Research Article

Parathyroid Hormone Levels and the Dyslipidemia in Hemodialysis Patients

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Abstract

Elevated levels of intact parathyroid hormone (iPTH) may play an important role in the pathogenesis of dyslipidemia in hemodialysis (HD) patients, but the underlying mechanisms are not clearly defined. **Aim**: In this cross-sectional study, we examined the effects of iPTH on dyslipidemia among HD patients. **Patients**: Forty five patients with chronic renal failure patients on maintenance hemodialysis classified according to their iPTH into group I (iPTH<٣٠٠ pg/microlitre) and group II (iPTH >٣٠٠ pg/microlitre). **Methods**: On enrollment, we measured lipid profile, alkaline phosphatase, calcium, phosphorus and the duration that they were on HD, and evaluated the correlation of these parameters with iPTH level using Spearman's rank analysis. **Results**: There is significant positive correlation between parathyroid hormone level and triglycride level in patients of group I and group II (p = ٠.٠٢٩, ٠.٠٠١) respectively. Also there is significant positive correlation between parathyroid hormone level and total cholesterol level in both groups (p =٠.٠١١, ٠.٠٣٥) respectively. There is a non significant correlation between HDL and LDL in both groups with iPTH. A significant positive correlation was found between iPTH and alkaline phosphatase (ALP), between iPTH and HD duration, whereas there was a significant negative correlation between: iPTH and Ca, Body Mass Index. **Conclusion:** Elevated Parathyroid hormone levels in hemodialysis patients may play a role in pathogenesis and progression of dialysis dyslipidemia**.**

Key Words: Parathyroid hormone, dyslipidemia**,**

Introduction

Dyslipidemia is a primary risk factor for cardiovascular disease and a common complication of progressive kidney disease. Most patients with chronic kidney disease have an abnormal lipid panel that increases their risk for atherogenesis. Dyslipidemia contributes to cardiovascular mortality[١,٢].

The most noticeable lipid abnormality in chronic kidney disease is an elevated triglyceride level, possibly because of defective clearance[٣]. Patients with chronic kidney disease also have an elevated ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol. LDL cholesterols, including lipoprotein(a), are pro-atherogenic, and levels are slightly elevated in patients with chronic kidney disease. Levels of oxidized LDL cholesterol also are elevated; these cholesterols activate pro-inflammatory pathways, thereby promoting atherogenesis and endothelial dysfunction.[٤]

Although no large randomized controlled trials have studied the effects of lipid reduction on the progression of kidney disease, animal models suggest that dyslipidemia worsens kidney function. A recent meta-analysis of ١٣ small studies showed that lipid reduction preserves GFR and reduces proteinuria[٥].

Progressive kidney dysfunction results in hyperphosphatemia and calcitriol deficiency. These result in hypocalcaemia. These abnormalities directly increase PTH levels[٦]. Patients with chronic renal failure display type IV lipoproteinemia. They have

elevated serum levels of very-low-density, intermediate-density, and low-density lipoprotein. Serum cholesterol levels are usually normal and those of high-density lipoprotein are low [٧]. Hypertriglyceridemia in CRF is due to decreased removal from the blood secondary to reduced activity of lipoprotein lipase and hepatic lipase. Secondary hyperparathyroidism and elevated blood levels of parathyroid hormone (PTH) may play an important role in the pathogenesis of the triglyceridemia of chronic renal failure [٧]. This defect was apparently due to the rise in calcium content of the liver mediated by the state of secondary hyperparathyroidism of CRF. An increase in calcium content of the liver may reflect an elevation in cytosolic calcium of hepatocytes. The elevation in Ca of hepatocytes in CRF down regulates the mRNA of hepatic lipase[٨].

