AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 09, November, 2022

Relation of Urinary Phosphate and carotid intimal medial thickness in chronic kidney disease Patients

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Keywords:
chronic kidney disease intima-medial thickness fraction excretion of phosphorus

ABSTRACT

Patients with chronic kidney disease (CKD) have an increased risk of cardiovascular events including atherosclerosis-related complications. In uremic patients, increased serum phosphate concentration is a significant risk factor for vascular calcification. a cross-sectional study included 90 CKD adult patients, using B-mode ultrasonography, we examined intima-medial thickness (IMT) of the carotid artery of patients and analyzed risk factors for increased IMT. 24 h urinary phosphate excretion (mg/day) and creatinine clearance was calculated. The study cohort included ninety CKD patients. Carotid intima media thickness (cIMT) of patients increased significantly with progression of CKD P=0.001. Mean cIMT showed significant positive correlation with duration of hypertension, uric acid, serum phosphorus, PTH& fraction excretion of phosphorus (FeP) (r .365; p .001, r .380; p .000, r .376**p .000, r .422; p .000 & r .268; p .011) respectively. While calcium & CKD-epi negatively correlated significantly with mean cIMT (r -.255; p .015 & r-.421; p.000 respectively). linear regression analysis showed higher FeP was associated with higher PTH levels as well as higher FGF23 levels. negative correlation was seen between measured GFR and FeP (r -0.365, p = 0.000). The cIMT is early marker for atherosclerosis.it was significantly higher in patients with advanced CKD. increased serum phosphorus, PTH& fraction excretion of phosphorus are risk factors for increased CIMT in patients with CKD.

1. Introduction

Kidney failure is a worldwide public health problem, with increasing incidence and prevalence, high costs, and poor outcomes [1]. There is even a substantially higher prevalence of the earlier stages of chronic kidney disease (CKD). It is important to improve the care and outcomes of CKD worldwide by increasing the efficiency of utilizing available expertise and resources [2]. Retention of vasotoxic substances or/and metabolic changes that occur with the impairment in kidney function is responsible for creation of atherogenic milieu, that leads to increased oxidative stress and subclinical inflammatory state [3]. Increased

cardiovascular risk in CKD is due to uremic toxins retention, dyslipidemia, hypertension, and secondary hyperparathyroidism as well as increased levels of IL-1 and TNFα [4]. In addition to traditional cardiovascular risk factors, disturbances in calcium-phosphate metabolism are regarded as strong contributing factors of higher cardiovascular mortality in CKD patients [5].

It is well established that metabolism of calcium and phosphate is disturbed in patients with CKD and begin since the early stages of CKD. In addition to phosphate and calcium, vitamin D, parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) are the most important regulators of mineral metabolism. As the calcitriol level decreases, total calcium also decreases, due to decreased calcium absorption from the intestine, and this results in an increase in PTH. Secondary hyperparathyroidism is the term used to describe such increase in the levels of PTH in response to previously described mechanism. Consequent to increased levels of PTH, Calcium and phosphorus are released from the bone, in addition to increased phosphate excretion by the kidney. However, Hyperphosphatemia is the end result in late stages of CKD as FGF23 and PTH decreases tubular phosphate reabsorption and the fractional excretion of phosphate can reach as high as 90% [6]. These alterations in mineral metabolism are associated with increased morbidity and mortality in patients with CKD [7- 9].

Phosphorus effects on vascular smooth muscle cells (VSMC) result in vascular calcification. High levels of inorganic phosphate induces calcification in the extracellular matrix surrounding the VSMC [10], and directly induces phenotypic changes in VSMCs including transformation from a contractile phenotype into an osteochondrogenic phenotype [11]. CKD mineral bone disorders and inflammation contribute to CKD-induced atherosclerosis as they alter the nature of endothelial, smooth muscle and periarterial cells.

Increased cIMT is associated with a higher cardiovascular risk, independently of known traditional risk factors [12], [13] An association between carotid atherosclerosis and kidney dysfunction was observed in several general population studies. Indeed, faster change in cIMT is strongly associated with impaired renal function [14].

Our study was aiming to identify the correlation between 24-hour urinary phosphorus and Ultrasound imaging of the carotid intimal medial thickness as a marker of atherosclerosis in the different stages of CKD especially pre dialysis stages.

2. SUBJECTS AND METHODS

A cross sectional study carried out at Mansoura University Hospital (Internal medicine department) over a period of 22 months from November 2019 to October 2021.

