

Association between Hyperparathyroidism and Intradialytic Hypertension in Prevalent Hemodialysis Patients

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ABSTRACT

Background: Over 80% of patients receiving hemodialysis have hyperparathyroidism, a common complication of chronic kidney disease (CKD) that is a major concern; given the increased cardiovascular risk and declining quality of life associated with CKD. Early stages of CKD are when the pathophysiologic mechanisms causing secondary hyperparathyroidism begin, and they intensify in direct proportion to the loss of renal function.

Objective: Investigate the association between hyperparathyroidism and intradialytic hypertension in prevalent hemodialysis patients.

Patients and Methods: We conducted a multicenter cross-sectional study at a total of 70 prevalent hemodialysis patients with hyperparathyroidism (iPTH>300), aged more than 18 years old and less than 60 years at El-Dakahlia Governorate hospitals. They have been recruited to our study design and assigned according to developing intradialytic hypertension into group 1: patients with intradialytic hypertension (n=10) and group 2: patients without intradialytic hypertension (n=60) and they were subjected to detailed medical history, examinations, and laboratory investigations.

Results: The patients with intradialytic hypertension had higher mean of weight gain (1.9 ± 0.9 kg) than patients without (0.9 ± 0.3 kg) with statistically significant differences between them as $p=0.025$. We also noted a statistically significant difference between both groups as regards the intradialytic blood pressure measurements ($p<0.05$) with a difference between post versus pre dialytic systolic blood pressure monitoring in the patients within each group ($p<0.001$). Lower mean of hemoglobin level has been detected in the patients with intradialytic hypertension with statistically significant differences between both groups as $p=0.011$.

Conclusion: Our study demonstrated that no statistically significant correlation noted between the prevalence of intradialytic hypertension and hyperparathyroidism among prevalent hemodialysis patients.

Keywords: Intradialytic hypertension, Prevalent hemodialysis, Hyperparathyroidism.

INTRODUCTION

A well-known CKD consequence that affects at least 80% of patients receiving hemodialysis is hyperparathyroidism. Given that CKD is already associated with a markedly elevated risk of cardiovascular disease and a declining quality of life, this consequence is quite concerning⁽¹⁾. Early stages of CKD are when pathophysiologic processes causing secondary hyperparathyroidism begin, and they intensify in direct proportion to the loss of renal function⁽²⁾.

Well-known changes in CKD include reduced active vitamin D production, hypocalcemia, and hyperphosphatemia, which constantly stimulate the parathyroid glands to produce more iPTH. The continual decrease in calcium-sensing receptors (CaSR) and vitamin D receptor expression in parathyroid glands caused by these triggers precedes the irreversible beginning of parathyroid gland hyperplasia⁽³⁾.

This histological change is particularly noteworthy for individuals on prevalent hemodialysis with tertiary hyperparathyroidism who have a higher possibility to develop cardiovascular incidents and musculoskeletal complications, likely bone fractures, along with the noticeable deterioration in their quality of life in addition to the augmented healthcare costs and mortality. In secondary hyperparathyroidism, the calcium deposition in the bony structure is diverted

into the blood vessels walls encouraging the development of atherosclerosis⁽⁴⁾.

As known, hemodialysis lowers blood pressure in most hypertensive prevalent hemodialysis individuals, yet some individuals develop a paradoxical rise in blood pressure monitoring during hemodialysis. This escalation in blood pressure throughout the hemodialysis session, termed intradialytic hypertension, has been identified for many decades⁽⁵⁾. There is no agreement as regard its definition, but clinical researches have lately described the intradialytic hypertension as an increase in systolic blood pressure more than ten mmHg over the level of pre-dialysis systolic blood pressure⁽⁶⁾.

The underlying pathogenesis of intradialytic hypertension, supposed to be multifactorial, remains to be determined. Researches have revealed that being older, lower dose of hemodialysis, increased cardiovascular and medical comorbidities, lower BMI, and decreased volume of intradialytic ultrafiltration were supposed to be the principal clinical features of prevalent hemodialysis patients presented with intradialytic hypertension⁽²⁾. Moreover, intravascular and interstitial volume expansion, positive sodium balance, and activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, low arterial oxygen saturation throughout the hemodialysis sessions were also considered to be additional co-factors for developing intradialytic hypertension⁽⁷⁾.

As the literature has extensively shown, hypertension is a highly frequent cardiovascular risk factor in the majority of hemodialysis patients. For these individuals, a number of pathophysiological variables have been identified. In fact, in patients receiving extracorporeal renal replacement treatment, the most common causes of high arterial blood pressure are volume overload, dialysate calcium content, and renin-angiotensin hyperactivity⁽⁸⁾.