It was suggested that secondary hyperparathyroidism is involved in the impaired catabolism of triglyceride-rich lipoproteins, provided an additional mechanism by which CKD may raise plasma triglyceride concentrations[٩]. Excess PTH suppresses insulin release from pancreatic islets and the insulin deficiency results in carbohydrate intolerance. Insulin deficiency also causes decreased synthesis of lipoprotein lipase and hence abnormal lipid metabolism. Thus, the hyperparathyroidism of chronic renal failure may play a paramount role in the genesis of the abnormal metabolism of both carbohydrates and lipids [٧].

Patients and Methods

A cross sectional study was carried out at Minia university hospital dialysis unit in the period between June ٢٠١٣ to November ٢٠١٤. Forty five patients of ESRD on maintenance hemodialysis treatment were studied. They were ١٩ males and ٢٦ females. Their mean duration of hemodialysis treatment was ٤.٤٥٥±٢.٥٦٥ years with frequency of three times per week, and each session for hemodialysis treatment lasting for four hours. Additionally ١٠ healthy individuals had no history of chronic illness were included as a control.

Exclusion criteria: HCV positive patients, Diabetic patients, Patients known to have dyslipidemia, Patients on lipid lowering drugs, patients on CCB, Patients with chronic liver disease. After they were informed about the study, written consent was obtained. Approval of the medical Ethical committee, Faculty of Medicine - Minia university was taken.

All patients of the study were subjected to the following:

Full history taking, clinical examination and laboratory investigations in form of: Complete blood count (CBC) determined by automated cell counter Sysmex KX-٢IN (TAO Medical Incorporation, Japan). Renal function tests (blood urea, serum creatinine), Liver function tests (ALT, AST, serum albumin and total protein) were assayed using fully automated clinical chemistry auto-analyzer system Konelab ٢٠i (ThermoElectron Incorporation, Finland). Calcium by Colorimetric Assay Kit from Biovision, phosphorous by column chromatography method and Parathyroid hormone (PTH) by Enzyme Immune Assay. Serum levels of triglyceride (enzymatic Gop-PAP method), total cholesterol (enzymatic calorimetric CHOP-PAP method), high-density lipoprotein cholesterol (HDLC; direct enzymatic method) and low-density lipoprotein cholesterol (LDLC; calculated with Freidwald equation). All these biochemical assays were done using diagnostic kits made by Bioactiva Diagnostica (Hamburg, Germany).

Statistical methodology: Analysis of data was done by IBM computer using SPSS v١٦. Description of quantitative variables as mean, SD. Description of qualitative variables as number and percentage. Independent sample t-test was used to compare quantitative variables in parametric data (SD<٥٠٪ mean). Chi-square test was used to compare two groups as regard qualitative variables. Analysis of variance test (ANOVA) was used to compare multinominal parameter as regard quantitative data. Multivariate linear regression analysis was done. P value >٠.٠٥ insignificant - P<٠.٠٥ significant - P<٠.٠١ highly significant [١٠].

Results

In our study, ٤٥ patients on dialysis and ١٠

healthy individual were included. They were classified into ٣ groups: **Group I**: Includes ٢٥ patients on dialysis their parathyroid hormone level less than ٣٠٠ pg/microlitre. **Group II**: Includes ٢٠ patients on dialysis their parathyroid hormone level more than ٣٠٠ pg/microlitre. **Group III**: Includes ١٠ healthy individuals of age and sex matched, as a control group. Patient's demographic characteristics is shown in **Table (١)**. There was highly significant statistical difference as regard duration of dialysis, between patients of group I and group II (p<٠.٠٠١). The three groups were compared as regard bone mineral parameters: PTH level, alkaline phosphatase level, serum calcium and phosphorus levels as shown in Table ٢ with a highly significant statistical difference between them (p<٠.٠٠١). Alkaline phosphatase level was highest in group II (١٦٥.٩٥ ± ٢٣.٥٩) with a highly significant statistical difference between the three groups (p<٠.٠٠١). Serum calcium level was lowest in group II (٧.٩٩ ± ٠.٥٥) with a highly significant statistical difference between the three groups (p<٠.٠٠١) (table ٢).

