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ORIGINAL ARTICLE

Etiology of Chronic Kidney Disease and Comorbidities in Chronic Hemodialysis Patients

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Abstract: *Introduction: As general population tends to have increasing life expectancy, the risk associated with developing chronic kidney disease (CKD) with multiple incapacitating concequences, also increases. Method: For the present study, we registered the data from the observation files of 37 patients diagnosed with CKD undergoing treatment by chronic hemodialysis and noted the CKD associated diagnoses included in the notion of comorbidities. We monitored their statistical incidence both in the whole group and separately, in women and men using TTEST and CORREL. Results: The median age of the subjects was 55.86 (± 12.00) years. The study population mean weight was 74.90 (± 14.44) kg, with a mean weight of 69.33 kg for female subjects, and 77.92 kg for males, respectively. Diabetes was identified in 35.13% of patients, whilst heart failure was present in 16.21% of patients. Conclusions: Following the analysis of the information about the patients with CKD in the dialysis program, which we included in the study group, we observed the existence of variations that occur with age, significant correlations between age and weight and between albuminemia and weight. The most common comorbidity is high blood pressure followed by anemia.*

Keywords: *chronic kidney disease; chronic hemodialysis patients; comorbidities; plasma albumin*

INTRODUCTION

Chronic kidney disease (CKD) can develop due to a multitude of pathologies that all have in common the evolution to kidney failure, with gradual or rapid loss of the main function of the kidneys, that is to remove waste products and excess fluid from the body [1]. The last stage of the development of CKD, especially in patients who are treated by peritoneal dialysis or hemodialysis, is characterized by multiple organs and systems damage [2].

Not only CKD, but also the treatment of its various manifestations, mainly affect the body tissues and systems, at all levels: nervous, cardiovascular, respiratory, endocrine, hematopoietic, digestive, renourinary [2].

The tendency to increase life expectancy of the population is also associated with an increase of the incidence and prevalence of CKD, considering the already known relationship between aging and decreased kidney function, which is seen as a consequence of the physiological aging of the kidneys [2,3]. An even steeper increase in the number of patients with CKD is expected in the coming years. In this context, the medical goal becomes to slow down the progression to terminal stages, achievable primarily by diagnosing the condition as early as possible [1].

Compared to conservative treatment, extrarenal treatment methods provided clear advantages for patients with chronic end-stage renal disease, the duration and quality of life being

considerably superior. There are several methods of extrarenal purrification: peritoneal dialysis, hemodialysis, hemodiafiltration. The decision for each type of treatment is based primarily on medical considerations, depending on the underlying disease and the comorbidities present [4]. Diabetic patients are usually at higher risk of developing more severe forms of chronic diseases (e.g. cancer) [5,6,7]. Peritoneal dialysis is preferred for diabetic patients with CKD as this method of treatment ensures the maintenance of a residual diuresis for a longer time, the prevention of complications due to the present vascular damage, the possibility of intraperitoneal administration of insulin and a better hemodynamic stability than chronic hemodialysis. In cases where the patient has a poor state of hygiene or if peritoneal dialysis does not allow a satisfactory volume control to be maintained, chronic hemodialysis is preferred [4].

MATERIALS AND METHODS

For the study we performed, we registered the data from the observation files of 37 patients diagnosed with CKD undergoing treatment by chronic hemodialysis, in the Nephrology Department of the Bucharest University Emergency Hospital.

We noted their general data and the presence of associated comorbidities, as well as the determined values of plasma albumin concentration.

The statistical data processing regarding the incidence of comorbidities revealed important information for understanding the clinical and biochemical context of this particular type of patient in the hemodialysis department.

Among the tests performed on the patients that had presented for chronic dialysis, we noted the value of plasma albumin concentration, because it is a parameter that provides information about the loss of protein in the urine and the nutritional status of renal patients. We determined the statistical differences between the values from women and men, as well as the correlations between this parameter and age, respectively weight.