2.1 Patient selection

The study included ninety CKD adult patients, who were recruited from Nephrology department at Mansoura University Hospital and its outpatient clinic. They were diagnosed according to The KDIGO 2012 [15] definition for CKD as abnormalities of kidney structure or function, present for >3 months, with implications for health, and requires one of two criteria documented or inferred for >3 months: either GFR <60 ml/min/1.73 m2 or markers of kidney damage. Patients were divided into 3 different groups according to measured glomerular filtration rate (GFR) for comparison in different study parameters. Group 1 GFR ranged from 30 to 59 mL/min per 1.73 m ^{2}", Group 2: GFR ranged from 15 to 29 mL/min per 1.73 m ^{2} and Group 3 GFR less than 15 mL/min per 1.73 m ^{2} and not on hemodialysis.

2.2 Inclusion and exclusion criteria

ISSN: 0005-2523
Volume 62, Issue 09, November, 2022

We included CKD patients aged ≥18 and ≤60 years old who agreed to participate in the study, share their clinical and laboratory data and assign for the written consent. While patients who had acute renal insult on top of CKD, active malignancy, active infection and/or active inflammatory processes, decompensated heart failure, recent acute coronary event, age>60 years old and on hemodialysis were excluded.

2.3 Sample size calculation

Sample size was calculated by PASS software for Windows, version 11.0.8. (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com). Calculation relied upon a previous similar study done by [16]. Our sample size achieves 80% power to detect a difference of -0.1 between the null hypothesis mean of 0.8 and the alternative hypothesis mean of 0.9 with an estimated standard deviation of 0.2 and with a significance level (alpha) of 0.05000 using a two-sided one-sample t-test.

2.4 Data collection

All patients were subjected to: history taking, physical examination and Laboratory evaluation including Serum calcium, serum phosphorus, intact parathyroid hormone (iPTH) and 24-hour urinary collection for measuring creatinine clearance and daily phosphate excretion. Serum phosphorus was measured using the Technicon Autoanalyzer (Technicon Instruments, Tarrytown, New York, USA). Intact parathyroid hormone (iPTH) was measured using an antiserum (GP-1) directed against both amino and carboxy terminal parts of the PTH molecule using radioimmunoassay. Total urine collected for 24 hours was sent to the laboratory for estimating creatinine clearance and fractional excretion of phosphate (FEP) using the following formulae: GFR= creatinine clearance (Ccrn) = urinary creatinine (Ucrn) × volume of urine (V) / plasma creatinine (Pcrn). FEP = [Urinary P (mg/dl) × Serum Creatinine (mg/dl)] / [Serum P (mg/dl) × Urinary creatinine (mg/dl)] × 100.

Radiological evaluation of patients included the measurement of cIMT as a surrogate marker of subclinical atherosclerosis. It was measured using B-mode ultrasonography using LOGIQ F6 device, GE Healthcare, Waukesha, WI 53188, USA with a superficial probe. cIMT was defined as a hypoechogenic space between two echogenic lines containing intima media interface and media–adventitia interface on the posterior wall of the carotid artery.

2.5 Ethical approval

Study protocol was approved by Institutional Research Board (IRB), faculty of medicine, in Mansoura University, approval of the managers of the hospital in which the study was conducted and Informed written consent was obtained from each participant in the study after assuring confidentiality and patient was free to be withdrawn. Confidentiality and personal privacy were respected in all levels of the study.

2.6 Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Number and percent was used for describing qualitative data. while, Quantitative data were described using median (minimum and maximum) and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. For qualitative data Chi-Square test was done for comparing of 2 or more groups, student t-test was used to compare 2 independent group and one way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison.

The Spearman's rank-order correlation is used to determine the strength and direction of a linear

relationship between two non-normally distributed continuous variables and / or ordinal variables. While pearson test for variables with normal distribution, P value less than 0.05 was considered statistically significant.

3. RESULTS

Table (1) lists clinical characteristics of CKD patients, The mean age was 47.59±10.49 with a higher prevalence of males (51.1%). Diabetic patients constituted 47.8 % of patients while hypertensive patients were 80 %. Thirty-one patients were CKD stage 3, Thirty-six patients were stage 4 and twenty-three patients were stage 5.

