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RESEARCH ARTICLE

THE PREVALENCE OF SECONDARY AND TERTIARY HYPERPARATHYROIDISM AMONG PATIENTS WITH CHRONIC RENAL FAILURE WHO ATTEND AL ZAWIYAH KIDNEY HOSPITAL FOR HEMODIALYSIS

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ABSTRACT

A descriptive, cross-sectional study was designed to determine the prevalence of secondary and tertiary hyperparathyroidism among patients with chronic renal failure who attend Az Zawiyah Kidney Hospital for hemodialysis. The duration of hemodialysis, blood level of iPTH (intact parathyroid hormone), calcium and phosphate were considered. This study has found that, among the fifty patients, forty-seven of them have hyperparathyroidism, and 35 patients from these 47 patients has tertiary hyperparathyroidism. While, only 12 patients have SHPT. However, the level of iPTH was much higher among patients with SHPT than that among patients with tertiary hyperparathyroidism. Moreover, there was a significant coefficient correlation between iPTH level and the duration of hemodialysis among the 47 patients (p-value≤0.05). In CKD SHPT develops, because parathyroid gland tries to correct the calcium-phosphorus imbalance by releasing more and more of parathyroid hormone. This continues stimulation of the parathyroid gland causes increase of the gland's size and hyperplasia of its cells, which lead to tertiary hyperparathyroidism. CKD patients must have a good follow up and they should take a proper supplements and prophylaxes drugs to avoid the development of secondary hyperparathyroidism in order to decrease their morbidity and mortality.

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INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem around the world [(1)]. The diagnosis is made based on abnormalities in a marker of kidney function or structure in which the Kidneys can lose function as a result of a physical injury or a disease such as hypertension or diabetes mellitus (DM). Once the kidneys have damaged, they cannot filter blood or perform other activities. This is usually associated with proteinuria or decrease of estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m2) for more than three months, with health effects [(1,2)]. The National Kidney Foundation 2002 classified CKD into five stages according to estimated GFR (eGFR) as shown in Table 1. In 2012, the recommended guidelines for prescribing chronic kidney diseases do not depend only on the GFR category but also albuminuria category. Parathyroid gland secrets parathyroid hormone (PTH), which is composed of a polypeptide protein [(3)] PTH maintains calcium, phosphate, and bone mineralization by promoting calcium reabsorption in the renal tubules, calcium uptake in the gut , calcium mobilization from the bones, and excretion of phosphate by the kidneys[(4)]. Therefore, the secretion of parathyroid hormone is depended on the calcium and phosphorus levels. Renal hyperparathyroidism (RHPT) is a common complication of CKD, which characterizes by calcium, Phosphorus, and vitamin D imbalances in patients on hemodialysis. RHPT is classified into two types according to the level of serum calcium of the patients [(5)]. Secondary hyperparathyroidism (SHPT) is occur when, phosphate retention is increased and the synthesis of active 1,25-dihydroxyvitamin D is decreased leading to rising the concentration of phosphate and reducing concentration of the ionized calcium both stimulate the secretion of parathyroid hormone (PTH) [(4,6)]. Secondary hyperparathyroidism is affecting more than half of the patients with stage 3 or 4 CKD [(4,7)]. Tertiary hyperparathyroidism is caused by functioning parathyroid cell autonomously leads to hypersecretion of parathyroid hormone (PTH). This functioning parathyroid cell autonomously is occurred in patient with secondary hyperparathyroidism who has hemodialysis for long time [(8,9)]. Thus, in tertiary hyperparathyroidism, the excessive secretion of PTH is not caused by the disturbance of calcium or phosphorus levels, and patients have normal calcium level. Approximately 90% of CKD patients suffer from Secondary or tertiary hyperparathyroidism with end-stage kidney disease (ESRD).[(10,11)] Renal Hyperparathyroidism (RHPT) related with ESRD can cause; Itching, muscular pain, fibrosis osteitis, cardiovascular disease ,and tissue calcifications . During last decade, many observational studies have found that abnormalities in mineral and bone metabolism are associated with an increase in cardiovascular morbidity and mortality in hemodialysis patients [(12)]. Recently, Studies have indicated this increase significantly in cardiovascular mortality in those patients is due to secondary hyperparathyroidism[(13)].