We performed the statistical processing using the Student test (t-test) to determine the statistical significance of the differences in the values of the parameters determined in women and men and the Correl test to determine whether there are correlations with statistical significance between the parameters we tracked.

We noted the diagnoses associated with CKD, included in the notion of comorbidities and we monitored their statistical incidence both in the whole group and separately, in women and men.

RESULTS

In terms of gender distribution, of the 37 patients, 13 (35.13%) were women and 24 (64.86%) were men.

The median age of the subjects was 55.86 (± 12.00) years. For the women, the median age was 56.46 (± 10.86) years, whereas for the men it 55.54 (± 12.78) years. Although there is a slight gender difference regarding age, this failed to be statistically significant (p> 0.05).

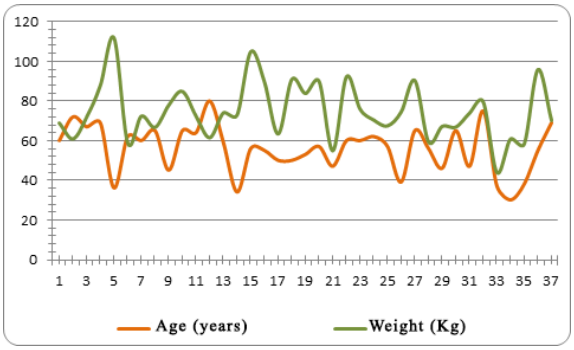
Regarding weight, as presented in Table 1, the study population mean weight was 74.90 (± 14.44) kg, with a mean weight of 69.33 kg for female subjects, and 77.92 kg for males, respectively. As presented in Table 1, this difference was found to be statistically significant, p = 0.01.

Table 1: Average weight and the statistical difference between men and women

	Average weight in women (kg)	Average weight in men (kg)
Average value	56.46	52.27
Standard Deviation	10.87	17.16
p (t-test) 0.43		

Applying the Correl test, we observed that age and weight are two parameters that correlate statistically significantly (p = 0.04) (Figure 1).

Figure 1: Significant correlation between the values of weight and age



For the 37 patients, we noted the value of the plasma albumin concentration and determined the difference in values according to the gender of the patients and the statistical significance of this difference, using the Student test (t-test) (Table 2).

It is observed that the albuminemia values that were determined in these patients are not outside the normal laboratory limits of 3.5-5.2 g/dl (Table 2). By applying the

Correl test, we calculated the statistical significance of the correlations of albuminemia with age and weight (Table 3).

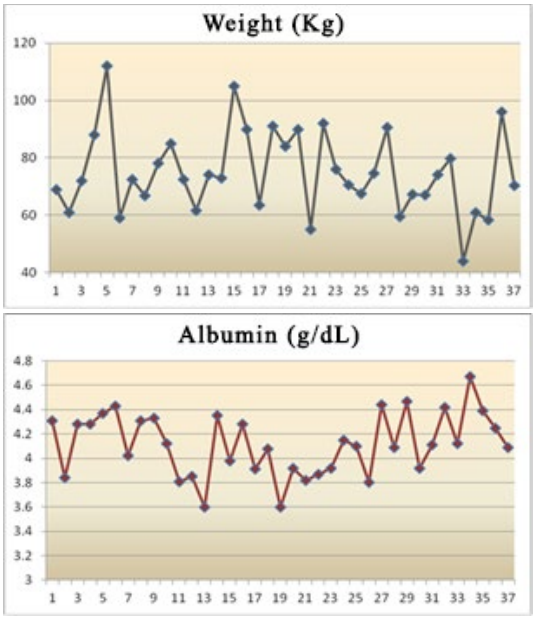
Table 2: Statistical significance of differences in plasma albumin concentrations in patients in the group by sex

Albuminemia(g/dl)		
	Women	Men
Average value	4.10	4.25
Standard deviation	0.24	0.27
t-test	p = 0.41	

Table 3: Statistical significance of correlations between plasma albumin concentrations with age and weight in patients in the group and by sex

Significance of the correlation between plasma albumin concentration and		
	Age	**Weight**
Women	p = 0.1	p = -0.2
Men	p = -0.37	p = 0.1
Total	p = -0.24	p = 0.02

Figure 2: Correlation weight-albuminemia



We observed that separately, in women and men, the plasma concentrations of albumin do not correlate significantly with age or weight, but, after using the Correl test for the whole study group, a significant correlation between albuminemia and weight has been identified.