Fraction excretion of phosphorus showed significant increase in advanced CKD (P=0.003) with significant difference between stage 3 & 5 (P2 =0.007) Table (2). Atherosclerotic changes in the 3 cohorts of CKD was higher in stage 5, where carotid intima thickness increased with CKD progression (p .001) Figure (1). Relationship between CIMT and clinical parameters were examined for the groups for all patients, Mean CMT showed significant positive correlation with duration of hypertension, Uric acid, po4, PTH, scr and Fraction_excretion_of_po4 (r .365** p .001, r .380**p .000, r .376**p .000, r .422**p .000, r .435**p .000r .268* p .011 respectively. While ph, Hco3, HB, ca & CKD_epi negatively correlated significantly with mean CMT (r -.220* P .037, r -.309**p .003, r -.239* p .023, r -.255*p .015 & r-.421** p.000 respectively). CIMT significantly increases with the progression in the stages of the GFR (r-0.341, P < 0.001) Figure (3).

Correlation between Fraction excretion of po4 and PTH and measured GFR among studied cases showed higher FeP was associated with higher PTH levels (r 0.280, p = 0.007) as well as negative correlation was seen between measured GFR and FePO4 (r -0.365, p = 0.000) Figure (2).

4. DISCUSSION

Cardiovascular morbidity and mortality are high in CKD patients compared to the general population. Systemic inflammation may contribute to accelerated atherosclerosis in CKD patients [17]. We assessed the correlation of radiological markers of atherosclerosis with serum and urinary phosphorus among different CKD patients' stages.

cIMT is a reliable diagnostic tool for cardiovascular risk in subjects with normal renal function [18], [19]. Studies have tested its use in the CKD population [14], [17], [20], [21]. Previous studies have mostly encompassed severe CKD [14], [22] dialysis patients [20], [23], renal transplant recipients [24], or pediatric CKD population [25- 27].

Observational multicenter study done by [17] found that cIMT was higher in CKD stage 3, and progressively lower with more advanced stages, which was explained by survival bias, the cross-sectional nature of this data, and an incidence-prevalence bias, since only patients free of prior cardiovascular events were included. It is likely that patients with more advanced CKD had a lower CIMT because those who would have had a higher CIMT probably already had a cardiovascular event.

While our cross-sectional study demonstrated atherosclerotic changes in the 3 cohorts of CKD patients, where carotid intima thickness increased with CKD progression and it showed significant negative correlation with measured GFR (r-0.341 &P < 0.001). Our results were coincident with [28] as their results showed significant association between CKD stage and mean CIMT. Those with stage 5 CKD had higher mean CIMT compared to other stages p <0.001, The lower the eGFR, the higher the CIMT. Studies done earlier by [29], [30] showed similar findings. So it is evident that accelerated atherosclerosis is a serious

ISSN: 0005-2523
Volume 62, Issue 09, November, 2022

problem in CKD patients, with more patients dying prematurely from cardiovascular related diseases than progressing to end stage renal disease [31]. CIMT is an alternative end point for cardiovascular morbidity and mortality. We recommend that it should be assessed in our high-risk CKD patients since the procedure for its detection is non-invasive and can be done repeatedly.

In CKD patients, development of secondary hyperparathyroidism and uremic bone disease is associated with hyperphosphatemia [32], [33] Hyperphosphatemia has been reported to be a significant risk factor for vascular calcification and reducing phosphate level by phosphate binders has been reported to reduce and slow progression of vascular calcification [34], [35]. These studies examined vascular calcification, not the degree of arterial thickness itself.

Our study revealed significant positive correlation of mean cIMT with po4 and Fraction excretion of phosphorus (r .376**p .000& r .268* p .011 respectively). There was very strong correlation between cIMT and serum phosphate in [36] study group ($P < 0.0001$). [37] in an examination of 39 patients with young onset chronic renal failure, also found a significant correlation between serum phosphate level, and CIMT in their study ($P \leq 0.001$).

In our study, linear regression analysis showed higher fraction excretion of phosphorus was associated with higher PTH levels (p 0.007) respectively. Our findings appear to contrast with the report by [38]. This difference could be explained by many oissible factors. The most important factor is the difference in patient population and outcome. [38] studied patients who participated in the Heart and Soul study, this study included patients with higher prevalence of occlusive coronary artery disease and normal to slightly decreased eGFR, mainly attributed to vascular disease. Importantly, in the Heart and Soul study, the eGFR range (stage II CKD), CKD was not an important contributor to overall metabolic changes in the study population [39]. In contrast, our patients had moderate-severe CKD and so changes were mainly determined by renal failure.

