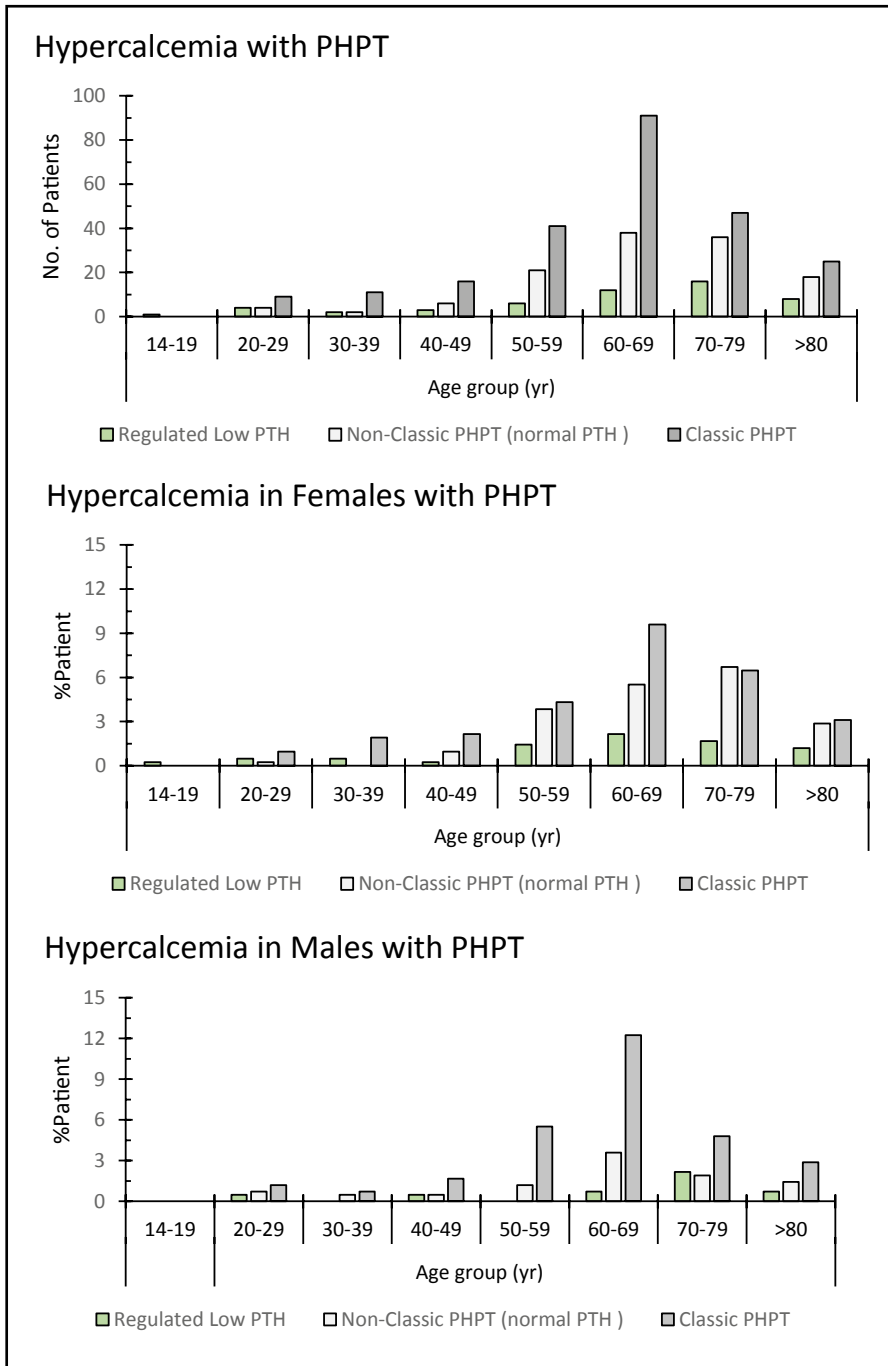


Fig. 3a. The age-distribution of patients who developed hypercalcemia with either classic, non-classic PHPT or high PTH/early PHPT, and the percentage of male and female patients in each condition.