Nonetheless, research has also been done on other hypertensive etiological ideas. The evidence of blood pressure stabilisation after parathyroidectomy has led to extensive observations of a potential pathophysiological relationship between hypertension and hyperparathyroidism⁽⁹⁾. Therefore, hyperparathyroidism-related hypertension etiology in hemodialysis patients has been examined with outstanding findings. In fact, the influence of calcium distribution abnormalities and direct hypertensive actions induced by parathyroid hormone has been seen and characterised⁽¹⁰⁾.

Notwithstanding the correlation between secondary hyperparathyroidism and intradialytic hypertension being very common in prevalent hemodialysis patients with a possible augmented rise of the cardiovascular risk and morbidities⁽¹¹⁾. These two entities are still approached in a discrete way by nephrology specialists.

The purpose of this study was to investigate the association between hyperparathyroidism and intradialytic hypertension in prevalent hemodialysis patients, addressing the role of sociodemographic characteristics, underlying medical comorbidities, and the hemodialysis history and data on increasing the possibilities to develop intradialytic hypertension.

PATIENTS AND METHODS

We conducted a multicenter cross-sectional study at a total of 70 prevalent hemodialysis patients with hyperparathyroidism (iPTH>300) aged more than 18 years old and less than 60 years at El-Dakahlia Governorate hospitals, excluding patients with an anticipated survival duration of fewer than six months and patients who were expected to undergo renal transplantation within three months following the time of recruitment, as well as patients who had a history of trauma, surgery, serious infection within the last 3 months or a settled diagnosis of active malignancies.

Have been recruited to our study design and assigned according to developing intradialytic hypertension into group 1: patients with intradialytic hypertension (n=10) and group 2: patients without intradialytic hypertension (n=60) and subjected to a detailed medical history, clinical examination and laboratory investigations.

Comparison and correlations between both groups according to sociodemographic data, underlying medical comorbidities, hemodialysis statistics (primary kidney disease, predialytic body weight and height;

inter-dialytic weight gain), peri-dialysis blood pressure measurements and monitoring were recorded and documented.

Both groups provided relevant clinical, laboratory and demographic data, which included age, gender, blood pressure and smoking history.

Drug history during the study was recorded regarding the anti-hypertensive medications as angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARBs), calcium channel blocker, beta blocker, alfa blocker and diuretics.

Measurement of blood pressure: Sphygmomanometer was used for the measurement of blood pressure in the non-arteriovenous fistula side of the upper arm, and in the dominant upper arm in patients with central venous catheters.

Intradialytic blood pressure was measured 2 hours after the start of haemodialysis session and was recorded in every hemodialysis session while **predialytic blood pressure** was measured after resting for 30 minutes before initiating the hemodialysis session and **postdialytic blood pressure** was measured immediately after the end of dialysis.

Accordingly, the peri-dialytic change in blood pressure was calculated as follows: Peri-dialytic blood pressure change = postdialytic blood pressure subtracted from predialytic blood pressure.

All patients were followed and their postdialytic blood pressures, and peri-dialytic systolic blood pressure changes were collected during each hemodialysis session. Patients with an average peri-dialytic systolic blood pressure rise of ≥ 10 mm Hg throughout a 3-month observation period were classified as having chronic intradialytic hypertension.

Routine laboratory tests at each data collection point were done through venous blood samples collected shortly before the hemodialysis session to evaluate the following parameters: hemoglobin level, serum creatinine, serum urea, BUN (blood urea nitrogen), serum phosphorus, serum potassium, serum calcium, serum sodium, serum albumin and intact parathyroid hormone (iPTH).

Ethical approval:

The study was carried out in compliance with the Declaration of Helsinki's for studies involving humans. The ICMJE and CONSORT criteria were adhered to in this clinical trial. The Ethics Committee at Ain Shams University's Faculty of Medicine accepted the procedure (Approved No.: FMASU MS 821/2022). Before beginning the trial, all patients gave written informed permission, and they were made aware of the study's procedure. Patients were also given the option to withdraw from the study at any time.

Statistical analysis

The statistical presentation and analysis of the current study were carried out using SPSS V. 20. Qualitative data were presented as frequency and percentage and were compared by Fisher’s exact test. Quantitative data were presented the mean ± standard deviation (SD) and range and were compared by student t-test. The correlation between two quantitative variables within a single group was found using the linear correlation coefficient. When it is equal to or less than 0.05, a significant p-value was taken into account.