Limitations of the present study include its cross-sectional nature, relatively small sample size, use of vitamin D supplements, serum vitamin D concentrations, and klotho measurements were not available. We were unable to investigate the effect of additional risk factors such as smoking, body mass index, controlled diabetic and hypertensive state, dyslipidemia and original kidney disease. We recommend larger study with more sample size, longitudinal study to assess progression of Atherosclerosis in CKD, interventional longitudinal study to see whether rigid control of hyperphosphatemia and hyperparathyroidism would be helpful in decreasing Atherosclerosis and study of various other parameters responsible for atherosclerosis.

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Table (1): Demographic and medical data of studied patients (n = 90)

Age in years (Mean±SD)	47.59±10.49
Gender: Male, n (%) **Female, n (%)**	46 (51.1%) 44 (48.9%)
DM, n (%)	43 (47.8%)
Duration of DM in years, Median (IQR)	8(4-12)
HTN, n (%)	72 (80%)
Duration of HTN in years, Median(IQR)	5.5(3-10)
CKD Staging: Stage 3 n (%) **Stage 4 n (%)** **Stage 5 n (%)**	31 (34.4%) 36 (40%) 23 (25.6%)

AMJ
ISSN: 0005-2523
ISSN: 0005-2523
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Table (2): Relation between CKD categories and clinical data of studied patients:

	CKD stages			Test of significance	Within group significance
	3 N=31	4 N=36	5 N=23		
Hb (gm/dL)	11.76±1.48	11.15±1.54	10.54±1.81	F=3.93 P=0.023*	p1=0.118 p2=0.006* p3=0.157
phosphorus(mg/dl)	3.88±0.83	5.36±1.31	7.73±1.28	F=72.82 P<0.001*	p1<0.001* p2<0.001* p3<0.001*
24 hour urinary phosphorus	1932.0(715-4060)	2139(825-5010)	1273(245-4375)	KW=7.09 P=0.029	p1=1 p2=0.157 p3=0.026
Fraction excretion of phosphorus	90.25(25.82-161.54)	123.94(49.18-247.09)	130.76(15.67-1101.53)	KW=11.66 P=0.003	P1 =0.014 P2 =0.007 P3=1
HCO3 (mEq/L)	20.39±3.68	19.78±3.79	17.66±3.56	F=3.85 P=0.025*	p1=0.499 p2=0.009* p3=0.035*
Serum Creatinine (mg/dl)	1.89±0.32	3.23±0.71	6.55±2.58	F=76.54 P<0.001*	p1<0.001* p2<0.001* p3<0.001*
Parathyroid hormone (P.T.H) (pg/ml)	130.2(92-188)	231.5(135.78-318.38)	775(555-954)	KW=43.02 P<0.001*	p1=0.029* p2<0.001* p3<0.001*

Calcium (mg/dl)	**8.74±0.76**	**8.43±0.66**	**8.13±0.80**	**F=4.50** **P=0.014***	**p1=0.089** **p2=0.004*** **p3=0.139**
Ph	**7.37±0.06**	**7.35±0.07**	**7.32±0.06**	**F=3.97** **P=0.02***	**p1=0.138** **p2=0.006*** **p3=0.131**
Uric acid	**4.65±0.94**	**5.76±0.91**	**7.30±0.80**	**F=58.12** **P<0.001***	**p1<0.001*** **p2<0.001*** **p3<0.001***
Carotid intima media thickness (CIMT) (cm)	**0.07(0.06-0.085)**	**0.08(0.07-0.09)**	**0.09(0.08-0.10)**	**KW=14.79** **P=0.001***	**p1=0.200** **p2<0.001*** **p3=0.006***

KW:Kruskal Wallis test , F:One Way ANOVA test, *statistically significant , parameters described as mean±SD or as median (interquartile range), P1:difference between stage 3 & 4 , P2: difference between stage 3 & 5 , P3: difference between stage 4 & 5.

