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RELATIONSHIP BETWEEN SERUM MAGNESIUM AND ERYTHROPOIETIN RESPONSIVENESS IN HEMODIALYSIS PATIENTS

By

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ABSTRACT

Background: Serum magnesium is associated with anemia. But the roles of magnesium in anemia and erythropoietin (EPO) responsiveness remain not well knwon in maintenance hemodialysis (MHD) patients.

Objective: to study the level of serum magnesium and its relationship with EPO responsiveness in MHD patients.

Patients and methods: This study was done in hemodialysis unit at Bab El-Shaareya University Hospital, during the period of January 2020 to June 2020. A total of 60 regular hemodialysis (RHD) patients were recruited for this survey. Their anthropometrics and laboratory data were collected. EPO responsiveness was evaluated by the erythropoietin resistance index (ERI). The patients were divided into 2 groups according to EPO resistance Index (ERI) Group A, the patients with higher ERI than 1.52, and group B with lower ERI than 1.52. Multivariate logistic regressions were conducted to evaluate the factors that may be associated with EPO responsiveness.

Results: The mean serum magnesium level was higher than normal levels in RHD patients, while nearly no hypomagnesemia was observed. A multivariate logistic regression model revealed that lower serum magnesium levels were correlated with a high ERI. The OR of a high ERI was found to be 2.89 (93% CI 1.197–4.715, p = 0.005) for group A and 1.57 (94% CI 0.779—2.941, p > 0.05) for group.

Conclusion: Serum magnesium levels were found to be higher than normal levels in RHD patients. A high serum magnesium level was shown to be correlated with good EPO responsiveness and it has a protective role from EPO hyporesponsiveness.

Keywords: Hemodialysis, serum magnesium, erythropoietin responsiveness, erythropoietin resistance index.

INTRODUCTION

ESRD is defined as Kidney damage for ≥3 months by structural or functional abnormalities of the kidney, with GFR<15 ml/min *(Yu et al., 2017)*. The current prevalence and projected growth in the ESRD population worldwide reflects the increasing burden of CKD and the conditions that cause CKD. The Global Burden of Disease study ranked CKD as the 19th leading cause of global years of life lost in 2013, an increase from 36th in 1990 *(GBD, 2013)*. The goal of renal replacement therapy is primarily to restore the chemical and fluid balance in uremia

(milieu interior). In hemodialysis (HD), the processes of diffusion and convection are combined to achieve solute exchange and water removal across a semipermeable membrane to provide the necessary blood purification. Diffusion takes place through random movement of molecules that lead to a net solute transfer from higher to lower concentration between compartments separated by the semipermeable membrane. The diffusive capacity depends on the concentration gradient, the diffusive coefficient of the solute, and membrane properties *(Locatelli et al., 2009)*. The major cause of anemia is insufficient erythropoietin (EPO) levels in MHD patients *(Lau et al., 2015)*. The administration of erythropoiesis stimulating agents (ESAs) in the treatment of anemia of ESRD has been the single most important aspect of anemia protocols for over three decades. However, current ESA dosing guidelines do not appear to provide information about optimal ESA therapies *(Chait et al., 2014)*. Unfortunately, a considerable proportion of end-stage renal disease patients exhibit a suboptimal hematologic response to EPO, as evidenced by the persistence of anemia despite adequate dosing or by the need for high-dose EPO therapy to achieve the recommended hemoglobin target *(Ogawa et al., 2014)*. The definition of EPO hyporesponsiveness has been introduced to identify the inability to achieve or maintain target hemoglobin levels despite higher than usual doses of EPO. However, observational studies suggested that higher EPO doses were needed to achieve anemia correction associated with higher risks of all-cause mortality and cardiovascular events *(Bellinghieri et al., 2015)*. Several risk factors for EPO hypo responsiveness have been identified, including inadequate iron administration, inflammation, malnutrition, suboptimal dialysis, secondary hyperparathyroidism, and malignancy *(Kanbay et al., 2010)*. Serum magnesium was associated with C-reactive protein *(Sakaguchi et al., 2014)*, intact parathyroid hormone (i PTH) and hemoglobin in MHD patients *(Yu et al., 2017)*. Magnesium deficiency may increase the risks for cardiovascular and all-cause mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) *(Xiong J et al., 2019)*. However, the evidence to support the relationship between serum magnesium and EPO responsiveness is limited *(Blaine et al. 2015)*.

The present work aimed to evaluate the relationship between serum Mg level and EPO responsiveness in regular hemodialysis patients.

PATIENTS AND METHODS

This was an observational cohort study with retrospective data analysis including sixty (age and sex matched) patients with end stage renal disease. The study was conducted in Nephrology Unit Bab El-Shaareya University Hospital during the period of January 2020 to June 2020.

