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Research Article

# SECONDARY HYPERPARATHYROIDISM AMONG END-STAGE RENAL DISEASE PATIENTS

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**ABSTRACT**

**Objectives:** The study aims to determine the incidence of secondary hyperparathyroidism (SHPT) in chronic kidney disease patients, the correlation between creatinine, parathyroid hormone (PTH) and phosphate, and calcium in renal disease.

**Methods:** A retrospective cross-sectional study was performed, a total of 100 hemodialysis patients' reports were analyzed from January 2019 to December 2019, at Hebron Governmental Hospital, in Hebron, Palestine. The patients' data were collected, including creatinine level, calcium, and phosphorus in addition to PTH concentrations. Twenty-five healthy persons with normal kidney function were also included in the study as a control for comparison. Statistical Package for the Social Sciences version 22 was used to analyze the data. T-test and Pearson's tests were used to study the results. R (Pearson's test) was used to determine the correlation between creatinine, PTH, phosphate, and calcium.

**Results:** The mean values of serum of creatinine, phosphate, calcium, and PTH were determined for both patients and the control. Levels of PTH were significantly higher in kidney failure patients and positively correlated with creatinine and phosphate. However, levels of PTH were significantly negatively correlated with calcium. All patients included in the study have very high levels of PTH PTH. This increase might be due to many factors that contributed to the hypersecretion of PTH. The correlations between these predisposing factors of SHPT are explained.

**Conclusion:** The study showed that SHPT is common among patients with end-stage renal disease. The most complications of SHPT are mineral and bone metabolism disorders and cardiovascular diseases. Thus, early detection and treatment of SHPT may control these complications.

**Keywords:** Chronic kidney disease, Secondary hyperparathyroidism, Parathyroid hormone, Calcium, Phosphate, Creatinine, Vitamin D.

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## INTRODUCTION

There is a relationship between kidney failure and secondary hyperparathyroidism (SHPT) which should be considered to prevent any consequences such as mineral and bone metabolism disorders and cardiovascular diseases. SHPT is known to be one of the complications of kidney failure. Usually, patients that start from stage three of kidney failure, their glomerular filtration rate (GFR) is less than 60 (mL/min/1.73 $m^2$) [1]. This causes an imbalance of Vitamin D, calcium, parathyroid hormone (PTH), phosphorus, and fibroblast growth factor 23 (FGF 23) concentrations in the blood [2]. In the context of the pathophysiology of kidney failure, there is a decrease in the concentration of Vitamin D due to a reduction in the production of the 25-Hydroxyvitamin $D_3$ 1-alpha-hydroxylase (VD3 1A hydroxylase) enzyme that converts 25-hydroxy Vitamin D to 1,25-dihydroxy Vitamin $D_3$ ($1,25(OH)_2D$) [3]. This effect decreases the absorption of calcium and causes hypocalcemia. However, this situation can activate the parathyroid gland and enhances the secretion of PTH; as a compensation effect for a deficiency of calcium in the body. The improper nephron function may cause a decrease in the excretion of phosphorus in the urine and increases the reabsorption to the blood, leading to hyperphosphatemia. Besides, this situation increases the concentration of FGF, which further decreases $1,25(OH)_2D$ levels by decreasing the expression of VD3 1A hydroxylase. FGF-23 acts directly on the parathyroid gland and suppresses PTH secretion through the FGFR-1-Klotho complex [4]. On the other hand, other factors can cause hyperparathyroidism, including a reduction of expression of Vitamin D receptors, calcium-sensing receptors, and FGF-23 receptors in the parathyroid glands [5]. At this stage, hyperphosphatemia decreases $1,25(OH)_2D$ and calcium (hypocalcemia), these all contribute to increasing PTH messenger ribonucleic acid levels and PTH synthesis. These changes can cause many complications, for example, stimulating osteoclast activity which, in turn, leads to a high turnover of bone disease and fragility fractures. These complications were 2–4 times more frequent in patients with SHP compared with normal individuals. However, SHP may play a causal role in the development of vascular calcifications, ischemic cardiovascular events, and cardiac failure. This research aimed to determine the relationship between renal failure and hyperparathyroidism by measuring the levels of creatinine, phosphorus, calcium, and PTH in patients with kidney failure.