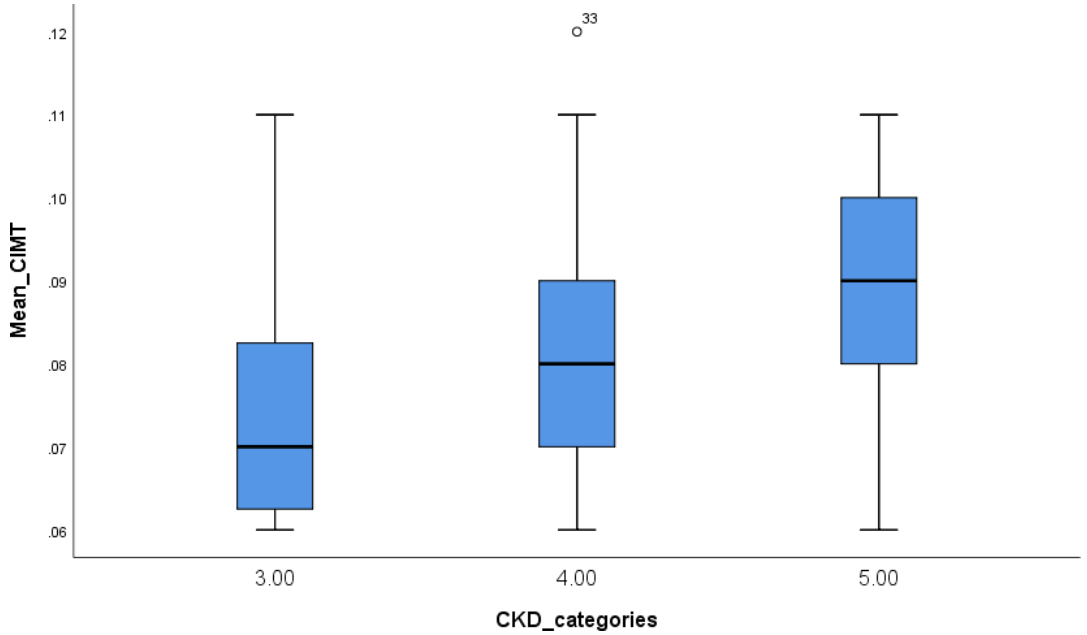

Figure (1): Boxplot showing mean CIMT in three cohort of CKD patients

Table (3): correlation between mean CMT and sociodemographic and clinical dataof the studied cases

		Mean_CIMT

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Age	**r**	**.170**
	p	**.109**
HB	**r**	**-.239***
	p	**.023**
CRP	**r**	**-.083**
	P	**.437**
Uric_acid	**r**	**.380****
	p	**.000**
Po4(mg/dl)	**r**	**.376****
	p	**.000**
Ca(mg/dl)	**r**	**-.255***
	p	**.015**
PTH(pg/ml)	**r**	**.422****
	p	**.000**
CKD_epi	**r**	**-.421****
	p	**.000**
Scr(mg/dl)	**r**	**.435****
	p	**.000**
UOP	**r**	**-.164**
	p	**.123**
urinarypo4_24h	**r**	**.077**
	p	**.470**
Fraction_excretion_of_po4	**r**	**.268***
	p	**.011**

r:Spearman correlation co-efficient

Table (4): Correlation between Fraction excretion of po4 and PTH and measured GFRamong studied cases

