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Prevalence and Risk factors of Proteinuria associated with Hypomagnesaemia among Chronic Kidney Disease Patients

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Abstract

Background: Magnesium is the second-most abundant intracellularcation after potassium and, which plays an important role in several biological processes Hypomagnesaemia is involved in the pathophysiology of hypertension, vascular calcification and metabolic derangements including diabetes mellitus and dyslipidemia, which are all risk factors for cardiovascular disease; the leading cause of mortality and morbidity in all stages of chronic kidney disease (CKD)

Aim of the Study: Our study aimed at investigatingthe prevalence and risk factors of Hypomagnesaemia associated with proteinuria and its impact on CKD patients

Patients and Methods: Our study was a cross-sectional study, included 132 subjects in 3 groups; Group I**:** comprised 50 proteinuricpatients with a mean age 50.64±13.48 years, Group II: comprised 50 non proteinuric with a mean age 50.16 ± 11.31years and Group III: comprised 32 end stage renal disease patients with a mean age 46.94±13.89 years.All subjects of this study underwent full medical history talking ,clinical examination and laboratory investigations.**Results:**There was statistically highly significant difference between the studied groups as regard Magnesium level; and the prevalence of hypomagnesaemia among proteinuric patients was 22%.

Conclusion: Patients with CKD have a high prevalence of proteinuria associated Hypomagnesaemia which may be considered as a good predictor of mortality among CKD patients.

INTRODUCTION

Magnesium is the second most abundant intracellular electrolyte and plays a significant role in essentially every biologic function within the cell **[1]**. It is important for bone and mineral metabolism, as well as for regulating vascular tone and heart rhythm **[2, 3]**. Magnesium does not appear to be controlled by any hormonal systems. Rather, the regulation of magnesium balance is dependent on intestinal absorption and renal excretion. Given the essential role of the kidneys in maintaining magnesium homeostasis, abnormalities in magnesium levels, including hypomagnesemia and hypermagnesemia, are not uncommon in patients with chronic kidney disease (CKD).

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Hypomagnesemia in CKD is usually the result of medication use **[4]** such as diuretics, calcineurin inhibitors or proton pump inhibitors **[5]** but it can also be caused by associated conditions like diabetes or volume expansion **[6]**. Hypomagnesemia has been investigated in non-CKD, CKD, and end stage renal disease (ESRD) patient populations and has been found to be associated with increased mortality **[7]**, notably increased cardiovascular mortality **[8,9]**. Hypomagnesemia has also been linked to a worsening rate of decline in eGFR, though this has not been clearly established **[10]**.

Hypermagnesemia in CKD is the result of decreased Glomerular Filtration Rate (GFR). Since urinary excretion is the primary magnesium regulatory system, plasma magnesium levels rise as renal function decreases **[11].** The relationship between hypermagnesemia and mortality is not as clear. Some studies suggest that mild elevations in serum magnesium levels are associated with a survival advantage **[12]**. There are no studies examining the associations between hypermagnesemia and CKD progression.

Our study examines the association between serum magnesium levels, all-cause mortality and progression of CKD in a large cohort of CKD patients.

PATIENTS AND METHODS:

This study was conducted at Internal Medicine Department, at both Zagazig University Hospitals and Kafr El Sheikh University Hospitals in 6 months; in the period from February 2020 to August 2020.Written informed consent was taken from the patients to participate in the study. Approval for performing the study was obtained from Internal Medicine Department, Zagazig University Hospitals after taking institutional review board (IRB) approval.

Study design and Population:

Our study was a cross-sectional study, conducted on 132 CKD patients divided into 3 groups:

Group I: comprised 50 proteinuric patients (21 females and 29 males with percentage of 58 % and 42 % respectively) with a mean age 50.64±13.48 years.

Group II: comprised 50 non proteinuric patients (25 females and 25 males with equal percentage of both gender) with a mean age 50.16 ± 11.31years.