Table ١: Demographic characteristics of patients on dialysis with PTH < ٣٠٠ (Group I), patients on dialysis with PTH > ٣٠٠ (Group II) and control group (Group III).

	Group III Control N = ١٠	Group I PTH < ٣٠٠ N= ٢٥	Group II PTH > ٣٠٠ N= ٢٠	P value		
Age (years) :				٠.٢٩٦		
				I vs II	**I vs III**	**II vs III**
(range) M ± SD	(٣٦-٤٥) ٤٠.٩ ± ٣.١٤	(٢٠-٦٧) ٤٥.٦٤ ± ١٤.٠٨	(٢٨-٧٠) ٤٨.٧٥ ± ١٤.١١	٠.٣٣٠	٠.١٢٢	٠.٤٢٥
Sex:				٠.٣٧٤		
				I vs II	**I vs III**	**II vs III**
Male	٦ (٦٠٪)	٩ (٣٦٪)	١٠ (٥٠٪)			
Female	٤ (٤٠٪)	١٦ (٦٤٪)	١٠ (٥٠٪)	٠.٢٦٦	٠.٧٠٩	٠.٣٧٩

Table ٢: Comparative study of bone mineral parameters between patients and control.

	Group I PTH < ٣٠٠ N= ٢٥	Group II PTH > ٣٠٠ N= ٢٠	Group III Control N = ١٠	P value		
PTH (pg/ml) (range) M ± SD	(١١٧-٢٧١) ١٨٦.٧٦ ± ٤٣.٨٧	(٣٠٤-١١٣١) ٥١٢.١ ± ٢٤١.٣	(٢٦-٤٤) ٣٤.٨ ± ٦.١	< ٠.٠٠١*		
				I vs II	**I vs III**	**II vs III**
				< ٠.٠٠١*	< ٠.٠٠١*	< ٠.٠٠١*
ALP (u/l): (rang) M ± SD	(٨٢-١٤٨) ١٢٢.٠٤ ± ١٧.٥٧	(١١٨-١٩٨) ١٦٥.٩٥ ± ٢٣.٥٩	(٥٥-٨٦) ٦٩.٣٠ ± ٨.٧٨	< ٠.٠٠١*		
				I vs II	**I vs III**	**II vs III**
				< ٠.٠٠١*	< ٠.٠٠١*	< ٠.٠٠١*
Ca^{2+} (mg/dl) (range) M ± SD	(٨.١-٨.٦) ٨.٣٣ ± ٠.١٧	(٧-٨.٦) ٧.٩٩ ± ٠.٥٥	(٩.٣-١٠.٣) ٩.٩ ± ٠.٣٣	< ٠.٠٠١*		
				I vs II	**I vs III**	**II vs III**
				< ٠.٠٠١*	< ٠.٠٠١*	٠.٠٠٥*
Ph. (mg/dl): (range) M ± SD	(٥-٦.٨) ٥.٦٢ ± ٠.٤٤	(٥-٦.٨) ٥.٦٣ ± ٠.٥٦	(٤.١-٥.٩) ٥.٢٤ ± ٠.٥٥	٠.١١١		
				I vs II	**I vs III**	**II vs III**
				٠.٩٧٤	٠.٠٥٢	٠.٠٥٧

Lipid profile parameters: were compared between patients on dialysis as a whole and

control group and revealed that there is highly significant difference between triglycride and cholesterol level of both groups (p<٠.٠٠١), while comparison of LDL level between control group and patient on dialysis showed no significant statistical difference (p=٠.٣٢٤), and no significant statistical difference between HDL level of both groups (p=٠.٥١٦) (table ٣).

Table ٣: Comparative study of Lipid Profile Parameters between Patients on Dialysis as a whole and control Group.