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Table 1. Classification of CKD stages according to National Kidney Foundation in 2002

CKD stage	Description	GFR (ml/min/1.73 m2)
1	Kidney damage with normal or increased kidney function	≥ 90
2	Kidney damage with mildly diminished kidney function	60 – 89
3	Moderately reduced kidney Function	30 – 59
4	Severely decreased kidney Function	15 – 29
5	Kidney failure	< 15

Table The minimum, maximum, mean and SD of calcium, phosphate, iPTH and duration of hemodialysis of all patients

Variable	N	Minimum	Maximum	Mean	Std.
Ca+. level	50	7.13	10.16	8.6920	.73596
Ph+. Level	50	3.09	15.84	6.4482	2.30319
iPTH level	50	24.63	4612.00	710.0902	759.79926
Duration of hemodialysis	50	1	9	3.4400	1.7

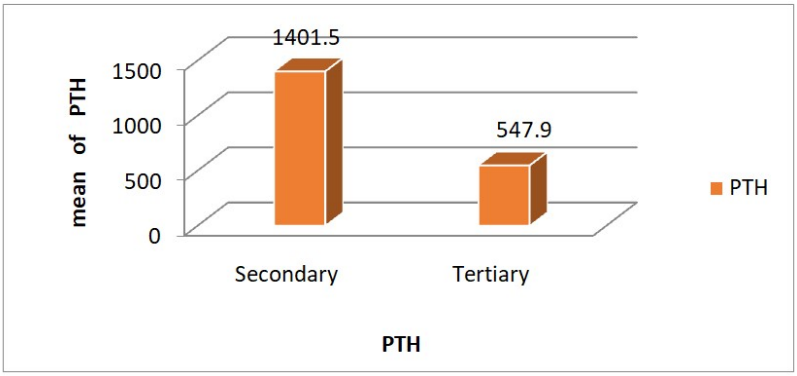

Figure 1. The level of iPTH among patients with secondary and tertiary hyperparathyroidism. The mean of iPTH is higher in patients with secondary than that of patients with tertiary

Moreover, those patients are suffering from; metabolic lipid abnormalities, impaired insulin sensitivity, hypertension, cardiac hypertrophy and fibrosis, myocardial calcium deposition, valvular calcification, and vascular stiffness and calcification [14]. The aim of this study is to detect the prevalence of secondary and tertiary hyperparathyroidism in end- stage chronic kidney disease patients who are on hemodialysis, and to find the relation between hyperparathyroidism and the duration of dialysis in those patients.

METHODS

A descriptive, cross-sectional study was designed to examine the prevalence of secondary and tertiary hyperparathyroidism among patients with chronic renal failure who attend Az Zawiyah Kidney Hospital for hemodialysis regularly. Patients are undergoing hemodialysis in the hospital three times a week, and they take the needed supplements as vitamin D, calcium, iron, folic acid as well as erythropoietin. Patients who included in this study were chosen randomly from both genders and aged ≥ 18 years old. Some of the patients have started hemodialysis years ago, however, others have started hemodialysis just few months ago. The duration of hemodialysis for patients who included in the study ranged between (1- 9 years). In addition to demographic characteristics: age, gender and duration of Hemodialysis, the blood level of iPTH (intact parathyroid hormone), calcium and phosphate were measured. Blood samples were collected from 50 patients in August 2022. The samples were analyzed at IBN RUSHD LABORATORY, where serum iPTH, serum calcium and serum phosphate were measured for the fifty patients. Serum iPTH level between 10–73 was considered normal, serum calcium level between 8.4–10.2 was considered normal and serum phosphate level between 2.7–4.5 was considered normal[15]. As mentioned before secondary hyperparathyroidism (SHPT) is when parathyroid hormone level is high and calcium level is low while phosphate level is high. However, tertiary hyperparathyroidism is when parathyroid hormone level is high while calcium level is within normal or high and phosphate level is within

RESULTS

The fifty patients who included in this study were adults; the mean of age is 48 years old with standard deviation (SD) 14.54. Thirty-four of the patients are males while females are sixteen from total 50 patient.