Group III: comprised 32 end stage renal disease patients (16 females and 16 males with equal percentage of both gender) with a mean age 46.94±13.89 years.

Inclusion and Exclusion Criteria:

Inclusion criteria:

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Age group above 18 years old for both genders and CKD patients; not on dialysis and a small group on maintenance hemodialysis sessions on a schedule of 3 times/week, 3-4 h for each session.

Exclusion criteria:

Age group below 18 years old, Patients with chronic diarrhea, Patients having ileostomy or colostomy, Patients with malignancy and Unwilling patients to participate.

Physical Examination:

All participants were submitted to the following:

1) **History taking** (Hx of DM, HTN, CKD, drug history, previous operations).
2) **Full physical examination:**Vital signs,Blood pressure, Pulse examination , Temperature and respiratory rate, General Examination, Head and Neck, chest, abdomen and both limbs.

3) Investigations: Routine Investigations to fulfill inclusion and exclusion criteria including: S. albumin level (gm/dl)**,** S. potassium level(mg/dl), S. magnesium level(mg/dl), S. calcium level.(total and ionized)(mg/dl), Total cholesterol and triglycerides (mg/dl), Urine analysis dipsticks, CRP (mg/dl)

Pelvi-Abdominal U/S

Special Investigations:

- U.Albumin/Creatinine ratio (mg albumin/gm creat.) wasdetectedbyCayman'sHASEIAKit (competitiveassay)CaymanChemicalCompany,AnnArbor, Michigan48108USA.
- Urinary protein was measured both semi quantitatively with a dipstick test and quantitatively using the urinary albumin / creat. Ratio (mg albumin/gm creat)
- eGFR (ml/min/1.73 m^2) The estimated GFR was calculatedusingtheabbreviatedequationdevelopedbythe ModificationofDietinRenalDisease(**MDRD**)study.

RESULTS:

Fifty-three percent of the studied patients were males. Age ranged from 18 to 75 years with mean age 49.561 years **(Table1) (Figure1)**.

Table (1): Distribution of the studied patients according to demographic data:

Parameters	**N=132**	**%**

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Gender:		
• Female	62	47%
• Male	70	53%
Age (year):		
• Mean ±	49.561 ± 12.797	
• Range	18 – 75	

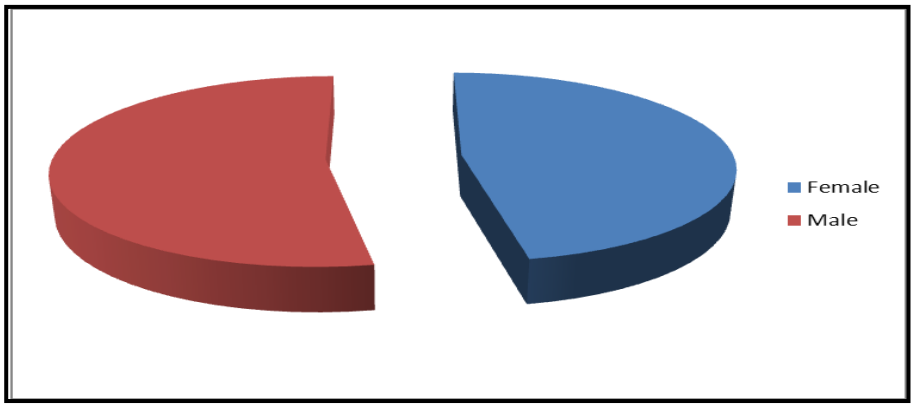

Fig. (1): Pie chart showing distribution of the studied patients according to gender.

Urinary albumin creatinine ratio ranged from 5 to 3214 with median 19.5. 37.9% of patients were non-proteinuric, 37.9% had proteinuria while 24.2% were ESRD on regular hemodialysis **(Table2) (Figure2)**.