	Control N = ١٠	Patients on dialysis N= ٤٥	P value
TG (mg/dl) : (range) M ± SD	(١١٢-١٣٢) ١٢٢.٢ ± ٦.٧٧	(١١٠-٣١٥) ١٧٧.٢٩ ± ٥٦.٤٩	< ٠.٠٠١*
TC (mg/dl): (range) M ± SD	(١٧٢-١٨٦) ١٧٧.٧ ± ٤.٩٢	(١٩٣-٢٩٥) ٢٣١.٣٣ ± ٢١.٨٩	< ٠.٠٠١*
LDL (mg/dl) : (range) M ± SD	(٤٢-٦٤) ٨٤.٦ ± ٣.٣١	(٩٥-١٧٥) ٨٦.٤٢ ± ٥.٥٥	٠.٣٢٤
HDL (mg/dl): (range) M ± SD	(٦٥-٨٠) ٤٩.٥ ± ٣.٠٣	(٣٢-٥٠) ٥٠.٢٧ ± ٣.٤٢	٠.٥١٦

Comparison of lipid profile parameters between group I and group II showed that the mean value of triglyceride level was ١٥٢.٦±٤٢.٥٦ for group I and ٢٠٨.١٥±٥٧.٤١ for group II with a highly significant statistical difference between both groups (p = ٠.٠٠١) , and the mean value of total cholesterol was ٢٢٥.٢٤ ± ١٩.٢٠ for patients of group I and ٢٣٨.٩٥ ± ٢٣.١١ for patients of group II with significant statistical difference between both groups (p =٠.٠٣٥) **(table ٥), (Figure ١)** , while no significant statistical difference was found between LDL (p=٠.٣٢١) and HDL levels (p=٠.٣١٢) of both groups.

Table ٤: Comparative Study Of Lipid Profile Parameters Between Patients On Dialysis With PTH < ٣٠٠ (Group I) , Patients On Dialysis With PTH > ٣٠٠ (Group II) .

	Group I PTH < ٣٠٠ N= ٢٥	Group II PTH > ٣٠٠ N= ٢٠	P value
TG (mg/dl) : (range) M ± SD	(١١٨-٢٣٥) ١٥٢.٦ ± ٤٢.٥٦	(١١٠-٣١٥) ٢٠٨.١٥ ± ٥٧.٤١	٠.٠٠١*
TC (mg/dl): (range) M ± SD	(١٩٣-٢٥١) ٢٢٥.٢٤ ± ١٩.٢٠	(١٩٨-٢٩٥) ٢٣٨.٩٥ ± ٢٣.١١	٠.٠٣٥*
LDL (mg/dl) : (range) M ± SD	(٧٥-٩٥) ٨٥.٦٨ ± ٦.٠٦	(٨٠-٩٥) ٨٧.٣٥ ± ٤.٨٢	٠.٣٢١
HDL (mg/dl): (range)	(٤٥-٥٥)	(٤٥-٥٦)	٠.٣١٢

M ± SD	٤٩.٨ ± ٣.٥٧	٥٠.٨٥ ± ٣.٢٢	

In patients of group I : There was significant positive correlation between parathyroid hormone level and triglyceride level, total cholesterol, duration of Dialysis, alkaline phosphatase (p =٠.٠٢٩,٠.٠١١,٠.٠٠١,٠.٠٠٤) respectively **(table ٥), (figure ١,٢)**, while there was a non significant correlation between parathyroid hormone level and LDL & HDL **(table ٦)**.

Table ٥: Correlation between Parathyriod Hormone Level and Lipid profile, Alkaline Phosphatase Level, Serum Calcium Level, Body Mass Index and duration Of Dialysis in (Group I).