We made this determination, knowing that the albumin dosage is a test to assess the general state of nutrition, especially in elderly patients with various conditions, in this category falling most of the patients with CKD in the lot we studied.

COMORBIDITIES DIAGNOSED IN THE STUDIED GROUP

Diabetes mellitus, dyslipidemia, atherosclerosis, hypertension, arteriopathy obliterans of the lower limbs

Diabetes is present in 35.13% of patients, 3 of women and 10 of men, which means 23.07% and 41.66%, respectively. Dyslipidemia occurs in a number of 3 male patients, which means a percentage of 8.1% of the total group. Atherosclerosis is noted in a female patient with kidney disease and in 9 male patients, the incidence rate being 27.02% in the whole group. High blood pressure is a more common comorbidity in patients in the study group: 11 out of 13 women are hypertensive and 23 out of 24 men with CKD are hypertensive. Lower limb arteriopathy is present in only 2 of the male patients, which means 5.4% of the group. Both patients also have diabetes and high blood pressure.

Heart failure, cardiomyopathy, arrithmia, valvulopathy, chronic coronary heart disease

Heart failure is present in 5 of the women and only 1 of the men, this comorbidity is therefore found in 16.21% of patients. Cardiomyopathy is rarer, 1 female patient and 2 of the men in the group, ie 8.1% also have this diagnosis. Arrhythmias are more common in women, 5 out of 14, ie 35.7%, presenting this manifestation in the form of atrial fibrillation with medium or large ventricular allure or in the form of supraventricular tachycardia. Among men, only 2.33% have atrial fibrillation with a medium ventricular allure. Thus, 18.91% of the total group have a form of arrhythmia. Valvular damage is identified in 4 patients out of a total of 37, ie 10.81%, more frequently in women 3 out of 14 and only in 1 male patient. Coronary ischemic disease is diagnosed in 3 women and 6 men, the incidence being 24.32%.

Diabetic/hypertensive/mixed nephropathy, chronic tubule-interstitial nephropathy, autosomal dominant polycystic kidney disease, single kidney, chronic pyelonephritis, chronic glomerulonephritis

Chronic tubulointerstitial nephropathy is diagnosed in a single male patient. The incidence at group level is 2.7%. Out of 13 women in the group, hypertensive nephropathy is present in 2 and diabetic nephropathy in 3 of them, a total of 38.46% with nephropathy. Of the 24 men in the group, 6 have diabetic nephropathy, 4 have hypertensive nephropathy and 2 have mixed nephropathy, a total of 50% of patients with nephropathy. A number of 4 of the 13 women, 30.76%, are also diagnosed with autosomal dominant polycystic kidney disease. Of the 24 men, 4 also have this diagnosis, representing

16.66%. At the level of the whole group, the percentage is 21.62%. Only one male patient has a single kidney, the cause being congenital. The incidence at group level is 2.7%. And pyelonephritis rarely occurs, only one patient, a woman, has this diagnosis. The incidence at group level is 2.7%. More common is chronic glomerulonephritis, which is present in 6 of the men, respectively 25%, and in 2 of the women, respectively 15.38%, with an incidence in the whole group of 21.62%.

Kidney stones, parathyroidectomy, secondary hyperparathyroidism, anemia, chronic viral hepatitis

Kidney stones are present in 2 women and 3 men in the group, which means an incidence of 13.51%. Secondary hyperparathyroidism is diagnosed in only 2 patients, a man and a woman, the incidence is 5.4% in the whole group. Surgical removal of the parathyroid glands was performed in 3 women and 1 man in the group, the frequency being 10.81%. Anemia is more common, 7 of the 13 women, ie 53.8% and 15 of the 24 men, ie 62.5%, have pathologically low hemoglobin. Out of the whole lot 59.45% of patients have anemia. Chronic hepatitis B infection is uncommon as viral hepatitis B is present in 2 women, 1 man in the group is infected with hepatitis B virus and 1 is coinfected with hepatitis B + C viruses. The frequency of chronic viral hepatitis in the group is 10.81%.