RESULTS

The demographics of the study population included 38 males and 32 females, with an average age of 41.24 years (± 6.95 SD) and mean BMI was 28.6 kg/m² (± 1.7 SD). Among the study population, 42.9% were non-smokers with no statistically significant difference between both groups (Table 1).

Table (1): Demographic data, smoking history and BMI analysis of the studied groups.

Cases (n=70)	
Age (years)	
Range	30 – 58
Mean ± SD	41.24 ± 6.95
Gender	
Male	38(54.3%)
Female	32(45.7%)
Smoking	
Current smokers	14(20%)
Ex-smokers	26(37.1%)
Non-smokers	30(42.9%)
BMI (Kg/m²)	
Range.	23 – 32
Mean ± SD	28.6 ± 1.7

By reviewing the history of medical comorbidities in both groups, 80% of the patients in group 1 (prevalent hemodialysis patients with intradialytic hypertension) have previous medical comorbidities mostly in the form of diabetes mellitus while 46.7% of the patients in group 2 have previous medical comorbidities, which showed insignificant differences between both groups (Table 2).

On comparing both groups as regard the number of antihypertensive medication, they were compliant on, most of the patients on both groups were compliant on dual antihypertensive therapies, which showed non-statistically significant difference between both groups as well as the duration of kidney affection and the duration of being on maintenance hemodialysis sessions, which also didn't show a statistical significance between both groups (Tables 2, 3).

Table (2): Comparison between both groups as regard the previous medical comorbidities and the compliance on anti-hypertensive medications.

	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value	
Comorbidities				
Yes	8(80%)	28(46.7%)	0.085	
No	2(20%)	32(53.3%)		
Cardiac disease				
	1(10%)	9(15%)	0.209	
Liver disease				
	2(20%)	10(16.7%)		
Diabetes mellitus				
	5(50%)	9(15%)		
Anti-hypertensive drugs				
ACEI/ARBs	2(20%)	26(43.3%)	0.235	
Calcium channel blocker	3(30%)	25(41.7%)		
Beta blocker	4(40%)	31(51.7%)		
Alpha blocker	0(0%)	7(11.7%)		
Number of drugs				
Monotherapy	2(20%)	10(16.7%)	0.089	
Dual therapy	4(40%)	36(60%)		
Triple therapy	1(10%)	12(20%)		
More than 3 therapy	0(0%)	5(8.3%)		

Table (3): Comparison between both groups as regard the duration of kidney affection and the duration of being on maintenance hemodialysis sessions

	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
Duration of kidney affection (years)			
Range	4 - 10	4 - 10	0.346
Mean ± SD.	7.20 ± 1.93	6.58 ± 1.99	
Duration of being on hemodialysis (years)			
Range	2 - 9	3 - 8	0.231
Mean ± SD.	5.20 ± 1.69	4.50 ± 1.95	

Our analysis revealed a significant difference between both groups as regard the inter-dialytic weight gain, higher mean of weight gain was noticed in patients with intradialytic hypertension versus without (Table 4).

Table (4): Comparison between both groups as regard the inter-dialytic weight gain.

Weight gain (kg)	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
Range	2 - 4	1 - 2	0.025*
Mean ± SD.	1.9 ± 0.9	0.9 ± 0.3	

Statistically significant differences between both groups were noted as regard the intradialytic and postdialytic systolic blood pressure measurements, which was also noted between post versus predialytic SBP and post- versus predialytic DBP in the patients within each group (Tables 5, 6).

Table (5): Comparison between both groups as regard serial systolic blood pressure measurements and monitoring

SBP (mmHg)	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
Predialytic Mean ± SD	149.3 ± 10.3	143.9 ± 9.3	0.099
2 hours after the start of hemodialysis Mean ± SD	159.5 ± 10.1	147.6 ± 9.5	<0.001*
Postdialytic Mean ± SD	164 ± 10.4	150.5 ± 9.6	<0.001*
P-value	<0.001*	<0.001*	

*: Significant

Table (6): Comparison between both groups as regard serial diastolic blood pressure measurements and monitoring:

DBP (mmHg)	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
Predialytic Mean ± SD	75.3 ± 4.1	77.5 ± 4.4	0.137
2 hours after the start of hemodialysis Mean ± SD	75.3 ± 4.9	72.8 ± 5.3	0.168
Postdialytic Mean ± SD	77.2 ± 4.4	74.3 ± 4.1	0.034*
P-value	0.003*²	0.026*²	

*: Significant

Notably, both groups exhibited a highly significant decrease in the hemoglobin level (10.5 gm/dl ± 1.1 in group 1 versus 11.6 gm/dl ± 1.0) with P-value 0.011 and negative significant correlations have been noted with the rest of laboratory investigations (Table 7).