PTH with:	**Group I PTH < ٣٠٠ N= ٢٥**	
	R	**P**
TG	٠.٤٣٨	٠.٠٢٩*
TC	٠.٤٩٧	٠.٠١١*
ALP	٠.٥٥٣	٠.٠٠٤*
Ca^{++}	-٠.٤٤٣	٠.٠٢٧*
BMI	-٠.٤١٦	٠.٠٣٩*
Dialysis duration	٠.٧٥٤	< ٠.٠٠١*

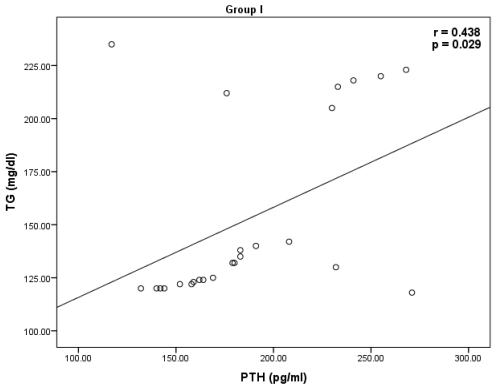

Figure (١):Correlation between parathyroid hormone level and triglycride level in patients of group I.

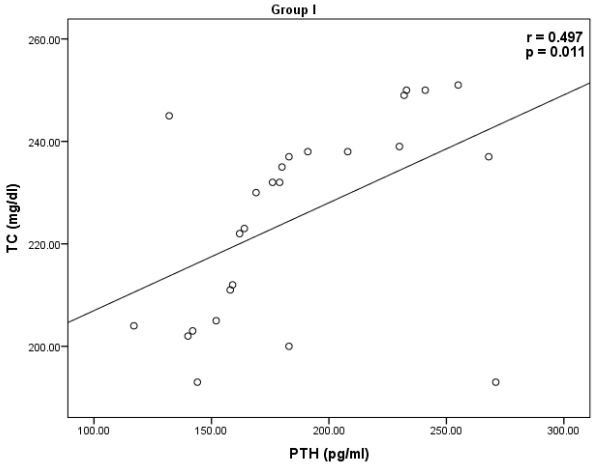

Figure (٢): Correlation between parathyroid hormone level and total cholesterol level in patients of group I.

In patients of group II : There was highly significant positive correlation between parathyroid hormone level and triglyceride level (r = ٠.٧١٩, p < ٠.٠٠١)**,** significant positive correlation between parathyroid hormone level and total cholesterol level (r = ٠.٤٧٣ , p < ٠.٠٣٥) **(table ٦), (figure٣)**, highly significant positive correlation between parathyroid hormone level and duration of dialysis (r= ٠.٦٧٥ , p < ٠.٠٠١)**,** and between parathyroid hormone and alkaline phosphatase level (r = ٠.٧٨٢ , p < ٠.٠٠١). There was a significant negative correlation between parathyroid hormone level and serum calcium level (r = - ٠.٥٦٦ , p < ٠.٠٠٩), and between parathyroid hormone level and BMI (r = - ٠.٧٢١ , p < ٠.٠٠١), while there was a non significant correlation between parathyroid hormone level and LDL (r= ٠.١٥٩ , p<٠.٥٠٣), also a non significant correlation was found between parathyroid hormone level and HDL(r=٠.١٠٧ , p<٠.٦٥٣)**.**

Table ٦: Correlation between Parathyriod Hormone Level and lipid profile, Alkaline phosphatase Level, Serum Calcium Level, Body Mass Index and duration of Dialysis in (Group II).

PTH with:	Group II PTH > ٣٠٠ N= ٢٠	
	r	P
TG	٠.٧١٩	< ٠.٠٠١*
TC	٠.٤٧٣	٠.٠٣٥
ALP	٠.٧٨٢	< ٠.٠٠١*
Ca^{++}	-٠.٥٦٦	٠.٠٠٩*
BMI	-٠.٧٢١	< ٠.٠٠١*
Dialysis duration	٠.٦٧٥	٠.٠٠١*

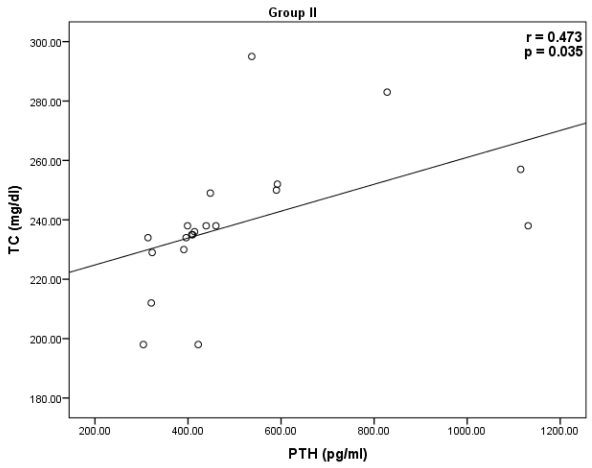

Figure (٣): Correlation between parathyroid hormone level and total cholesterol level in patients of group II.