Calcium, phosphorus, iPTH and duration of hemodialysis of all patients in the study: The level of serum calcium, phosphorus and iPTH of the fifty patients were detected. The calcium levels of the patients were ranged from low (7.13) to normal level (10.16) and the mean was about 8.7. However, The phosphorus levels of all patients were ranged from normal level (3.09) to extremely high level (15.84) and the mean was about 6.45. As well as, the iPTH levels of the patients were ranged from normal (24.63) to extremely high level (4612) and the mean was about 710, as shown in Table 1.

Hyperparathyroidism among the patient of this study: Among the fifty patients, forty-seven of them have high parathyroid hormone level (more than 73). As mentioned in the method, the criteria of classification of hyperparathyroidism is depend on the level of calcium and phosphate. Secondary hyperparathyroidism is when iPTH level is high, phosphate is high, and however the calcium level is low. While tertiary hyperparathyroidism is when iPTH level is high, however, calcium and phosphate levels are within normal. This study has found that 35 patients from total patient with hyperparathyroidism (47), has tertiary hyperparathyroidism. However, only 12 patients have secondary hyperparathyroidism. In addition, the study found that the level of parathyroid hormone (iPTH) is much higher among patients with secondary hyperparathyroidism than that among patients with tertiary hyperparathyroidism, as shown in Figure 1.

Secondary Hyperparathyroidism: The twelve patient who have secondary hyperparathyroidism are from both gender; eight males and four females.

The serum calcium levels of the twelve patients were low, ranged from (7.13 to 8.38) and the mean was about 7.8. However, the phosphorus levels of these patients were high, ranged from (4.61 to 15.84) and the mean was about 7.7. As well as, the iPTH levels of the patients were extremely high, ranged from (549.7 to 4612) and the mean was about 1401.6, as shown in Table 2.

was about 6.3. In addition, the iPTH levels of the patients were high, ranged from (85.11 to 1552.3) and the mean was about 548, as shown in table 4. On the other hand, the study shows a significant coefficient correlation between iPTH level and the duration of hemodialysis in the patient with tertiary hyperparathyroidism where the correlation significant (p-value ≈ 0.01<0.05), as shown in Table 5 and Figure 3.

Table 2. The minimum, maximum, mean and SD of calcium, phosphate, iPTH levels of the patients with secondary hyperparathyroidism

Variable	N	Minimum	Maximum	Mean	Std.
Ca+. level	12	7.13	8.38	7.7825	.48737
Ph+. Level	12	4.61	15.84	7.7367	2.96961
iPTH level	12	549.70	4612.00	1401.5583	1207.71629

Table 3. Shows the coefficient correlation between iPTH level and the duration of hemodialysis in patient with secondary hyperparathyroidism