Table (2): Distribution of the studied patients according to presence of proteinuria:

Parameters	**N=132**	**%**
Proteinuria:		
Proteinuric group	50	37.9%
Non-proteinuruic group/Normoproteinuric	50	37.9%
ESRD on regular hemodialysis	32	24.2%
Urinary albumin/creatinine ratio (n=124)		
Mean ± SD	347.573 ± 560.311	
Median (Range)	19.5 (5 – 3214)	

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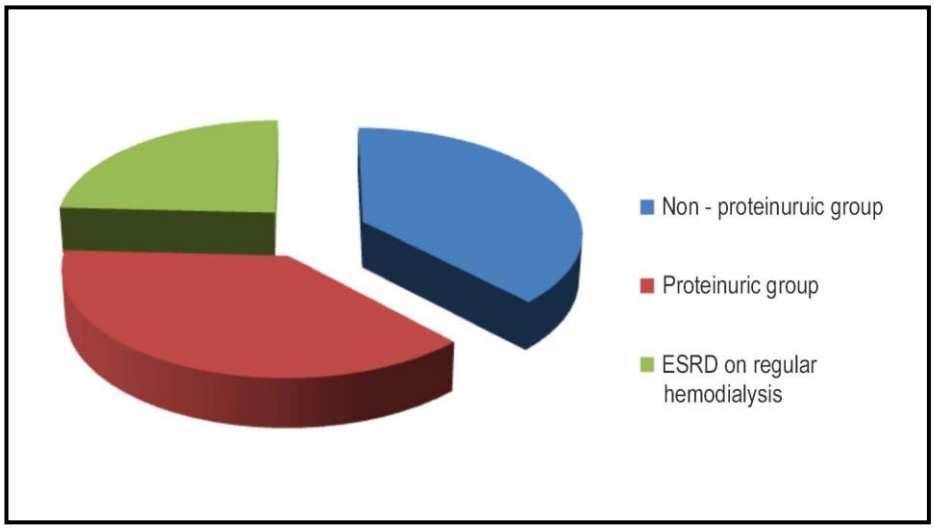

Fig. (2): Pie chart showing distribution of the studied patients according to presence of proteinuria.

There wasa statistically significant difference between the studied groups as regard comorbidities and diuretic use **(Table3) (Figure3)**.

Table (3): Demographic and clinical data of the studied groups:

Parameter	Groups			Test		
	Non-proteinur group	Proteinuric group	ESRD on regular hemodialysis group	χ^2/F	p	Pairwise comparison
	N=50 (%)	N=50 (%)	N=32 (%)			
Gender:						
Female	25 (50)	21 (42)	16 (50)	0.798	0.671	
Male	25 (50)	29 (58)	16 (50)			
Age (year):						
Mean ± SD	50.16 ± 11.31	50.64±13.48	46.94±13.89	0.904	0.408	
Range	29 – 75	23 – 75	18 – 68			
Diuretic use:						
No	5 (10)	2 (4)	11 (34.4)	17.1	0.001**	P_1 0.33
Loop diuretics	22 (44)	28 (56)	11 (34.4)			P_2 0.001**
Thiazide diuretics	23 (46)	20 (40)	10 (31.2)			P_3 0.024*

χ^2 Chi square test **p≤0.001 is statistically highly significant *p<0.05 is statistically significant f One Way ANOVA p1 the difference between non-proteiuric and proteinuricgroups, p2 the difference between proteiuric and ESRD on HD groups and p3 the difference between non-proteiuric and ESRD on HD groups