Discussion

Lipid abnormalities have been postulated to contribute to renal insufficiency by a mechanism that is analogous to athero-genesis. The majority of patients treated for chronic renal failure die of cardiovascular complications. Lipid abnormalities in this group are thought to contribute to this high

mortality. Proving a causal association between dyslipidemia and accelerated atherosclerosis in end-stage renal disease population has been confounded by the presence of other pro-atherogenic conditions in this population [١١].
We designed this study to assess the relation between PTH abnormalities (secondary hyperparathyroidism) and dyslipidemia in haemodialysis patients and to investigate the role of PTH in development of uremic dyslipidemia. We exclude secondary causes of dyslipidemia as diabetic patients, as diabetes has other effects on the lipid parameters and this is in agreement with the study of Zanos et al., [١٢].

The classification of the patients into group I and group II based on the level ٣٠٠ pg/ml of PTH was in agreement with Ahmadi et al.,[١٣] who studied ٥١ patients on hemodialysis and classified them according to the level ٣٠٠ pg/ml into ٢ groups and also in agreement of Zanos et al.,[١٢]. Also the level ٣٠٠ pg/ml was suitable in our study as it provide ٢ comparable groups of nearly equal numbers of patients.

There was high positive significant correlation between parathyroid hormone level and duration of dialysis in group I and II ($p < ٠.٠٠١$). This is in agreement with Rezende et al.,[١٤] who stated that PTH level positively correlated with the duration of dialysis ($r=٠.٥٣$, $p<٠.٠٥$).

AS regards Alkaline phosphatase level it was (١٢٢.٠٤ ± ١٧.٥٧, ١٦٥.٩٥ ± ٢٣.٥٩, ٦٩.٣٠ ± ٨.٧٨) for groups I, II, III respectively with a highly significant statistical difference with $p<٠.٠٠١$ for all, and there was significant positive correlation between parathyroid hormone level and alkaline phosphatase level in patients groups ($p = ٠.٠٠٤$, ٠.٠٠١) respectively. This in accord-ance with the study of Ahmadi et al., [١٣] & Rahimian et al.,[١٥] who reported a significant positive correlation between PTH level and alkaline phosphatase level in hemodialysis patients. This correlation could be explained by the fact that in CKD, high bone turnover condition occurs due to excess PTH which binds to its receptors on osteoblasts and osteocytes stimulating their proliferation and production of several non collagenous proteins as osteocalcin and alkaline phosphatase[١٦].

As regards serum calcium level it was (٨.٣٣ ± ٠.١٧, ٧.٩٩ ± ٠.٥٥, ٩.٩ ± ٠.٣٣) for groups I, II, III respectively with a highly significant statistical difference between the three groups ($p<٠.٠٠١$). Also there was signi-ficant negative correlation between PTH level and serum calcium level. This is in accordance with Ahmadi et al.,[١٣]. This could be explained the fact that phosphate retention, as a result of reductions in GFR, would cause transient decreases in the levels of ionized calcium, which would, in turn, trigger an increase in PTH secretion and a new steady state would be achieved[١٧].

