

BIOMARKERS INVOLVED IN THE MINERAL-BONE DISORDERS SECONDARY TO CHRONIC HEMODIALYSIS

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Abstract

Introduction. Chronic kidney disease (CKD) is one of the most prevalent public health problems of the elderly population. End-Stage Renal Disease (ESRD)'s most common treatment is dialysis. There are some dissimilarities between the sexes that are apparent in the status and the possible outcomes of CKD. This study aims to shed some light on these somewhat overlooked variations and their implications.

Materials and methods. We conducted an observational study on subjects with CKD, undergoing hemodialysis for at least 2 years. For participation, we selected an equal number of men and women, which were divided into 2 groups according to gender. Plasma levels of the following parameters were monitored: creatinine, urea, bicarbonate, phosphorus, calcium, alkaline phosphatase, vitamin D, FGF-23 and TNF-alpha. The differences of the variables between the two groups were evaluated using TTEST and CORREL test.

Results. A significant correlation was between the plasma levels of FGF-23 and gender ($p = 0.02$). Regarding the plasmatic levels of urea, besides the expected difference in pre- and post- dialysis levels, we obtained a significant correlation between its post-dialysis value and gender ($p = 0.045$). In regard to the plasmatic levels of the alkaline phosphatase, there was a significant correlation between its value and gender ($p = 0.01$).

Conclusions. There is a significant correlation between the plasmatic levels of creatinine, urea, alkaline phosphatase, vitamin D, FGF-23 and gender. Women present lower levels of creatinine and urea, while men present lower plasmatic levels of vitamin D, alkaline phosphatase and FGF-23.

Keywords: chronic kidney disease, hemodialysis, biomarkers.



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Abstract

Introducere. Boala cronică de rinichi este una dintre cele mai răspândite probleme de sănătate publică în rândul populației vârstnice. Cel mai frecvent tratament al bolii renale în stadiu terminal (IRST) este dializa. Există unele diferențe între sexe, care sunt evidente în evoluția și prognosticul posibil al bolii cronice de rinichi. Acest studiu își propune să arunce o lumină asupra acestor variații oarecum trecute cu vederea și a implicațiilor lor.

Material și metodă. Am realizat un studiu observațional care a inclus subiecți cu boală cronică de rinichi, supuși hemodializei cel puțin 2 ani. Pentru participare, am selectat un număr egal de bărbați și femei, care au fost împărțiți în două grupe în funcție de sex. Au fost monitorizate nivelurile plasmatice ale următorilor parametri: creatinină, uree, bicarbonat, fosfor, calciu, fosfatază alcalină, vitamina D, FGF-23 și TNF-alfa. Diferențele variabilelor dintre cele două grupuri au fost evaluate folosind testul TTEST și CORREL.

Rezultate. S-a înregistrat o corelație semnificativă între nivelurile plasmatice de FGF-23 și sex ($p=0,02$). În ceea ce privește nivelurile plasmatice de uree, pe lângă diferența anticipată între valorile pre și post-dializă, am obținut o corelație semnificativă între valoarea post-dializă și sex ($p=0,045$). În ceea ce privește nivelurile plasmatice ale fosfatazei alcaline, a existat o corelație semnificativă între valoarea acesteia și gen ($p=0,01$).

Concluzii. Există o corelație semnificativă între nivelurile plasmatice de creatinină, uree, fosfatază alcalină, vitamina D, FGF-23 și sex. Femeile prezintă niveluri mai scăzute de creatinină și uree, în timp ce bărbații prezintă niveluri plasmatice mai scăzute de vitamina D, fosfatază alcalină și FGF-23.

Cuvinte cheie: boală renală cronică, hemodializă, biomarkeri.

Introduction

Chronic kidney disease (CKD) is a slow and progressive loss of kidney function over several years. It is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m² for 3 months or more, irrespective of cause⁽¹⁾.

CKD is associated with a higher risk of development of cardiovascular disease such as high blood pressure, cardiac failure and myocarditis. Also, because of the hydric and electrolytic imbalances present in CKD, it is frequently associated with mineral and bone disorders affecting the skeletal system⁽²⁾. Regarding chronic diseases, there is a continuously focus and ongoing study results are still emerging, somehow suggesting an association with CKD IIIb, IV or V to cancer in diabetic patients^(3,4).

As a result of the overall ageing of the population, CKD cases have been continuously increasing, with approximately 13% of all adults being affected in 2021. Consequently, there has been a 7% increase in ESRD, which is the main cause for hemodialysis in patients⁽⁵⁾.

Hemodialysis is a form of renal replacement therapy, where the kidney's role of filtration of the blood is supplemented by artificial equipment, which removes excess water, solutes, and toxins.