Inclusion criteria:

Patients aging 16 years or more. Duration of dialysis > 3 months, in stable condition. Use of arteriovenous fistula in the patients.

Exclusion criteria:

Age <16 years, Active bleeding or pure red cell aplasia & nonuse of EPO. Patients who have malignant diseases. Patients

with hepatic impairment or infectious diseases in nearly a month. Patients receiving phosphate chelators containing magnesium or laxatives containing magnesium

At enrollment, all patients were subjected to the following: Full history taking from patients including sex, age, weight, primary kidney disease, EPO use, and iron treatments. Complete clinical examination. Basal laboratory work-up: (serum creatinine, Blood Urea, BUN pre, BUN post, CRP, iron profile, S .Albumin, CBC, iPTH and serum magnesium). All patients were undergoing hemodialysis 3 times per week and 4 h per dialysis. All patients were using heparin anticoagulants and standard dialysis fluids; the dialysate flow was 500 mL/min, and the blood flow rate was 200–350 mL/min, All patients have URR> 60%. All patients were taking recombinant human EPO injection. The EPO responsiveness was evaluated by the erythropoietin resistance index (ERI). The ERI was calculated by dividing the weekly weight-adjusted (kg) dose of EPO (IU) by the hemoglobin level (g/dL).

All patients were divided into 2 groups by the median of the ERI as follows: low ERI group (ERI ≤11.52 IU/week (g/dL)–1/kg) and high ERI group (ERI > 11.52 IU/week (g/dL)–1/kg).

Statistical Analyses were done to evaluate the results.

The SPSS 17.0 statistics package for Windows was used for statistical analysis. Normally distributed continuous variables were expressed as the mean ± SD, and Student t tests were used for comparing the mean values of the data. Nonnormally distributed variables were shown as medians (P25, P75), and comparisons between the 2 groups were analyzed by Mann-Whitney U tests. Categorical variables were expressed as the number and percentage for each item, and chi-square analysis was used. The comparison among > 2 groups was analyzed by one-way ANOVA (normally distributed continuous variables) or Kruskal-Wallis tests (no normally distributed variables). $p < 0.05$ was considered statistically significant.

All procedures followed Al-Azhar University ethical committee regulations, and patients gave written consents.

No financial support.

RESULTS

Patient Characteristics:

A total of 60 patients were involved in this study. The mean age was 39.8 ± 17.3 years, (33/60) 55% of the patients were males, and the mean dialysis vintage was 87 ± 41 months. The primary diseases of the patients included diabetic renal disease, (21/60) (35%), chronic glomerulonephritis, (7/60) (11.7%); hypertensive-related nephropathy, (21/60) (35%); chronic tubulointerstitial nephritis, (5/60) (8.3%); and obstructive and other diseases, 6 (10 %).

There was no significant difference between the 2 groups as regard age and sex distribution **(Table 1)**.

Table (1): Comparison between the 2 groups as regard age and sex distribution

Patients / Groups	Males	Females	P V	Age	P V
Group A	14	16	> 0.05	34.6 ± 5.85	> 0.05
Group B	15	15	> 0.05	36.7 ± 6.13	> 0.05

There was no significant difference between the 2 groups as regard dry body weight **(Table 2)**.

Table (2): Comparison between the 2 groups as regard DBW

DWt / Groups	MEAN	p- value
Group A	67.14 ± 1.62	> 0.05
Group B	70.23 ± 1.57	> 0.05

There was no significant difference between the 2 groups as regard kidney function tests **(Table 3)**.

Table (3): Comparison between the 2 groups as regard kidney function tests

KFTs / Groups	S. Creat	Urea	BUN pre	BUN post	p-value
Group A	9.18 ± 0.32	98.3 ± 2.87	45.85 ± 1.26	16.05 ± 0.62	> 0.05
Group B	9.43 ± 0.33	99.6 ± 2.56	46.30 ± 1.21	16.50 ± 0.57	> 0.05

There was no significant difference between the 2 groups as regard cause of end stage renal disease **(Table 4)**.

Table (4): Comparison between the 2 groups as regard cause of end stage renal disease

Cause of ESRD / Groups	DM	HTN	GN	CTIN	OBSTR.	UNKNWON
Group A	11	10	3	3	1	2
Group B	10	11	4	2	2	1

There was no significant difference between the 2 groups as regard TLC, PLT **(Table 5)**.