Pearson Correlation	0.424*
Sig. (2-tailed)	0.024
N	12

* Correlation significant at 0.05

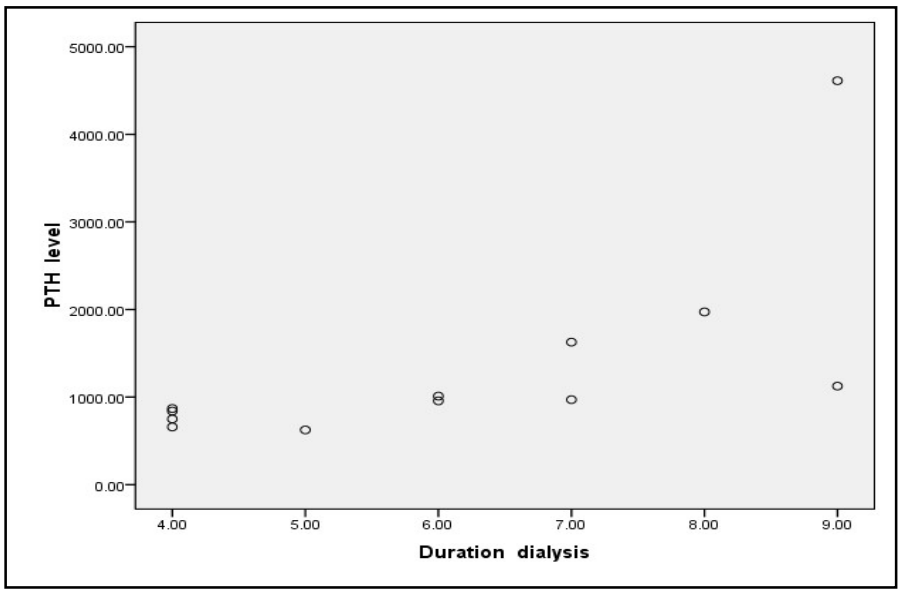

Figure 2. Shows the coefficient correlation between iPTH level and the duration of hemodialysis in patient with secondary hyperparathyroidism

Table 4. The minimum, maximum, mean and SD of calcium, phosphate, iPTH levels among patients with tertiary hyperparathyroidism

Variable	N	Minimum	Maximum	Mean	Std.
Ca+. level	35	7.98	10.07	8.9766	.50708
Ph+. Level	35	3.45	11.00	6.2571	1.77949
iPTH level	35	85.11	1552.30	547.9460	359.37122

Table 5. Shows the coefficient correlation between iPTH level and the duration of hemodialysis in patient with tertiary hyperparathyroidism

* Correlation significant at 0.01

Pearson Correlation	0.691**
Sig. (2-tailed)	0.0071
N	35

On the other hand, there was a significant coefficient correlation between iPTH level and the duration of hemodialysis in the patient with secondary hyperparathyroidism where the correlation significant (p-value= 0.024 <0.05), as shown in table 3 and Figure 2.

Tertiary Hyperparathyroidism: The thirty-five patients who have tertiary hyperparathyroidism are from both gender; twenty-two males and thirteen females. The serum calcium levels of the thirty-five patients were within normal level, ranged from (7.98 to 10.07) and the mean was about 9. However, the phosphorus levels of these patients were ranged from normal at 3.45 to high at 11 and the mean

DISCUSSION

This study was conducted to detect the prevalence of secondary and tertiary hyperparathyroidism in CKD patients who are on hemodialysis. The present study has found that forty-seven patients among the fifty patients who involved in the study have an increase in parathyroid hormone level (hyperparathyroidism). Aforementioned in the method, the criteria for the classification of hyperparathyroidism (secondary or tertiary) depends on the level of calcium and phosphate. In addition, this study has observed that prevalence of secondary

hyperparathyroidism is quite lower than tertiary hyperparathyroidism, where only 12 patients have secondary hyperparathyroidism while 35 patients have tertiary hyperparathyroidism (about 74.5 % of total patients with hyperparathyroidism).

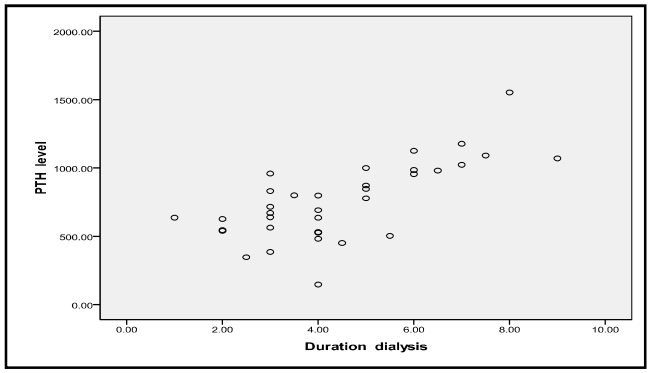

Figure 3. Shows the coefficient correlation between iPTH level and the duration of hemodialysis in patient with tertiary hyperparathyroidism