For this research paper we selected two groups of patients with CKD, undergoing hemodialysis, and we monitored the plasma levels of certain biochemical parameters specific to CKD and its bone comorbidities, such as: creatinine, urea, bicarbonate, phosphorus, calcium, alkaline phosphatase, vitamin D, FGF-23 and TNF-alpha, with the purpose of finding a correlation between their plasma values, the underlying renal condition that caused CKD and gender.

Materials and methods

In this study we managed to include a number of 24 subjects, 12 men and 12 women, with a mean age of 60.41 ± 11.31 years, diagnosed with CKD and undergoing hemodialysis for at least 2 years.

The time span of the dialysis treatment, the patients had undergone at the moment of the study, ranged between 2 and 8 years, with a mean duration of 5 ± 1.6 years.

We selected an equal number of men and women. The reason behind this, was so that we could divide the participants into 2 equal groups according to their gender, thus making it more convenient for us to observe the correlation between the underlying cause of their CKD, the plasma levels of their biomarkers and their gender.

Furthermore, we divided the 24 patients, according to their primary renal disorder, into 4 subgroups, as it follows: renovascular hypertension⁽⁹⁾, glomerulonephritis⁽⁶⁾, polycystic kidney disease⁽⁴⁾, other primary renal dysfunctions⁽⁵⁾.

The hemodialysis procedure was carried out in the exact same way for every subject, its length was 720 minutes, with a blood flow rate of 500ml/min. Blood collection was done in the morning, before dialysis. We monitored a number of different biochemical parameters such as: creatinine, bicarbonate, phosphorus, calcium, alkaline phosphatase, vitamin D, FGF-23, TNF-alpha and urea. The latter was determined pre- and post-dialysis.

We analyzed the differences of the variables between the two groups by using the Student's test (TTEST), where the values of $p < 0.05$ were considered statistically significant. For the correlations between the values of the biochemical parameters, the age of the subjects and the duration of the hemodialysis treatment we used the CORREL



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test, the correlations being significant if $p < 0.05$ and highly significant if $p < 0.01$.

Results

Following our analysis we were able to determine statistically significant correlations between the gender of the subjects and the plasmatic levels of urea, alkaline phosphatase, vitamin D and FGF-23. Regarding the plasmatic levels of urea, besides the expected difference in pre- and post- dialysis levels of urea, we obtained a significant correlation between its post-dialysis value and gender ($p = 0.045$). Men exhibit higher levels of post-dialysis urea than women (Figure 1).

For the analysis of the correlations between the plasma levels of creatinine and gender, we determined the values of p , which revealed there was significant difference ($p = 0.047$) between the two groups. Higher plasmatic values of creatinine were found in the group comprising of men (Figure 2).

In regard to the plasmatic levels of the alkaline phosphatase, there was a significant correlation between its value and gender ($p = 0.01$). There were significantly higher levels of alkaline phosphatase found in women (Figure 3). Also, there was an important difference between the types of primary renal disease, patients with polycystic kidney disease presenting almost double the values

of plasmatic alkaline phosphatase (Figure 4). After determining the value of p , we were able to establish a significant difference ($p = 0.04$) between the two groups, in regard to the plasmatic values of vitamin D. Women had slightly higher levels of vitamin D (Figure 5). Another significant correlation was between the plasma levels of FGF-23 and gender ($p = 0.02$). There were higher levels in the women group when compared to men (Figure 6).

Discussions

One explanation for the higher prevalence of CKD among women is their longer life expectancy and the declining kidney function associated with aging^(6,7). Neugarten et al.⁽⁸⁾ conducted a meta-analysis of 68 studies to evaluate the effect of gender on the progression of nondiabetic CKD and found that men show a more rapid decline in kidney function as compared with women.

There is a higher prevalence of women in the predialysis stage of CKD, although renal function deteriorates more rapidly in men. Gender differences in rates of CKD progression may be influenced by potential antifibrotic and antiapoptotic effects of estrogen or proinflammatory deleterious effects of testosterone⁽¹⁾. As result the number of men with kidney disease who need kidney replacement therapy is higher⁽⁹⁾.