Table (5): Comparison between the 2 groups as regard TLC, PLT

TLC&PLT / Groups	TLC	PLT	p- value
Group A	6.53 ± 0.29	330.32 ± 14.62	> 0.05
Group B	6.68 ± 0.27	313.80 ± 14.15	> 0.05

There was no significant difference between the 2 groups as regard Hb , Iron and Ferritin **(Table 6)**.

Table (6): Comparison between the 2 groups as regard Hb , Iron and Ferritin

FE / Groups	Hb	Iron	Ferritin	p- value
Group A	8.47 ± 0.148	89.07 ± 2.72	174.25 ± 11.85	> 0.05
Group B	10.34 ± 0.143	92.61 ± 2.63	251.70 ± 10.38	> 0.05

There was no significant difference between the 2 groups as regard S. Albumin and iPTH **(Table 7)**.

Table (7): Comparison between the 2 groups as regard S. Albumin and iPTH.

Alb&iPTH / Groups	Alb	iPTH	p- value
Group A	3.93 ± 0.075	204.03 ± 9.40	> 0.05
Group B	3.98 ± 0.078	206.47 ± 9.11	> 0.05

There was a significant difference between the 2 groups as regard S. Mg **(Table 8)**.

Table (8): Comparison between the 2 groups as regard S. Mg

Mg / Groups	Mg	p- value
Group A	1.825 ± 0.069	< 0.05
Group B	2.993 ± 0.067	< 0.05

There was a significant difference between the 2 groups as regard EPO dose/Wk and ERI **(Table 9)**.

Table (9): Comparison between the 2 groups as regard EPO dose/Wk and ERI:

EPO / Groups	EPO/Wk	ERI	p- value
Group A	8392.75 ± 288.95	14.90 ± 0.497	< 0.05
Group B	5982.2 ± 279.7	8.405 ± 0.481	< 0.05

In the investigated patients, the serum magnesium level ranged from 1.3 mg/dL to 3.5 mg/dL, and the mean serum magnesium level was 2.43 ± 0.47 mg/dL.

The ERI range of all patients was from 1.79 to 23.17 IU/week (g/dL)–1/kg, and the mean ERI was (11.67 ± 5.39) IU/week (g/dL)–1/kg. Serum magnesium levels were correlated with a high ERI according to the median ERI. The index of transferrin saturation, serum ferritin, and the proportion of venous iron replacement therapy, age, gender, serum albumin, serum creatinine, pre BUN, post BUN, PLT, WBCs were similar in the 2 ERI groups.

DISCUSSION

In our study, serum magnesium level was found significantly higher than the normal level in MHD patients, and a few of the patients had hypermagnesemia, that was consistent with a previous study done by *Ling Yu et al; in 2017* and was confirmed by the same authors in (2019). The intestinal intake and renal excretion

regulate serum magnesium *(Blaine et al., 2015)*.

In ESRD patients, where kidney function is lost, serum magnesium levels are elevated and are higher than in the normal population. Fatal hypermagnesemia is rare in hemodialysis patients, due to the excretion of magnesium by regular hemodialysis (dialysis liquid magnesium is 0.5 mmol/L) so excess Mg is lost on HD session *(Yoon et al., 2013)*.

EPO hyporesponsiveness is still observed in some ESRD patients who are on regular Hemodialysis. An association between EPO hyporesponsiveness and poor clinical outcomes, such as anemia, heart failure, and increased cardiovascular and all-cause mortality was observed *(Yu et al., 2017)*.

EPO responsiveness can be assessed by the ERI is a sensitive evaluation index of EPO responsiveness and ERI can predict composite events (CVD, infection, hospitalization, or death) and all-cause mortality in regular hemodialysis patients *(Okazaki et al., 2014)*.

This study demonstrated that ERI values were from 2.26 to 32.61 IU/week (g/dL)–1/kg, and the mean ERI value was (12.67 ± 6.17) IU/week (g/dL)–1/kg. These results are consistent with data reported by *Chang et al. (2011)* and *Yu et al. (2019)*.

The results of our study showed that a higher serum Mg level was associated with a lower risk of EPO hyporesponsiveness as established by the ERI, which were partly in line with the results reported by *Mallick et al. (2012)* and *Yu et al. (2019)*.

An inverse association between serum magnesium and anemia was found in a large cohort of Chinese adults *(Zhan et al., 2014)*.

We found that the risk of EPO hyporesponsiveness was 2.83 times greater in the lower magnesium group compared with that in the higher magnesium group. However, the mechanism of the effect of serum magnesium on EPO responsiveness is unclear. Serum magnesium may play a role in various ways. First, magnesium is the second most abundant intracellular cation after potassium and is a co-factor in > 300 enzymatic reactions involving energy metabolism, protein and nucleic acid synthesis, and the balance of membrane potential. Therefore, EPO responsiveness was improved by affecting the energy metabolism of erythrocytes and the synthesis of hemoglobin. Oxidative stress could induce EPO hyporesponsiveness in anemia during end stage renal disease *(Khalil et al., 2016)*.