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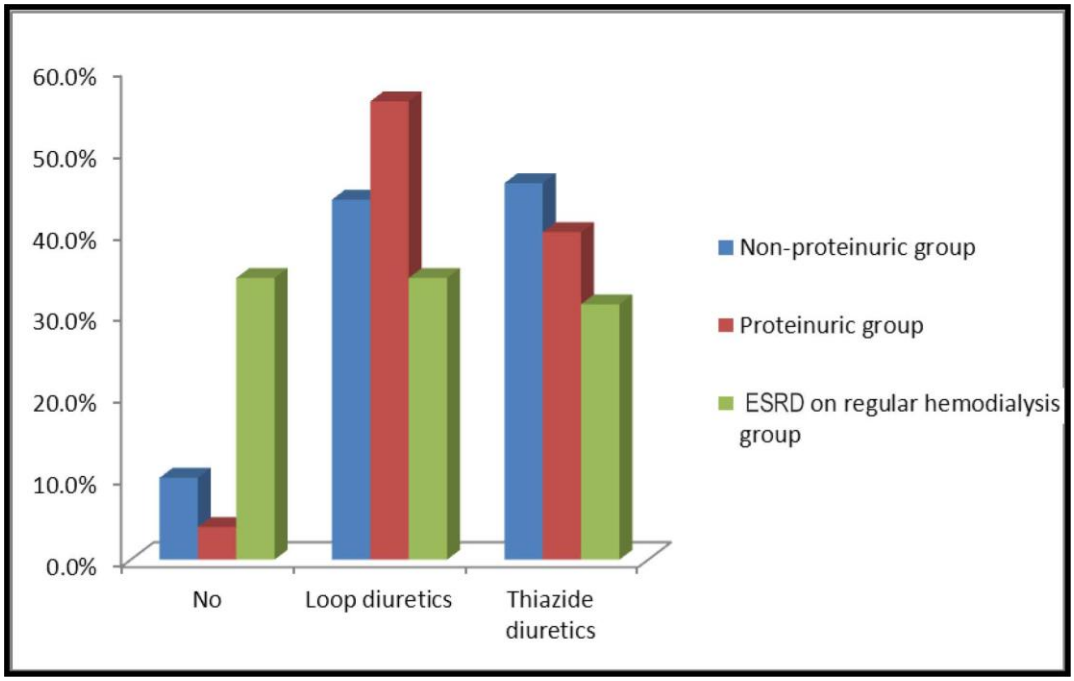

Fig. (3): Multiple bar chart showing comparison between the studied groups regarding diuretics

There wasa statistically significant difference between the studied groups regarding serum potassium, eGFR and parathyroid hormone. On LSD/pairwise comparison, the difference was significant between each two individual groups**(Table4).**

Table (4): Laboratory data of the studied groups:

Parameter	Groups			Test	
	Non-proteinuric group[(a)]	Proteinuric group[(b)]	ESRD on regular hemodialysis group[(c)]	F/KW	p
	Mean ± SD	Mean ± SD	Mean ± SD		
S. potassium(mg/d	4.12 ± 0.598 [a,b,c]	3.72±0.262[a,b,c]	4.51±0.796[a,b,c]	19.625	0.001**
Parathyroid horm (pg/ml)	158.14±95.85[a,b,c]	100.18±24.95[a,b,c]	261.34±97.47[a,b,c]	3.378[¥]	0.001**
eGFR(ml/min/1.73	19.108±7.73[a,b,c]	27.382±10.81[a,b,c]	8.197±1.56[a,b,c]	53.158	0.001**

F One way ANOVA *p<0.05 is statistically significant **p≤0.001 is statistically highly significant [¥]Kruskal Wallis test a non-proteniuric group b proteinuric group c ESRD on HD group [a,b] the difference is significant only between non-proteinuric and proteinuric groups [a,b,c] the difference is significant between each two individual groups

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There was a statistically significant difference between the studied groups regarding serum magnesium. On LSD comparison, the difference was significant between proteinuric group and each other group

Prevalence of hypomagnesaemia among proteinuric patients: number of patients with hypomagnesaemia/patients with proteinuria *1000=11/50*1000=220/1000.

Prevalence of proteinuria associated hypomagnesaemia among CKD patients= number of patients with proteinuric associated hypomagnesaemia/ patients with CKD* 1000= 11/ 132* 1000 =83.33/ 1000**(Table5) (Figure5)**.