		PTH(pg/ml)	**Measured GFR**

Fraction excretion of po4	**r**	**0.280**	**-0.365**
	p	**0.007**	**0.000**

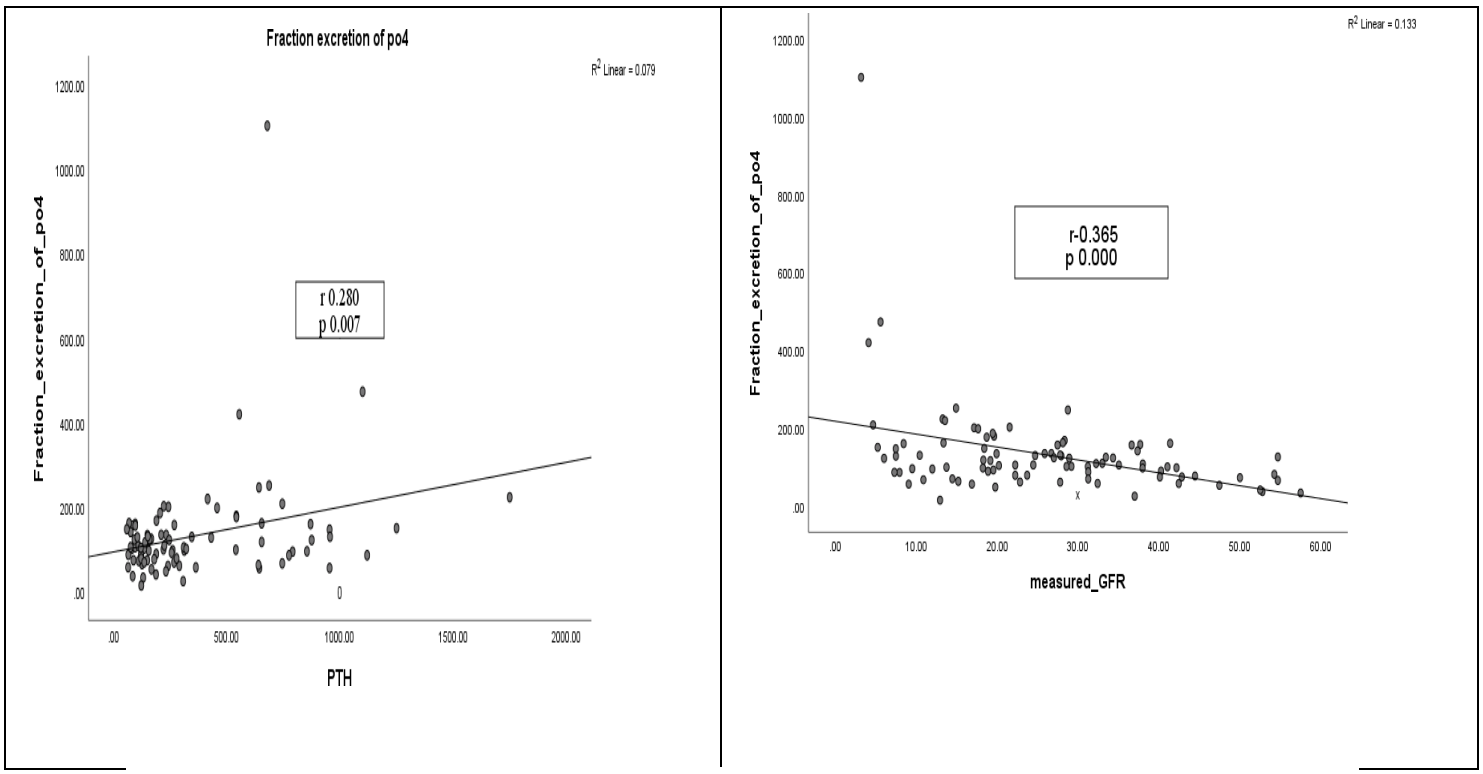

Figure (2): Scatter plots showing the correlation (between Fraction excretion of po4 and measured GFR and PTH among studied cases.

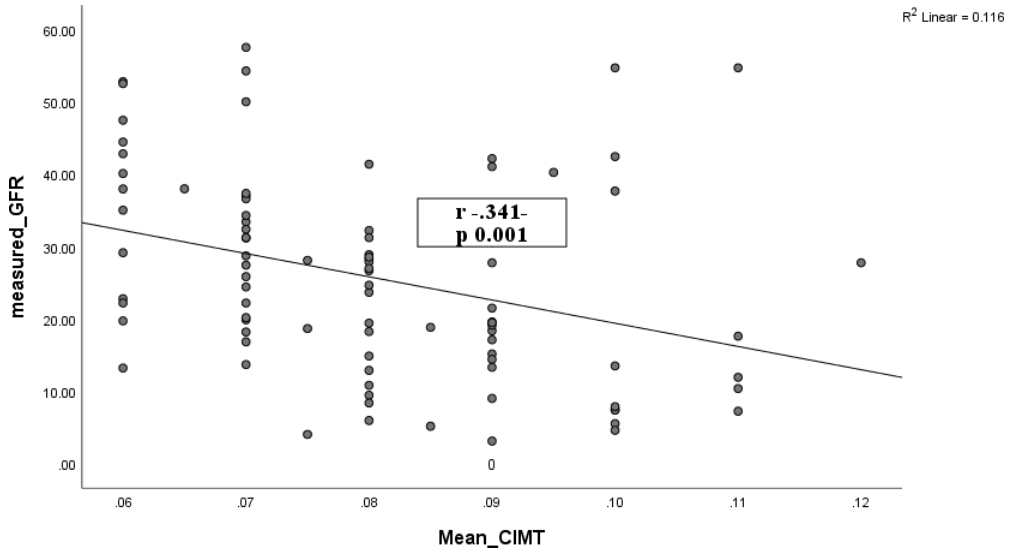

Figure (3): Correlation between carotid intimal–medial thickness (CIMT) and Measured GFR