Table (7): Laboratory results of the study groups.

	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
S. Creatinine (mg/dL)	8.25 ± 1.40	8.26 ± 1.12	0.963
BUN (mg/dL)	63.1 ± 14.5	66.2 ± 15.1	0.245
Serum sodium (mmol/l)	135.4 ± 3.9	134.9 ± 3.1	0.544
Serum potassium (mmol/l)	5.9 ± 1.1	5.6 ± 0.9	0.631
Serum Magnesium (mg/dL)	2.8 ± 0.5	2.6 ± 0.4	0.311
Serum Calcium (mg/dL)	5.5 ± 1.0	5.2 ± 0.5	0.091
Serum Phosphorus (mg/dL)	6.4 ± 0.4	6.1 ± 0.2	0.565
Hemoglobin (g/dL)	10.5 ± 1.1	11.6 ± 1.0	0.011*
Serum albumin (g/dl)	3.7 ± 0.2	3.8 ± 0.2	0.153

*: Significant

Interestingly, patients with intradialytic hypertension had lower mean of iPTH than patients without intradialytic hypertension with statistical significant differences between them as p=0.037 (Table 8).

Table (8): Mean IPTH of the study groups.

	Patients with intradialytic hypertension (n=10)	Patients without intradialytic hypertension (n=60)	P-value
Mean iPTH (pmol/l)	633.5 ± 152.8	711 ± 168.9	0.037*

There was also significant indirect moderate correlation between iPTH and serum creatinine, serum BUN, serum potassium and serum phosphorus (Table 9).

Table (9): Correlations between intact parathyroid hormone with laboratory results.

	iPTH(pmol/l)	
	P-value	rho
S. Creatinine (mg/dL)	0.009*	-0.312
BUN (mg/dL)	<0.001*	-0.600
S. Na (mmol/l)	0.098	0.199
S. K (mmol/l)	0.017*	0.284
S. Mg (mg/dL)	0.804	0.03
S. Ca (mg/dL)	0.499	0.082
S. PO4 (mg/dL)	0.003*	-0.354
Hb (g/dL)	0.056	0.100
S. albumin (g/dL)	0.263	-0.143

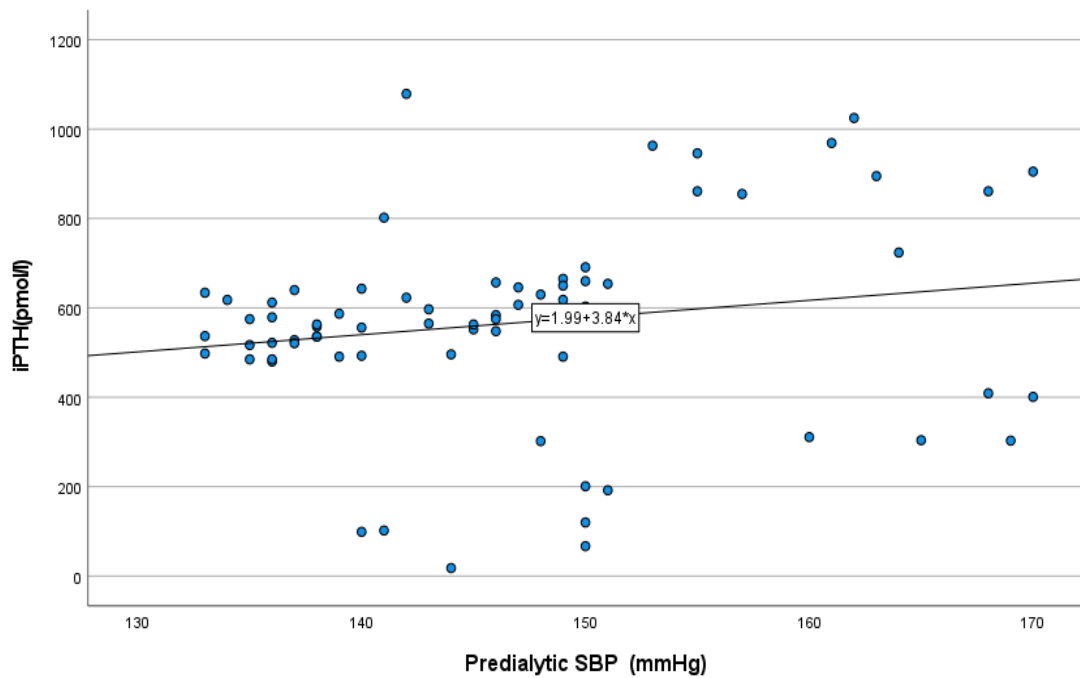


Figure (1): Correlation between iPTH and predialytic systolic blood pressure.