Table (5): Comparison of serum magnesium among the studied groups:

Parameter	**Groups**			**Test**	
	Non-proteinuric group[(a)]	**Proteinuric group[(b)]**	**ESRD on regular hemodialysis group[(c)]**	**F/χ^2**	**p**
	N=50 (%)	**N=50 (%)**	**N=32 (%)**		
S. magnesium(mg/dL): Mean ± SD	2.236 ± 0.17	1.908 ± 0.328[¥]	2.228 ± 0.167	28.075	<0.001**
Magnesium level:					
Hypomagnesaemia	0 (0)	11 (22)[¥]	0 (0)	19.68	<0.001**
Normal level	50 (100)	39 (78)	32 (100)		

f One way ANOVA **p≤0.001 is statistically highly significant χ^2chi square test

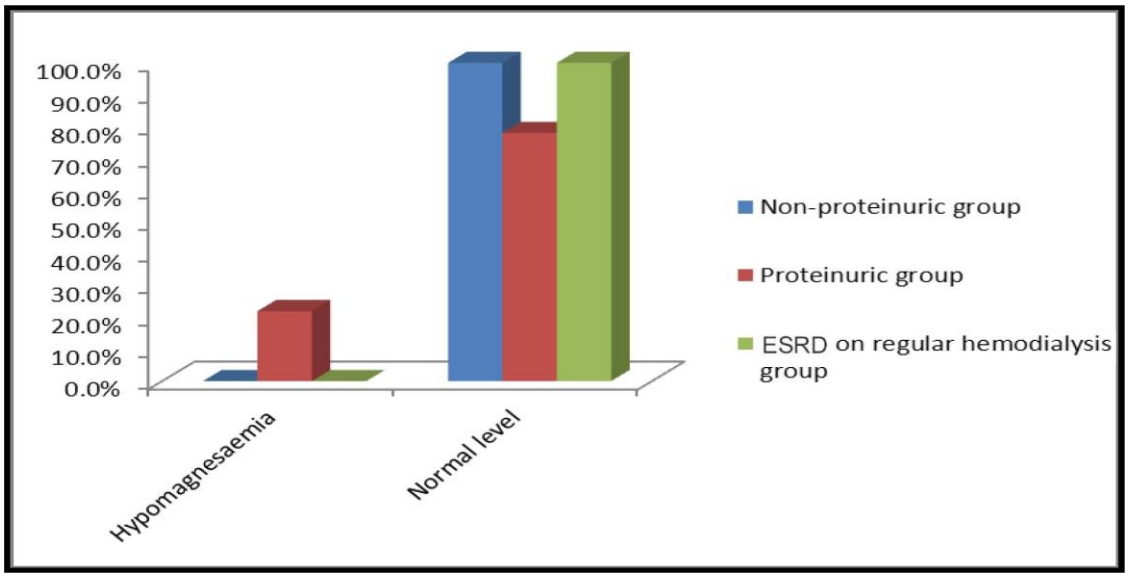

Fig. (5): Multiple bar chart showing comparison between the studied groups regarding presence of hypomagnesaemia

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There was no statistically significant correlation between either age, serum sodium, serum albumin, corrected calcium or triglycerides level **(Table 6)**.

Table (6): Correlation between serum magnesium and the studied laboratory parameters among the studied patients:

Parameters	Serum magnesium	
	R	p
Age (years)	-0.065	0.456
S. sodium(mg/dL)	0.056	0.523
S. albumin (g/dL)	0.126	0.15
Corrected calcium	-0.142	0.106
T. triglycerides(mg/dl)	0.015	0.865

r Pearson correlation coefficient ¥Spearman rank correlation coefficient **p≤0.001 is statistically highly significant

There was no statistically significant difference between normomagnesaemia and hypomagnesaemia patients regarding gender, age, comorbidities, diuretic or PPI use **(Table 7)**.