As regards Lipid profile parameters when compared between patients on dialysis as a whole and control group revealed that there is highly significant statistical difference between triglycride levels of both groups. This is in agreement with the study of Vasilis et al.,[١٨] which reported hypertriglycridemia in ٣١٪ of patients on hemodialysis and with the experimental study of Kyubok et al.,[١٩] in which the CRF rats had significantly higher TG level compared to control group. This significant difference is explained by the fact that LPL activity is reduced and several studies have demonstrated a marked reduction in plasma postheparin lipolytic activity in ESRD patients[٢٠,٢١]. CRF results in marked downergulation of hepatic lipase expression and activity [٨]. Also VLDL receptor mRNA and protein abundance in adipose tissue, skeletal muscle, and myocardium are severely reduced in CRF animals[٢٢].

As regard total cholesterol level, it was ٢٣١.٣٣ ± ٢١.٨٩ for patients on dialysis and ١٧٧.٧ ± ٤.٩٢ for control group with a highly significant statistical difference between both groups ($p<٠.٠٠١$), this is in agreement with Vasilis et al.,[١٨] who reported hyper-cholesterolemia in ١٩٪ of patients on hemodialysis, and with kyubok et al.,[١٩] who reported high significant difference in total cholesterol level between CRF rats and control group ($p<٠.٠٠١$), but against Maheshwari et al.,[٢٣] who reported

that there was no significant statistical difference between cholesterol level in hemodialysis patients and control group and this could be explained as that CRF increase both HMG-coA reductase activity which is the rate limiting step in cholesterol synthesis and cholesterol ٧-hydroxylase activity which is the rate limiting step in cholesterol catabolism[٢٤]. Also, there is significant positive correlation between PTH level and total cholesterol level in group I and group II. This is against what was reported by Ahmadi et al., ٢٠١٢[١٣] who did not find significant correlation between PTH level and total cholesterol level.

As regards HDL and LDL there was no significant difference when comparing control group and patients on dialysis as a whole and this is in agreement with Maheshwari et al.,[٢٣] who reported no significant difference between control group and hemodialysis patients.

As regards Triglycerides, it was significantly elevated in group II than group I ($p< ٠.٠٠١$) and a positive significant correlation was present between PTH and TG level in group I and group II ($p = ٠.٠٢٩$, $p<٠.٠٠١$) respectively and this is in agreement with Mitwalli et al.,[٢٥] who reported that the patients with hyperparathyroidism had significantly higher mean serum triglyceride levels compared to non-hyperparathyroid patients. Also in accordance with the study of Zanos et al.,[١٢] which showed that increased levels of PTH cause elevation of intracellular calcium predisposing to lipid metabolism abnormalities. Lacour et al.,[٢٦] showed that secondary hyperparathyroidism in rats produced either by feeding them low calcium diet or by administration of parathyroid extracts was associated with hypertriglyceridemia. This could be explained by excess PTH in CRF lead to downregulation of mRNA of hepatic lipase so decrease its production and activity[٢٦], alteration of hepatic lipase kinetics[٢٧], chronic exposure to high PTH level result in sustained elevation in the basal level of cytosolic calcium of hepatocytes, the abnormal intracellular calcium homeostasis is believed to be the basis of organ dysfunction as increased cytosolic calcium lead to inhibition of mitochondrial oxidation and ATP production[٢٨]. In contrast, Ahmadi et al.,[١٣] did not find significant correlation between PTH level and serum TG level ($p=٠.٣٢٣$). Also Navarro et al.,[٢٩] in a study on ٣٤ hemodialysis patients found no correlation between serum lipids and PTH levels and Lipid profile did not change in patients with severe secondary hyperparathyroidism after parathyroidectomy.

Because of the lack of evidence in treating lipid abnormalities in this specific patient populatio, future studies should focus on the pathophysiological mechanisms and treatment of dyslipidemia in these patients[٣٠].

Conclusion and recommendation:

Elevated Parathyroid levels in hemodialysis patients may play a role in pathogenesis and progression of dialysis dyslipidemia. Pathogenesis of dialysis dyslipidemia and the role of hyperparathyroidism remains a subject of debate. Further studies on larger number of patients and long term follow up for evaluation of the effect of secondary hyperparathyroidism on dialysis dyslipidemia.

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