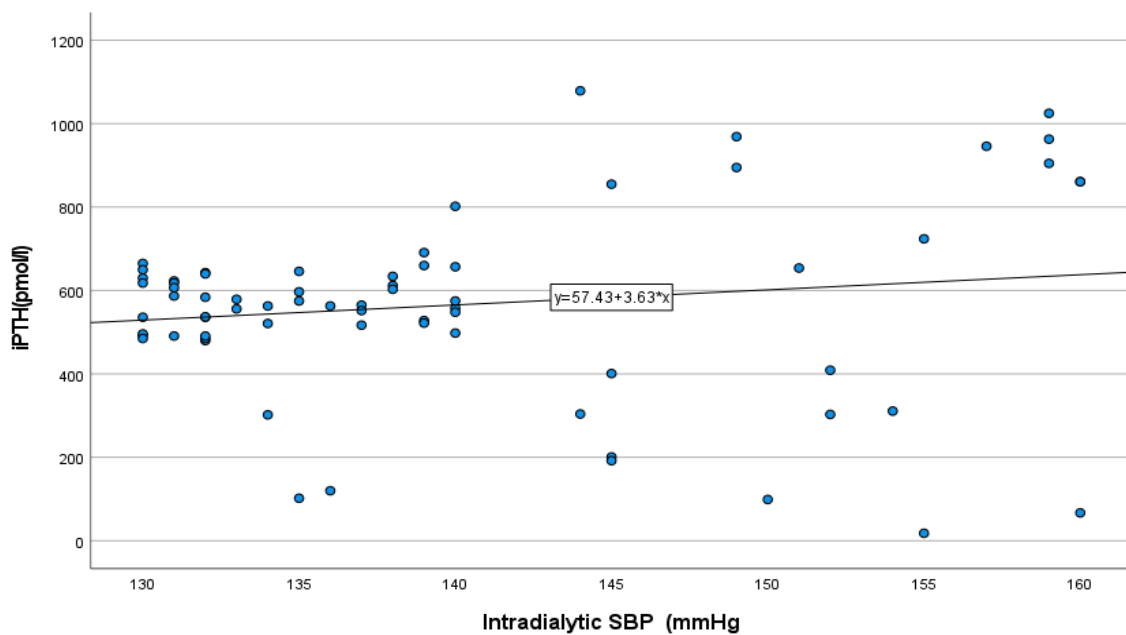


Figure (2): Correlation between iPTH and intradialytic SBP.

DISCUSSION

A portion of hemodialysis patients may exhibit hemodynamic anomalies or a paradoxical reaction to the dialysis process, which might explain the fluctuation in blood pressure during hemodialysis therapy, which is characterised by either intradialytic hypotension or intradialytic hypertension⁽¹²⁾. It has been shown that intradialytic hypertension has a larger risk of death than intradialytic hypotension, despite the fact that the latter occurs more frequently⁽¹³⁾.

Considering intradialytic hypertension as a short-term risk measure in addition to long-term mortality, it has been demonstrated that frequent bouts of intradialytic hypertension were related with higher 30-day morbidity and death⁽¹⁴⁾.

Hyperparathyroidism is one of the most common complications in CKD patients who results in a number of metabolic disorders and contributes to morbidity and mortality⁽¹⁰⁾.

Increasing PTH levels have been linked to an increased risk of hypertension, even in the absence of a PHPT diagnosis, according to earlier research. However, the precise mechanism and causal relationship remain unclear⁽¹⁰⁾.

In our cross-sectional study that was conducted at El Dakahlia Governate hospitals, 70 prevalent hemodialysis patients with hyperparathyroidism have been enrolled.

By reviewing the sociodemographic data of our study candidates, their smoking history and past history of their medical comorbidities and the non-statistically significant difference that has been noted between both groups, our results concurred with a study by **Wu et al.**⁽¹⁵⁾ that included 120 hemodialysis patients between the ages of 24 and 84 (mean age = 61.46 years) as study participants. 77.5 percent of participants were men. Among the subjects, 49.2% had common comorbidities, such as diabetes (47.5%), peripheral vascular disease (77.5%), and congestive heart failure (34.2%).