Table (7): Demographic and clinical data of the proteinuric patients classified according to their serum Mg level:

Parameter	Proteinuric group		Test	
	Hypomagnesae	Norma Mg lev	χ^2	p
	N=11 (%)	N=39 (		
Gender:				
Female	7 (63.6)	14 (35.9	Fi	166
Male	4 (36.4)	25 (64.1		
Age (year):			-	
Mean ± SD	48.64 ± 13.86	51.21±1	0.5	582
Comorbidit				
No	0 (12)	5 (12.8)		
Diabetes	6 (54.5)	19 (48.7	1.0	742
Hypertensio	3 (27.3)	8 (20.5)		
DM, hypertensio	2 (18.2)	7 (17.9)		
Diuretic us				
No	0 (10)	2 (5.1)		
Loop diureti	6 (54.5)	22 (56.4	0.0	99
Thiazide diuretics	5 (45.5)	15 (38.5		

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PPI use:			
No	7 (63.6)	24 (61.5	4.987
Yes	4 (36.4)	15 (38.5	

PPI Proton Pump inhibitor χ^2 **Chi square test**

Urinary ACR (>714), serum albumin (<3.4 g/dl) increased risk of proteinuria associated hypomagnesaemia by 20.795, 3.693 and 23.1 folds respectively **(Table 8)**.

Table (8): Multivariate analysis of factors significantly associated with hypomagnesaemia among proteinuric group:

Parameters	**β**	**p**	**AOR**	**95% C.I.**	
				Lower	**Upper**
Serum albumin (<3.4)	1.306	0.185	3.693	0.535	25.507
Urinary Albumin Creatir ratio (>714)	3.035	0.015*	20.795	1.813	238.47

AOR adjusted odds ratio *p<0.05 is statistically significant CI Confidence interval

There was statistically highly significant difference between the studied groups as regard Magnesium level; and the prevalence of hypomagnesaemia among proteinuric patients was 22%. While, There was non-significant positive correlation between each of sex, serum creatinine and serum urea with serum magnesium.

Besides, there was statistically significant difference between the studied groups regarding serum potassium, eGFR. On the other hand, there was statistically non-significant difference between the studied groups as regard age, gender or PPI use.

There was significant negative correlation and inverse relation between serum magnesium and CRP **(Table 9)**.

Table (9): LSD comparison:

Dependent Variable	**(I) Proteinuria.group**	**(J) Proteinuria.group**	**Sig.**
Age (years)	Non-proteinuric group	Proteinuric group	.852
		CKD on regular hemodia group	.268
	Proteinuric group	Non-proteinuric group	.852
		CKD on regular hemodia group	.204
	CKD on regular hemodia	Non-proteinuric group	.268

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	group	Proteinuric group	.204
	Non-proteinuric group	Proteinuric group	.303
		CKD on regular hemodia group	.055
Serum sodium (mg/dl)	Proteinuric group	Non-proteinuric group	.303
		CKD on regular hemodia group	.308
	CKD on regular hemodia group	Non-proteinuric group	.055
		Proteinuric group	.308
	Non-proteinuric group	Proteinuric group	.001
		CKD on regular hemodia group	.003
Serum potassium (mg/dl)	Proteinuric group	Non-proteinuric group	.001
		CKD on regular hemodia group	.000
	CKD on regular hemodia group	Non-proteinuric group	.003
		Proteinuric group	.000
	Non-proteinuric group	Proteinuric group	.000
		CKD on regular hemodia group	.886
Serum magnesium(mg/dl)	Proteinuric group	Non-proteinuric group	.000
		CKD on regular hemodia group	.000
	CKD on regular hemodia group	Non-proteinuric group	.886
		Proteinuric group	.000
	Non-proteinuric group	Proteinuric group	.000
		CKD on regular hemodia group	.000
Serum creatinine(mg/dl)	Proteinuric group	Non-proteinuric group	.000
		CKD on regular hemodia group	.000
	CKD on regular hemodia group	Non-proteinuric group	.000
		Proteinuric group	.000
	Non-proteinuric group	Proteinuric group	.000
		CKD on regular hemodia group	.000
Serum urea N(mg/dl)	Proteinuric group	Non-proteinuric group	.000
		CKD on regular hemodia group	.000
	CKD on regular hemodia group	Non-proteinuric group	.000
		Proteinuric group	.000
Total Trigelcrides(mg/dl)	Non-proteinuric group	Proteinuric group	.393