## METHODS

The consent of the Palestinian Ministry of Health (MOH) was obtained for this study, which was conducted during the period from 27 February 2020 to 07 March 2020. However, a retrospective study was performed, and data were collected from the information system unit in Hebron Governmental Hospital. A total of 100 reports of hemodialysis patients from the year 2019 were included in the study. Twenty-five healthy people with normal kidney function were included as a control. The control group met the inclusion criteria, which includes normal kidney function and normal kidney profile. The clinical biochemistry profile of PTH, calcium, creatinine, and phosphate was checked for both patients and control. The Statistical Package for the Social Sciences version 22 software was used to analyze the data. A t-test was used to check the differences between patients and normal control results. R (Pearson's test) was used to determine the correlation between phosphate, calcium, creatinine, and PTH. The significant result was determined at $p<0.05$.

## RESULTS

One hundred end-stage renal disease (ESRD) patients' data were collected and statistically analyzed. Their data indicate that there are associations between different elements (creatinine, phosphate,

calcium, and PTH). The mean value of serum creatinine was found to be (10±3.02 mg/dL), while for phosphate, calcium, and PTH were (6.03±1.13 mg/dL), (7.59±0.93 mg/dL), and (975.1±408 mg/dL), respectively. Twenty-five healthy persons with normal kidney functions were also statistically analyzed as normal control and their data were compared with kidney failure patients. The mean value of calcium was found to be (8.9±05 mg/dL) for the control, while their data for phosphate and PTH were found to be (4.14±0.61 mg/dL) and (53.96±12.7 mg/dL), respectively, as shown in Figs. 1 and 2. It was found that 32% (32 patients) had a normal level of serum calcium compared to the normal range which is (8.5–10.2 mg/dL), while 68% (68 patients) found to have serum calcium less than 8.5 mg/dL, as shown in Fig. 3. A Scatter plot shows that PTH has a significant negative correlation with calcium ($p<0.05$) (Fig. 4). Results show that there is a significant negative correlation between phosphate and calcium ($p<0.05$), as shown in Fig. 5. Data show that 28 patients (28%) had a normal level of serum phosphate, 2% (two patients) had a phosphate <3.5 mg/dL, and most patients (70 patients) had a high level of phosphate compare to the normal range which is (3.5–5.5 mg/dL). The 70 patients who have a high level of phosphate, their serum phosphate was above 5.5 mg/dL, as shown in Fig. 6. However, the phosphorus level has a significant positive correlation with creatinine in this study ($p<0.005$), as indicated in Fig. 7. A Scatter plot also shows that PTH has a significant positive correlation between phosphate and creatinine (Figs. 8, and 9).