Steroid hormones directly or indirectly

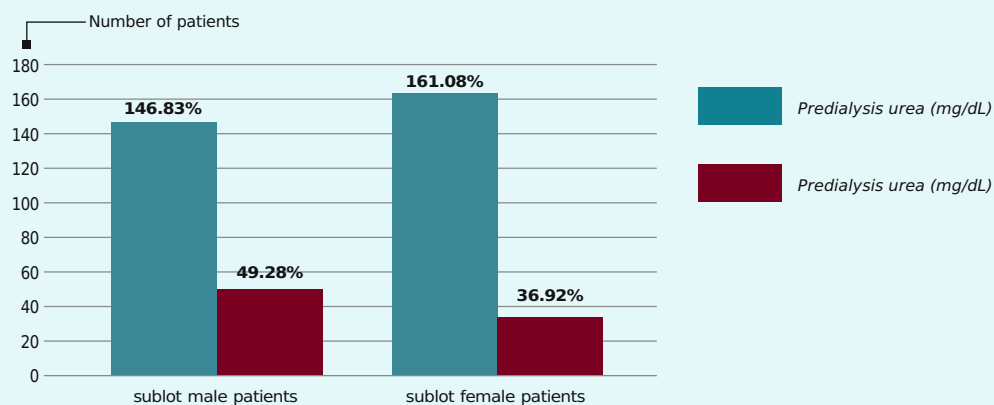


Figure 1. Mean plasmatic levels of pre- and post- dialysis urea in men and women

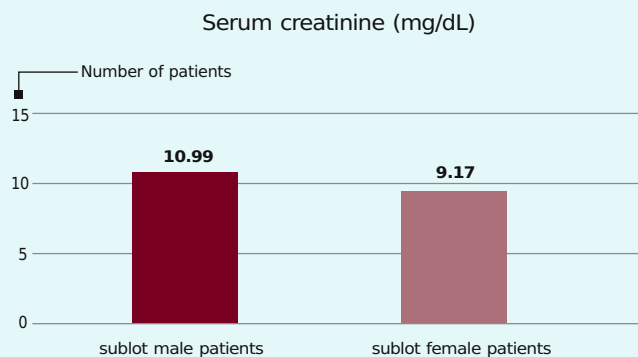


Figure 2. Mean plasmatic values of creatinine in men and women

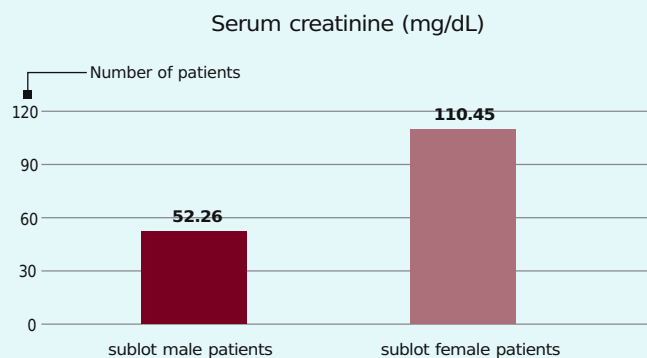


Figure 3. Mean plasmatic levels of alkaline phosphatase in men and women



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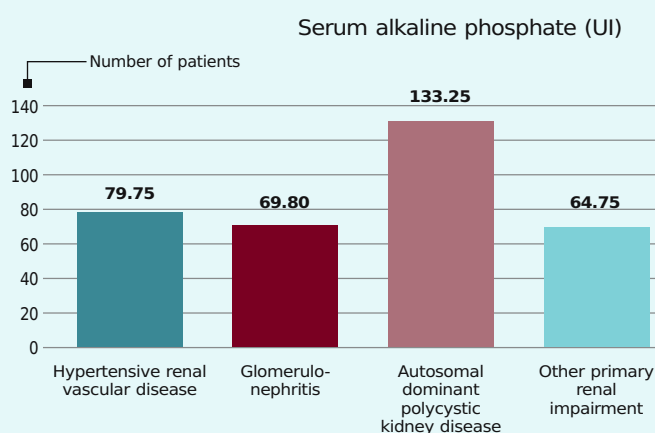


Figure 4. Mean plasmatic levels of alkaline phosphatase according to the primary kidney disease