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		CKD on regular hemodia group	.853
		Non-proteinuric group	.393
	Proteinuric group	CKD on regular hemodia group	.569
	CKD on regular hemodia group	Non-proteinuric group	.853
		Proteinuric group	.569
		Proteinuric group	.000
	Non-proteinuric group	CKD on regular hemodia group	.000
		Non-proteinuric group	.000
eGFR(ml/min/1.73 m²)	Proteinuric group	CKD on regular hemodia group	.000
	CKD on regular hemodia group	Non-proteinuric group	.000
		Proteinuric group	.000

DISCUSSION

Magnesium is the second-most abundant intracellularcation after potassium and, overall, the fourth-most abundant cation after sodium, potassium and calcium. It plays a fundamental role in many functions of the cell, including energy transfer, storage, and use; protein, carbohydrate, and fat metabolism; maintenance of normal cell membrane function; and the regulation of parathyroid hormone (PTH) secretion**[13].**

Systemically, magnesium lowers blood pressure and alters peripheral vascular resistance. Hypomagnesaemia is involved in the pathophysiology of hypertension, vascular calcification and metabolic derangements including diabetes mellitus and dyslipidemia, which are all risk factors for cardiovascular disease; the leading cause of mortality and morbidity in all stages of chronic kidney disease (CKD)**(Kanbay et al. [12]** including end-stage renal disease (ESRD)**[13].**

However, compared to the wide attention in the derangement of calcium and phosphate metabolism and the vascular/valvular calcification, the magnesium metabolism is usually neglected and is still among the less well understood clinical problems encountered by nephrologists**[14,15].**

In our study**,** there was statistically highly significant difference between the studied groups regarding **serum parathyroid hormone** (P = 0.001). On LSD/pairwise comparison, the difference is significant between each two individual groups and there is significant negative correlation between serum magnesium and PTH (r=-0.189, p=0.03). This is in agreement with **Ohya et al., (2014) [16]**whofound that the serum magnesium level was significantly higher in patients with low parathyroid hormone levels and they also concluded that serum parathyroid hormone levels had a significant negative correlation with the serum magnesium levels in their study on 1231 ESRD patients in Japan ($p < 0.01$) and **Mansour, Hayam H., et al.[17]**who found

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that there was a significant negative correlation between serum Mg level and iPTH ($r=-0.253$, $P<0.05$).

Since numerous studies suggested an association between magnesium disorders and risk factors of cardiovascular disease, such as diabetes mellitus, metabolic syndrome, coronary artery disease and atherosclerosis risk in the general population, so the impact of magnesium disorders on the prognosis of patients with chronic kidney disease has received a great deal of interest **[18].**

Therefore, this study was conducted in the period fromFebruary 2020 to August 2020 at the Internal Medicine Department and Clinical Pathology Department at both Zagazig University hospitals, Kafr El Sheikh university hospitals aiming toelucidate the prevalence and risk factors of decrease Mg level associated with proteinuria and its impact on chronic kidney disease patients. The study was approved by Institutional Review Board (IRB)approval and included a total of 132 patients; 50 patients (37.9%) - were non-proteinuric, 50 patients (37.9%) had proteinuria while 32 patients (24.2%) were ESRD on regular hemodialysis.

We found that 53% of the studied patients were males and 47% were female and the mean age (in years) in the non proteinuric, proteinuric and ESRD was 50.16 ± 11.31, 50.64±13.48 and 46.94±13.89 respectively.