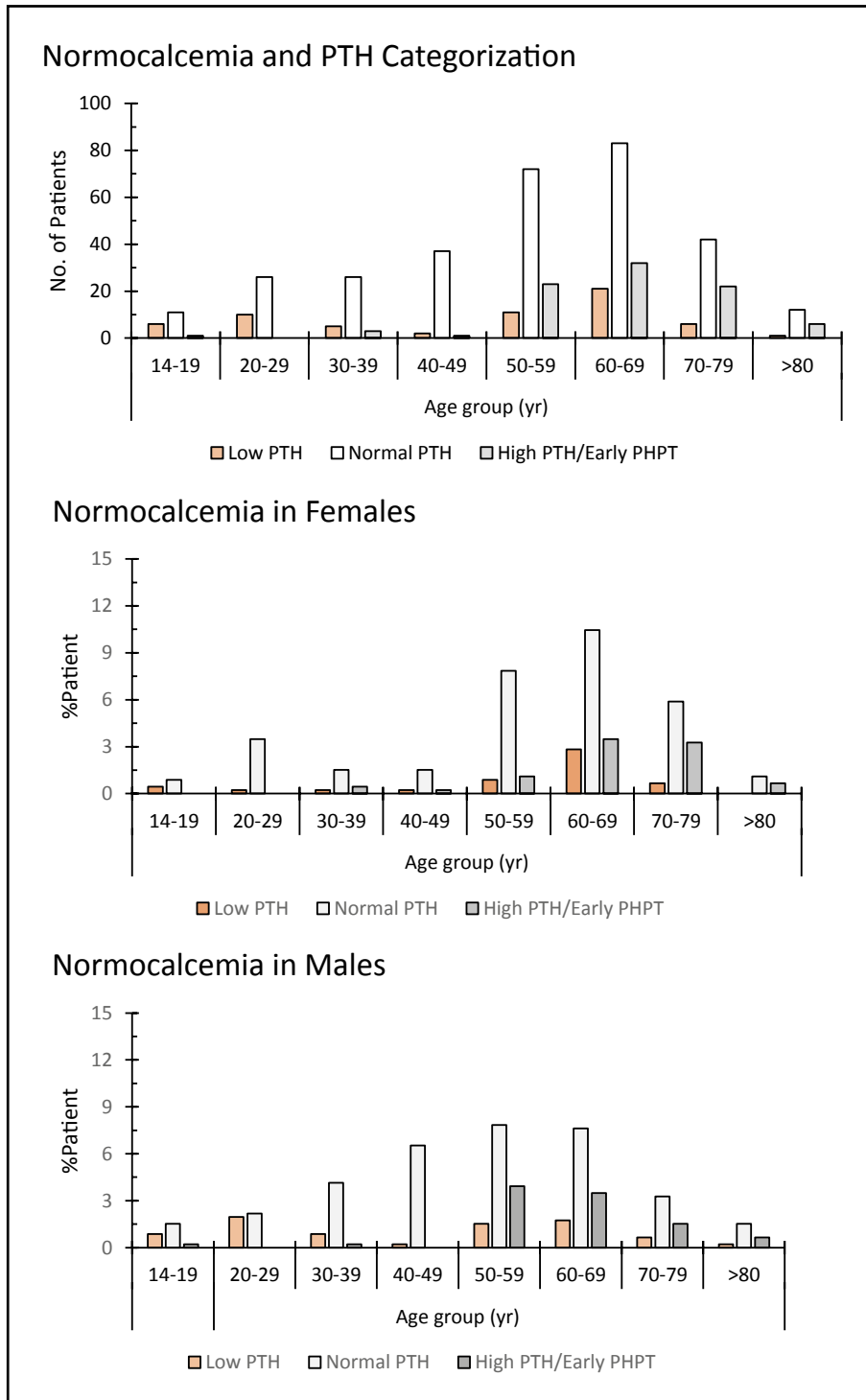
DISCUSSION

To the authors' knowledge, this is the first study in the Arab Middle Eastern country that investigated the prevalence and incidence of hyperparathyroidism. In the present study, the overall prevalence was 274 per 100,000 and the age-adjusted incidence of PHPT in Bahrain was 222, 181, and 134 in 100,000 patients for 2018, 2019, and 2020, respectively, whereby most (85-90%) of the PHPT cases occurred in 50 years of age and older. The latter incidence numbers were higher than those reported from a racially mixed population in the USA (110/100k patient in 2010) or Denmark (31/100k in 2010) (Yeh

et al. 2013; Abood & Vestergaard 2013), but somewhat less than those reported in Scotland (300/100k in 2013) and Spain (295/100k in 2017) (Collier et al. 2017; Darba et al. 2020).

Although the incidence of PHPT increased from mid-1990s to the end of the first decade of the 2000s, it fluctuated yearly (Yeh et al. 2013; Abood & Vestergaard 2013; Collier et al. 2017; Walker et al. 2018; Darba et al. 2020). Herein, the PHPT incidences in 2019 and 2020 were less than in 2018. However, it should be noted that in 2020 it was during the COVID-19 pandemic, and the percent of outpatients dropped 20%, which would be in part for the lower incidence rate of PHPT in 2020.

Fig. 3b. The age distribution of patients who had normocalcemia with either classic, non-classic PHPT or high PTH/early PHPT, and the percentage of male and female patients in each condition.



The incidence of PHPT is more common with aging and in females more than males. For instance, the incidence at least in females steadily increased from 1991 to 2010, especially in women aged 50 years and above (Yeh *et al.* 2013). Similarly, a recent study from Spain showed that PHPT incidence increased from 200 to 300 from 2003 to 2017, and most of this increase due to increased incidence in females (Darba *et al.* 2020). In the present study, hypercalcemia and non-classic PHPT incidences, but not the classic PHPT, were higher in females than in

Bahraini males. However, why the incidence of classic PHPT in females and males in Bahrain's population was equivalent remains to be explained. On the other hand, it should be noted that the most common endocrine disease, such as thyroid dysfunction in Bahrain, affects females three times more than males (Abdulla *et al.* 2020).