Also, by reviewing the statistics of our study, we found that 10 patients (14.3%) had intradialytic hypertension and 60 patients (85.7%) did not develop intradialytic blood pressure with the prevalence of intradialytic hypertension was 14.2% among the research population that support the findings of a study by **Raikou et al.**⁽¹⁶⁾ that was conducted on 76 patients on hemodialysis and concluded that in 5-20% of hemodialysis patients, intradialytic hypertension has been reported to be common. This also goes in the same line with a study by **Raikou and Kyriaki**⁽¹⁷⁾ that found that the prevalence of intradialytic hypertension reaches 19.7%.

Our study assessed the relation between the number of anti-hypertensive medications on which the prevalent hemodialysis patients were compliant and the possibility of developing intradialytic hypertension and found that no statistically significance differences were notes between both groups (**p value 0.08**) as most

of the patients in both groups were compliant on dual antihypertensive therapies. This goes in the same line with previous study by **Flythe et al.**⁽¹⁸⁾. It showed that intradialytic BP fluctuation was not substantially correlated with the antihypertensive number, class, or analyzability status.

This study found that individuals with intradialytic hypertension experienced a greater mean inter-dialytic weight increase (1.9 kg ± 0.9) than patients without intradialytic hypertension (0.9 kg ± 0.3) with statistically significant differences between them as p-value =0.025. This supports the fact that as patients with intradialytic hypertension have been found to be more chronically volume-overloaded than other hemodialysis patients, despite the fact that they typically may have small inter-dialytic weight gain and clinically do not appear to be volume-overloaded, hypervolemia is a well-known risk factor for hypertension among dialysis patients⁽¹⁹⁾.

Our results contradict the results by **Raikou et al.**⁽¹⁶⁾, who studied weight gain in hemodialysis patients and found that patients with intradialytic hypertension exhibited comparable inter-dialytic weight increase to those without intradialytic hypertension and no obvious peripheral edema or uncontrolled extra-dialytic hypertension.

By reviewing the basic laboratory data of the study groups, we found that no statistically significant differences between both groups was found as regards (creatinine, urea, sodium, potassium, magnesium, calcium, phosphorus and albumin), while patients with intradialytic hypertension, whose hemoglobin mean was noticeably lower (10.5 ± 1.1 g/dl) than patients without (11.6 ± 1.0 g/dl) with statistically significant differences between them as p-value =0.011.

This is consistent with earlier research that showed a number of characteristics, including ageing, being underweight, having lower serum creatinine and albumin levels, and using more antihypertensive drugs, are linked to an increase in intradialytic blood pressure. Additionally, small decreases in osmolarity during dialysis may be caused by lower albumin and pre-dialysis urea nitrogen levels, which keeps the blood pressure from dropping⁽²⁰⁻²¹⁾. Supporting our results, in **Raikou et al.**⁽¹⁶⁾ study, older and with noticeably lower hemoglobin levels were the participants with intradialytic hypertension.

Our study findings strengthened the assumption that malnutrition and dialysis patients who suffer from anemia have a higher cardiovascular risk, and the components of the malnutrition-inflammation-atherosclerosis syndrome all decrease these patients' chances of survival⁽²²⁾.

In our study, patients with intradialytic hypertension had significantly lower mean of iPTH than patients without intradialytic hypertension with statistically significant differences between them, which support **Rakiou et al.**⁽¹⁶⁾ observations in which patients with intradialytic hypertension had

significantly lower mean of iPTH than patients without.

In the current study, there were significant indirect moderate correlations between iPTH and systolic blood pressure in both groups in different time settings (pre, intra, and postdialytic). There was also significant indirect moderate correlation between iPTH and serum creatinine, serum BUN, serum potassium and serum phosphorus.

In the same line, **Pirklbauer *et al.*** ⁽²³⁾ found that during the first quarter of follow-up, patients with lower levels of iPTH were more likely to have greater blood calcium levels but lower phosphate levels. Ferritin, CRP, and albumin levels were all greater in patients with reduced iPTH, which is consistent with an active inflammatory response. Additionally, there was a higher probability of their hospitalisation in the initial quarter of the follow-up.

CONCLUSION

Our study demonstrated that no statistically significant correlation was noted between the prevalence of intradialytic hypertension and hyperparathyroidism among prevalent hemodialysis patients.

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