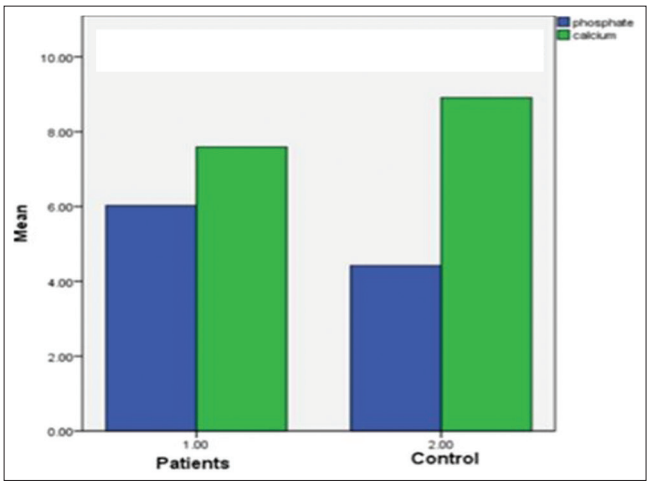


**Fig. 1: Control mean value patient mean value for calcium and phosphate**

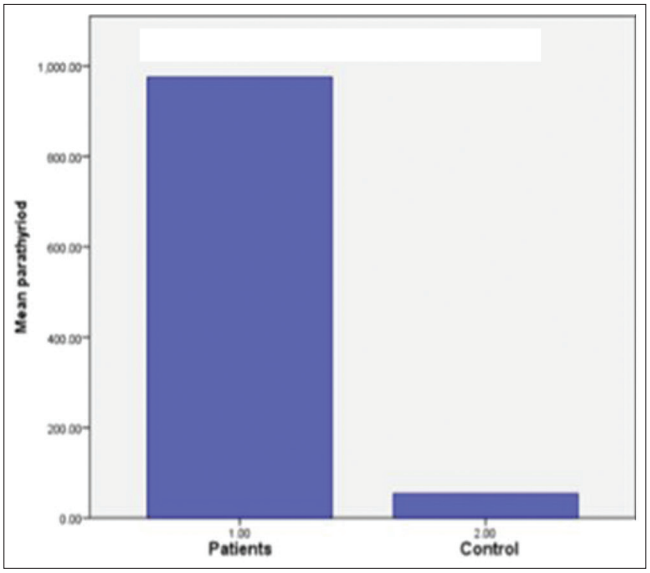


**Fig. 2: Control mean value versus patients mean value for parathyroid hormone**

## DISCUSSION

SHPT is one of the most common complications among ESRD patients that should be controlled to prevent other complications such as bone and mineral metabolism disorders and cardiovascular diseases. When the mean value of the control is compared to the mean value of patients, we have noticed that there are a significant difference in all parameters, as the mean values of phosphate and parathyroid were higher for kidney failure patients (Figs. 1 and 2), whereas the mean value of calcium (Fig. 1) was higher for control. These results confirmed that there are relationships between these parameters and SHPT as mentioned previously.

In this research study, it was found that all the patients had very high levels of PTH. The high level might be due to various factors that contributed to the hypersecretion of PTH. The correlation between these predisposing factors of SHPT is explained. Fig. 3 shows that 68% of patients have low levels of calcium, the main reason for this hypocalcemia is due to Vitamin D deficiency. It is worth mentioning that most patients have calcium levels less than the normal levels but close to the normal values; this because PTH compensates for the deficiency. For this reason, a significant negative correlation between PTH and calcium was observed, as shown in Fig. 4. On the other hand, Fig. 5 shows a significant negative correlation between calcium and phosphate, and thus phosphate levels increased. Therefore, calcium binds with phosphate and forms a calcium phosphate complex ($CaHPO_4$), this is another cause of hypocalcemia among ESRD patients.