It is known that the most common cause of hypercalcemia in ambulatory patients is PHPT (Lafferty FW 1991). In the present study, 57.6% of hypercalcemic

Tab. 3. Biochemical results of patients classified according to serum calcium status

Parameter	Serum Calcium Status			P value
	Normocalcemia	Borderline	Hypercalcemia	
Age	54.2 ± 17.1	59.4 ± 16.3*	63.8 ± 14.5*	p<0.001
Sex	M 21.9% F 18.3%	M 5.7% F 6.5%	M 20.7% F 26.9%	p<0.01
PTH (pg/ml)	29 (23)	36 (53)*	79 (139)**	p<0.001
Calcium (mmol/L)	2.43 (0.08)	2.53 (0.02)*	2.70 (0.19)**	p<0.001
Phosphorus (mmol/L)	1.20 (0.27)	1.25 (0.47)	1.29 (0.72)	n.s.
Vitamin D (nmol/L)	53 ± 23.8	60 ± 25	52 ± 29	n.s.

patients had a classic PHPT. A similar percentage (51.5%) was reported in the racially mixed population (Yeh *et al.* 2013). Also, in the present study, 53.3% of borderline hypercalcemic patients and only 8.8% of normocalcemic patients had high serum PTH. These percentages suggest the importance of measuring serum PTH levels in borderline hypercalcemic patients as well as overt hypercalcemic for detecting PHPT before bone fracture and other PHPT health consequences would occur (Yeh *et al.* 2013; Schini *et al.* 2020). On the other hand, the non-classic PHPT patients were 30% of the hypercalcemic group with normal serum PTH levels. This large percentage of patients require more attention regarding serum calcium, PTH, and bone density measurements to prevent bone fractures in non-classic PHPT.

Since the diagnosis of PHPT has been improved following the introduction of auto-analyzers and routine biochemical testing became more, finding patients with asymptomatic PHPT grew to be higher (Wu & Yeh 2016; Arya *et al.* 2021). For instance, in China, the percentage of asymptomatic PHPT increased from <21% to approximately 50% in 10 years (Zhao *et al.* 2013). However, in other countries such as India, only 10% of PHPT were reported to be asymptomatic cases (Arya *et al.* 2021). Although in the present study, we did not investigate the percentage of asymptomatic PHPT, which is a limitation of the study, a possible higher percentage than 20% of asymptomatic PHPT does exist.

The latter assumption is because BDF hospital serves military, government, and BDF staff and their relatives for no or low cost. Thus, there is no financial burden on the patient to do biochemical testing.

Several studies reported that serum vitamin D levels in males and females from the Middle Eastern region were lower than those in the western world (Mallah *et al.* 2011; Basel *et al.* 2013; Salman *et al.* 2021). This low vitamin D prevalence was not associated with hyperparathyroidism but was associated with lower calcium levels, low fortified vitamin D in food, religious dressing for females, and other possible genetic variations (Mallah *et al.* 2011; Bassil *et al.* 2013; Salman *et al.* 2021). Herein, the average serum vitamin D level was insufficient (i.e., <75 nmol/L). Besides, vitamin D levels in hypercalcemia and classic PHPT patients were significantly lower than the other hypercalcemic or normocalcemic subjects. Although it lacks scientific explanation, insufficient vitamin D is usually common in PHPT patients (Walker *et al.* 2018; Walker *et al.* 2015).

In conclusion, the present study showed a high incidence of PHPT. This should alarm physicians and clinical practices in Bahrain and the Middle East region to routinely investigate classic and non-classic PHPT to control and manage the complications arising from PHPT. However, more epidemiological studies in the Middle East region are warranted to investigate the reasons behind the high incidence of PHPT.

Tab. 4. Biochemical results of hypercalcemia patients classified according to their PTH

Parameter	Hypercalcemia Status			P value
	Regulated Hypercalcemia	Non-classic PHPT	Classic PHPT	
Age	63.4 ± 18.5	66.01 ± 13.6	62.7 ± 13.9	n.s.
Sex	M 5.6% F 7.9%	M 9.8% F 20.1%	M 29.0% F 28.5%	p<0.01
PTH (pg/ml)	10 (7)	34 (21)*	147 (169)**	p<0.001
Calcium (mmol/L)	2.77 (0.45)	2.68 (0.17)*	2.70 (0.17)	p<0.001
Phosphorus (mmol/L)	1.11 ± 0.45	1.10 ± 0.40	1.54 ± 0.59*	p<0.001
Vitamin D (nmol/L)	61 ± 36	56 ± 31	45 ± 22*	p<0.05

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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