There was statistically no significant difference between the studied groups as regard **age, gender**. This is in agreement with **Rao, Shariff.[19]**in their study they use sample size of 100 patients; 50% of them were proteinuric and 50% were non proteinuric. About 66% were males and 34% were females in both groups and the mean age (years) in proteinuric and non proteinuric were 53.06 ± 10.93 and 56.12 ± 11.754, respectively.

In our study**,** there was statistically highly significant difference between the studied groups as regard diuretic use (P value is 0.001). On pairwise comparison concerning diuretic use, the difference is highly significant between proteinuric and each other group; (p2 is 0.001) which represents the difference between proteinuric and ESRD on HD and (p3 is 0.024) which represents the difference between non-proteinuric and ESRD on HD groups.

This was in agreement with **Gröber, Schmidt et al.[20]** who found that hypertensive patients on long-term treatment with diuretics mainly thiazide diuretics should be monitored for magnesium deficiency, particularly those with additive risk factors, such as age >60, hydrochlorothiazide doses; 25 mg/day in more than 6 months duration therapy that can cause hypomagnesaemia in 48% of patients.

In our study**,** there was no significant difference between the studied groups as regard use of PPI (P=0.087), in contrast **Tamura, Sakaeda et al.[21]** who studied the effect of omeprazole and esomeprazole use on serum Mg level and found that long term use of PPI as omeprazole and esomeprazole is associated with hypomagnesaemia in around 13% of patients. It is may be due to low sample size in our study and short period of follow up.

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In our study**,** there was statistically highly significant difference between the studied groups as regard Mg level (P =0.001). The normal range of Magnesium level in our study was (1.7 - 2.4mg/dl).On LSD comparison, the difference is significant between proteinuric group and each other group;Prevalence of hypomagnesaemia among proteinuric patients= number of patients with hypomagnesaemia/patients with proteinuria =22%, Prevalence of proteinuric associated hypomagnesaemia among CKD patients= number of patients with proteinuric associated hypomagnesaemia/patients with CKD =0.08%.

This was in agreement with **Takayuki Hamano et al.[22]**, their study was on 5126 patients, hypomagnesaemia was the most common electrolyte abnormality (14.7%) with similar prevalence across stages of CKD. Positive proteinuria was a risk factor of hypo-Mg (odds ratio 2.2; 95% confidence interval 1.2–4.0).**Caibao Luet al.[23],** their study was on 413 CKD patients, among them 199 patients show hypomagnesaemia with mean Mg level (0.89±0.08mmol/l) with P value <0.001. **Rao, Shariff. [19],** their study on 100 CKD patients with type II DM, divided into 2 equal groups; proteinuric and non proteinuric, showed about 6% of proteinuric group had hypomagnesaemia (mean 2.09 ± 0.28 mg/dl).

In our study**,** there was statistically highly significant difference between the studied groups regarding serum parathyroid hormone (P = 0.001). On LSD/pairwise comparison, the difference is significant between each two individual groups and there is significant negative correlation between serum magnesium and PTH (r=-0.189, p=0.03). This was in agreement with **Ohya et al. [24]**whofound that the serum magnesium level was significantly higher in patients with low parathyroid hormone levels and they also concluded that serum parathyroid hormone levels had a significant negative correlation with the serum magnesium levels in their study on 1231 ESRD patients in Japan ($p < 0.01$) and **Mansour, Hayam H., et al.[17]**who found that there was a significant negative correlation between serum Mg level and iPTH ($r=-0.253$, $P<0.05$).

CONCLUSION:

From all of the above results we can conclude that patients with chronic kidney disease have a high prevalence of proteinuria associated hypomagnesaemia, proteinuria was an independent risk factor for hypomagnesaemia among CKD patients. Also, our results supported that a lower level of serum Mg was associated with high inflammatory response and hypomagnesaemia was a good predictor of mortality among CKD patients.

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