The twelve patients with SHPT in this study are from both gender and they have an increase in phosphorus levels and decrease in calcium levels, as shown in table 2. This increase of phosphorus levels in these patients is due to decrease of its excretion in the urine , promoting the risk go on the development of SHPT in hemodialysis patients [16]. On the other hand, phosphorus accumulation enhances the secretion of fibroblast growth factor 23 (FGF-23) and reduces active vitamin D, which causes decrease of calcium uptake in the gut, and lower calcium concentration in the blood. This imbalance in calcium and phosphorus homeostasis and decrease of vitamin D level, stimulate the parathyroid gland to secrete more PTH resulting in secondary hyperparathyroidism (SHPT)[4] **.** In addition, patients with SHPT have extremely high levels of iPTH when they compared with iPTH levels of patients with tertiary hyperparathyroidism, as shown in figure 1. That occurs due to parathyroid gland tries to correct the calcium phosphorus imbalance by releasing more and more of parathyroid hormone. When the patients with SHPT do not get a good follow up to treat and correct this mineral imbalance (vitamin D deficiency, hyperphosphatemia and hypocalcemia), that leads to increase of PTH secretion. Moreover, Hyperphosphatemia for long time has a direct stimulating effect on the cells of the parathyroid gland, resulting in nodular hyperplasia of the gland. Thus, the parathyroid glands will increase the secretion of PTH even if the phosphate level return to the normal, this called tertiary hyperparathyroidism**.**

Tertiary hyperparathyroidism occur when the size of the parathyroid glands progressively increases gradually, which is positively correlated with serum PTH levels. The gland increase in size is primarily due to diffuse cell hyperplasia, but there is also the growth of the monoclonal chief cell, which leads to the formation of nodules. Nodular hyperplastic glands have fewer VDRs and CASRs compared with diffusely hyperplastic glands, a fact increases parathyroid gland resistance to calcium and calcitriol. Because autonomous parathyroid glands function in some patients, PTH levels remain high persistently although calcium is within the normal range or even above normal [4,17], as shown in Table 4. Many studies have found that to prevent the development of SHPT in CKD patients, the dietary phosphate should be limited. As a first step, CKD patients should avoid the dietary products that rich with phosphate as meats, beans, dark sodas, and nuts. Many foods containing high phosphorus are also essential sources of protein, especially meats. In general, patients must avoid foods that are high in phosphorus but not rich in protein. Because reducing the protein source can lead to hypoalbuminemia, which has been associated with increased morbidity and mortality in CKD. Secondary, CKD patients should take calcium supplements, as well as, vitamin D therapy to avoid the over stimulation of PTH secretion [18]. Finally, if the patients have an increase of PTH, they should take Cinacalcet to reduce serum calcium and PTH [19]. Cinacalcet works by binding to and altering the calcium-sensing receptor (CaSR) on the chief cell of the parathyroid gland. This change causes an increase in the sensitivity of the receptor to calcium in the blood, which leads to reduced concentrations of iPTH and decreasing serum calcium and phosphorus levels [20] . In patients with tertiary hyperparathyroidism .There are no guidelines for treatment, but the main indication for treatment is continuous hypercalcemia and the increase of PTH level and the primary treatment is surgery. The goal of surgical treatment is to decrease the cell mass of parathyroid gland thus decrease PTH secretion and normalize the serum calcium concentration. Studies found that Patients on chronic hemodialysis, in 15% and 35% of patients after 10 years and 35 years from the start of hemodialysis required parathyroidectomy for control hyperparathyroidism. As well as, this study has found a significant correlation between the duration of hemodialysis and the development of hyperparathyroidism, and this correlation was stronger with tertiary hyperparathyroidism.

CONCLUSION

Chronic kidney disease (CKD) is one of common health problems in the entire world, its prevalence about 13% globally [1]. Chronic kidney disease causes physiological changes in minerals metabolism, the calcium and phosphorus imbalance is the most important complication of CKD. This imbalance and the deficiency of vitamin D in CKD patients cause an increase of stimulation of PTH secretion, as a physiological mechanism to correct this imbalance. CKD patients must have a good follow up and they should take a proper supplements and prophylaxes drugs to avoid the development of secondary hyperparathyroidism in order to decrease their morbidity and mortality.

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