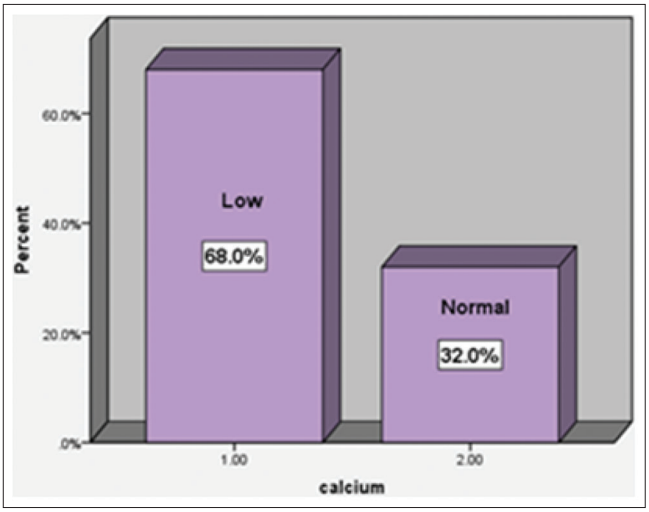


**Fig. 3: Distribution of calcium among hemodialysis patients**

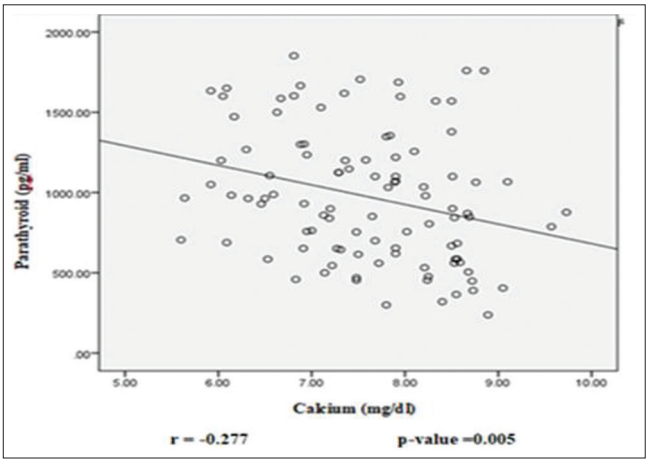


**Fig. 4: Correlation between calcium and parathyroid hormone**

Fig. 6 shows that 70% of patients have an elevation in phosphate levels (hyperphosphatemia), this situation is due to the role of FGF-23, which reduce the expression of type II sodium/phosphate cotransporters (NaPi-2a and NaPi-2c) and allow phosphate excretion [5], but FGFR1-Klotho complex is downregulated in kidneys [6]. However, this contributes to the resistance of the effect of FGF-23 and enhances phosphate retention. There is a significant positive correlation between creatinine and phosphate, as shown in Fig. 7, where Fig. 8 also shows a significant positive correlation between phosphate and PTH. This gives a further significant positive correlation between PTH and creatinine (Fig. 9).

It was found that among ESRD patients, there is low GFR, which leads to an increase in the level of creatinine, and decreased excretion of phosphate; thus, as a result, this causes hyperphosphatemia and hypersecretion of PTH by the mechanism of FGF-23. However, bone and mineral metabolism disorders occur in those patients, as PTH trying to compensate for the decline in calcium by increasing bone resorption. Cardiovascular diseases occur as a result due to the accumulation of calcium phosphate complex, leading to coronary artery calcification. Many other factors cause SHPT, not only kidney failure; these factors are not included in this study.

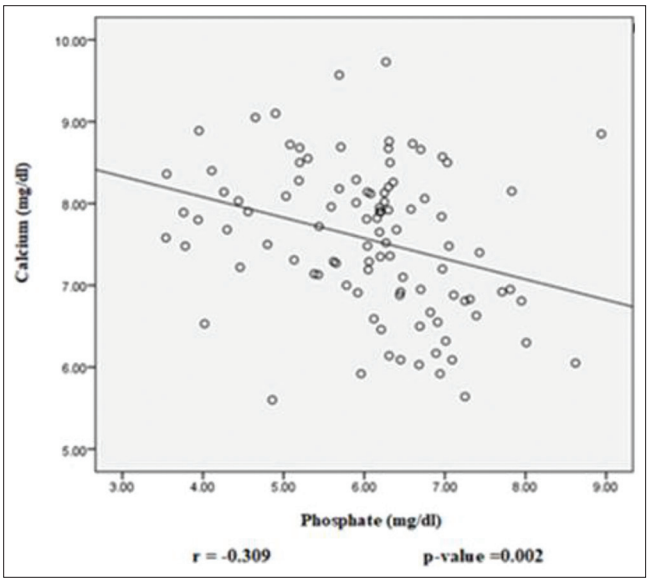


**Fig. 5: Correlation between phosphate and calcium**

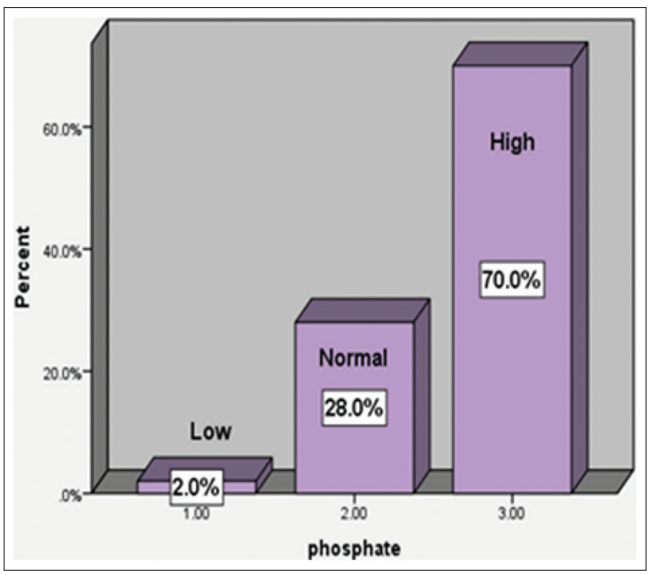


**Fig. 6: Distribution of phosphate among hemodialysis patients**

Our finding in this study was consistent with the other studies carried out in different countries [4,6]. A study by Arora *et al.* [6] was found that the mean value of calcium (7.90±1.16 mg/dL) and the mean value of phosphate was (6.44±1.72 mg/dL). Besides, in the same study, it was also found that there is a positive correlation between PTH and creatinine, and a negative correlation between PTH and calcium, which are similar to our results. Moreover, a study by Sliem *et al*. [4] was determined that the mean value of calcium was (8.2±1.05 mg/dL) and the mean value of phosphate was (5.94±1.7 mg/dL), which are also similar to our finding. Vitamin D was not included in our study because it is not measured regularly for all ESRD patients within the follow-up,