Magnesium deficiency may lead to the generation of reactive oxygen species by enhancing the recruitment of phagocytic cells or Magnesium deficiency may increase intracellular Ca2+ by activating the L-type calcium channel and enhance the activation of the N-methyl-D-aspartate receptor or initiate the inflammatory process, induces the production of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β *(Yu et al., 2019)*.

Higher magnesium intake or serum magnesium improved insulin sensitivity, which was associated with EPO responsiveness in regular HD patients *(Abe et al., 2011)*.

Magnesium improved EPO responsiveness, which may be mediated partly by increasing serum albumin as suggested by *Toprak et al. (2017).*

CONCLUSION

Serum magnesium levels were higher than normal levels in regular HD patients. Serum magnesium level was a factor correlated with EPO responsiveness. A high serum magne level was correlated with good EPO responsiveness.

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العلاقة بين مستوى الماغنيسيوم في الدم ومعدل الإستجابة لعقار الإريثروبيوتين في المرضى المعاشين على الاستصفاء الدموي

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خلفيـــة البحـــث: يـــرتبط الماغنيســـيوم مـــع فقـــر الـــدم. ولكـــن أدوار الماغنيســـيوم فـــي فقـــر الـــدم و نقـــص الاســـتجابة لعقـــار الإريثروبيـــوتين لا تـــزال غيـــر معروفة جيدا في مرضى الاستصفاء الدموي المزمن.

الهـــدف مـــن البحـــث: دراســـة مســـتوى الماغنيســـيوم فـــي المصـــل وعلاقتـــه باستجابة الإريثروبيوتين في مرضى الاستصفاء الدموي المزمن.

المرضـــى وطـــرق البحـــث: أجريـــت هـــذه الدراســـة فـــي وحـــدة الكلـــى الصـــناعية بمستشـــفي بـــاب الشـــعرية الجـــامعي فـــي الفتـــرة مـــن ينـــاير 2020م وحتـــي يونيـــو 2020م. وضـــمت الدراســـة 60 مريضًـــا مـــن مرضـــي الغســـيل الـــدموي المـــزمن. وقـــد جُمعـــت بيانـــات القياســـات البشـــرية والمختبـــرات الخاصـــة بهـــا. تـــم تقيـــيم اســـتجابة الإريثروبيـــوتين عـــن طريـــق مؤشـــر مقاومـــة الإريثروبـــويتين (ERI). تـــم تقســـيم المرضـــى إلـــى مجمـــوعتين وفقـــا لهـــذا المؤشـــر. مجموعـــة (أ) وتشـــمل المرضـــي الأكثـــر مـــن 1.52 ومجموعـــة (ب) الأقـــل مـــن ذلـــك الـــرقم بالنســـبة لمؤشـــر مقاومـــة الإريثروبيـــوتين. وتـــم عمـــل الدراســـات الإحصـــائية لتقيـــيم العوامـــل التـــي قـــد تـــرتبط بمقاومـــة الإريثروبيوتين.

نتـــائج البحـــث: متوســـط مســـتويات المصـــل مـــن الماغنيســـيوم وجـــد أنـــه أعلـــي مـــن الطبيعـــي فـــي المرضـــى المعاشـــين علـــي الاستصـــفاء الـــدموي بينمـــا لا

يكـــاد يلاحـــظ نقـــص فـــي الماغنيســـيوم فـــي مرضـــى الاستصـــفاء الـــدموي. ولـــوحظ أن نقـــص مســـتويات المصـــل مـــن الماغنيســـيوم مـــرتبط بزيـــادة المقاومة للإريثروبيوتين.

الاســـتنتاج: وجـــد أن متوســـط مســـتويات الماغنيســـيوم فـــي المصـــل تكـــون أعلـــى مـــن المســـتويات العاديـــة فـــي المرضـــى المعاشـــين علـــي الاستصـــفاء الـــدموي. وقـــد تبـــين أن ارتفـــاع مســـتوى الماغنيســـيوم بالمصـــل يكـــون مرتبطـــا مـــع اســـتجابة جيـــدة للإريثروبيـــوتين وأن الماغنيســـيوم لـــه دور وقـــائي مـــن نقص الاستجابة للإريثروبيوتين.

الكلمـــات الدالـــة: غســـيل كلـــوي، مســـتوي الماغنســـيوم فـــي الـــدم، الإســـتجابة لعقار الإريثروبيوتين، مؤشر مقاومة الإريثروبيوتين.