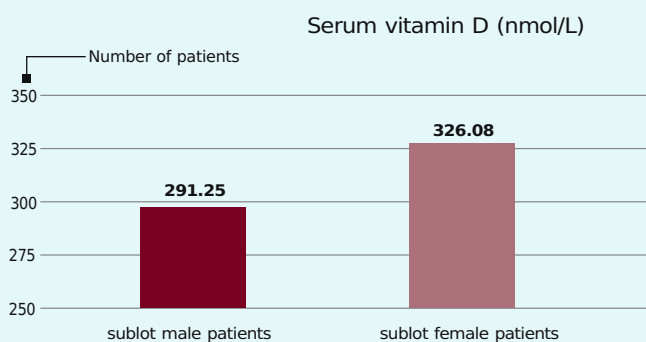


Figure 5. Mean plasmatic values of vitamin D in men and women

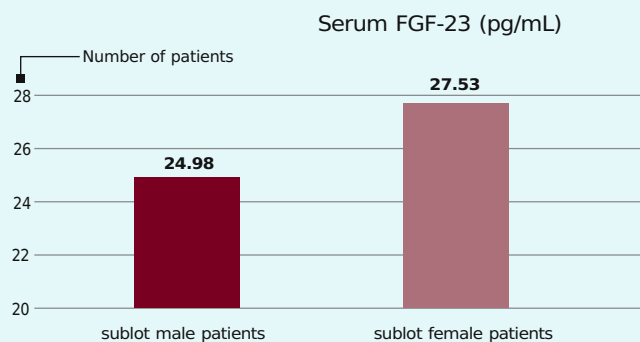


Figure 6. Mean plasmatic values of FGF-23 in men and women

modulate many cellular processes, such as the synthesis of cytokines, growth factors and vasoactive substances. Estrogens have an important effect on the renin-angiotensin-aldosterone system and influence the hemodynamic state that alters renal function even after the onset of chronic kidney disease. Some therapeutic agents have a selective modulatory effect on estrogen receptors and may improve the progression of kidney disease in postmenopausal women⁽¹⁰⁾. The dietary habits such as fructose ingestion, play a role in the genesis of the chronic kidney disease, due to its relation to driving hypertension and diabetes⁽¹¹⁾.

Elevations in total serum alkaline phosphatase (ALP) are a common feature of CKD mineral bone disorder, yet no therapeutic interventions are used to target ALP levels, also there are no defined 'target' serum levels for this enzyme. The lack of specific interventions triggered by elevations in ALP makes it possible to assess it as a risk factor without it being modified by therapeutic measures⁽¹²⁾.

Taliercio JJ et al.⁽¹³⁾ in his study highlighted the fact that even high-normal ALP values might be associated with risk of adverse outcomes. It was the first study to demonstrate that an elevated ALP level increases the risk of ESRD and confirm the associations between elevated ALP levels and mortality in a more heterogeneous population of patients with CKD stages 3-4 than had been reported previously.

There seems to be an inverse correlation between alkaline phosphatase and vitamin D, the increase in alkaline phosphatase concentration is accompanied by a decrease in vitamin D. This is caused by the elevated levels of the parathormone as a result of the bone disorders secondary to high levels of alkaline phosphatase^(12,13).

Observational studies have reported progressive vitamin D deficiency worsening from stage 3 to stage 5D⁽¹⁴⁾. However, in a cross-sectional study, Guesseous et al.⁽¹⁵⁾ reported that vitamin D deficiency is similarly observed in CKD patients and in the general population, thus making it unclear if there is actually a vitamin D deficiency caused by CKD, and the reason behind it. In a study conducted by Jacob et al.⁽¹⁶⁾, he reported that despite normal epidermal content of substrate, 7-dehydrocholesterol, chronic hemodialysis patients exhibit defective photoproduction of cholecalciferol⁽¹⁷⁾.

One of the largest studies to date on FGF23 was a prospective study of its levels at the initiation of dialysis and risk of subsequent mortality on dialysis. FGF23 seems to have a protective compensation in CKD, by helping to attenuate the severity of hyperphosphatemia. However, the high levels of FGF23 also inhibits the renal production of 1,25D leading to prolonged, severe 1,25D deficiency, which itself is a risk factor for mortality⁽¹⁸⁾.

Although our study did not focus on the immune status and its relationship to CKD, previously published data identified strong influences of ESRD on immune deficiency⁽¹⁹⁾. As related by current researches in the field, for patients with other chronic diseases (e.g. cancer, diabetes), increasing the pre-existing risk of lymphopenia due to treatment or infections may have significant negative prognostic value⁽²⁰⁻²³⁾.

Conclusions

Regarding the concentration of urea and creatinine, both markers of the kidney function, presented significantly higher levels in the men's group, thus revealing a more deteriorated renal function. Evaluating the values of the alkaline phosphatase, it showed



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that women presented considerably higher levels than men by almost twofold. When looking at the type of renal condition that determined the biggest increase in the value of the alkaline phosphatase, the polycystic kidney disease was at the top. Although there were no significant results regarding calcium, it appears that the plasmatic levels of vitamin D are lower in the men's group, thus correlating inversely with the plasmatic levels of the alkaline phosphatase, as shown in literature. Regarding the plasmatic concentration of the FGF23, higher levels were found in the women's group, raising the question: is FGF23 in excess a biomarker, or a uremic toxin? We found that there is no correlation between the levels of bicarbonate, phosphorus, calcium, TNF-alpha and gender in patients with CKD undergoing hemodialysis.

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