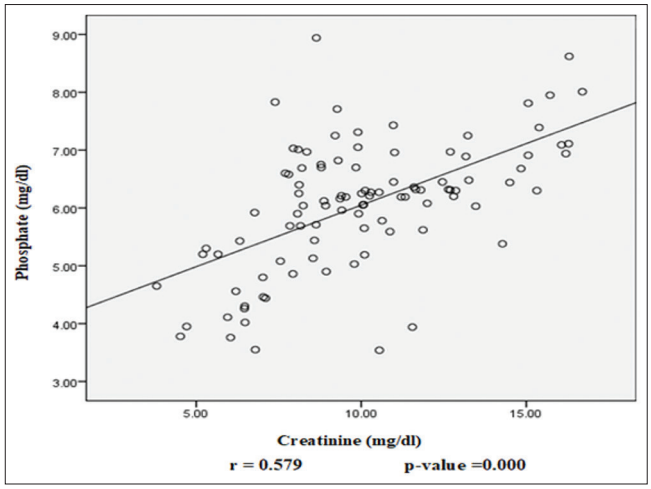


**Fig. 7: Correlation between phosphate and creatinine**

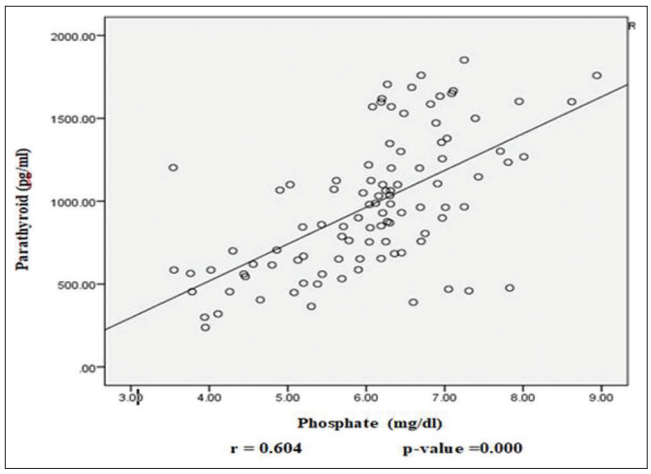


**Fig. 8: Correlation between phosphate and parathyroid hormone**

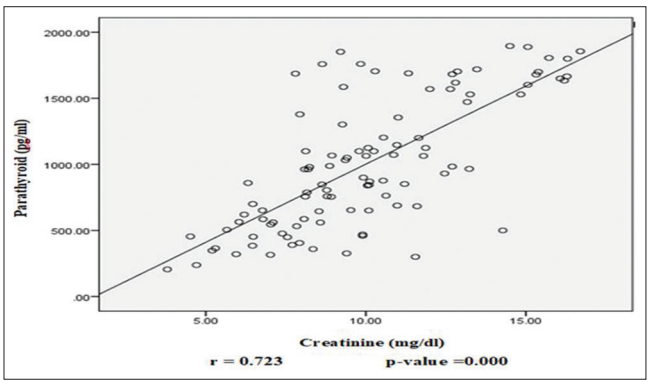


**Fig. 9: Correlation between creatinine and parathyroid hormone**

it is only measured to some patients according to the patient situation. Our study has some limitations such as it is only carried out for patient's reports in 2019 and one hospital.

## CONCLUSION

The study showed that SHPT is common among patients with ESRD. The most complications of SHPT are mineral and bone metabolism disorders and cardiovascular diseases. Thus, early detection and treatment of SHPT may control these complications. Further studies with a large sample size and different sites are needed to confirm accurately the different parameter correlations.

## ACKNOWLEDGMENT

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## ETHICAL CONSIDERATIONS

The study was approved by the Palestinian MOH. The identities of patients remained unknown and remained confidential and the data only used for research purposes.

## CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURE

The authors declare no competing financial interests and no conflicts of interest concerning the authorship and/or publication of this article.

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