DISCUSSIONS

Gender and age are factors that influence some characteristics related to CKD in patients with type 1 or type 2 diabetes, and certain particular aspects of pathogenesis, diagnosis and treatment management have been identified, but the mechanisms are incompletely known and more studies are needed to clarify these connections which would be very useful in order to reduce the number of cases of renal patients and to prevent or control the complications of this condition. Considering the data published by Eriksen O. et al. [5], old age and the male gender are predictors of worsening kidney disease and the rapid progression to severe kidney failure. In the study of Giandalia A et al. [8] the authors concluded that men are more affected, because in their studies, the number of men enrolled is higher than the number of women, results similar to our study where the percentage of men was 64.86%.

Weight is an important parameter in assessing the nutritional status of the patient with CKD. In obese people with CKD, the progression of the disease to renal failure is faster compared to cases of normal weight. Also kidney transplantation or hemodialysis, which may become necessary in advanced stages of the disease, may be more difficult and may have more frequent complications in obese people [9]. After initiating treatment with hemodialysis or peritoneal dialysis, in patients with a glomerular filtration rate below 35 ml/min/1.73 m^2, in stage 3 CKD, weight loss is a factor that increases the risk of mortality by 54% compared to with patients whose weight remains constant. Even in patients with moderate renal impairment, weight loss should be closely monitored and the patient's nutritional status monitored before dialysis is required [10].

In the final stages of the kidney disease, hypoalbuminemia is common, caused by factors that act simultaneously: reduced liver synthesis, increased degradation and renal loss and the glomerular filter membrane is damaged and becomes more permeable allowing the passage of negative albumin molecules from plasma. In our study we observed that separately, in women and men, the plasma concentrations of albumin do not correlate significantly with age or weight. However, applying the Correl test to the whole group, resulted in a significant correlation between albuminemia and weight. We made this determination, knowing that the albumin dosage is a test to assess the general state of nutrition, especially in elderly patients with various conditions, in this category falling most of the patients with CKD in the lot we studied. According to Haller C. et al. [11] the inflammatory phenomenon in kidney disease is also involved in the pathogenesis of hypoalbuminemia. Inflammation correlates with the risk of mortality, hypoalbuminemia is not in itself a pathogenic factor of renal impairment, but is a major predictor of unfavorable prognosis.

Diabetes mellitus is one of the main negative prognostic factors for chronic diseases [12]. According to Anders HJ. et al. [13] the prevalence of type 2 diabetes and CKD increases the incidence of diabetic kidney disease, also known as diabetic nephropathy. The combination of the two diseases can be in the form of diabetic kidney disease if the kidney damage is the consequence of diabetes, it can be a kidney disease caused by individual mechanism in the diabetic patient or it can be a coincidence of simultaneous occurrence of the two diseases. The involvement of the membrane-glucose cotransporter membrane and hyperglycemia are associated with the activation of the renin-angiotensin-aldosterone system, glomerular hyperfiltration and tubular hyperabsorption occur, which creates a particular situation that requires appropriate treatment. Whatever the mechanism, the patient's evolution is more unfavorable compared to those who have only one of the conditions [13,14]. Our study results for 35,13% of the patients, that were diagnosed with diabetus mellitus type II, found that 69.23% of them have further developed diabetic nefropathy.

In the study of Tsimihodimos V et al. [15] it was shown that lipid metabolism is disrupted in patients with CKD even in the early stages and can be very severe in some cases, further impairing kidney function. The pathogenic mechanisms are not

fully understood, but studies show that dyslipidemia is a pathogenic factor for both kidney disease and the associated cardiovascular disease [16]. In our study dyslipidemia was identified in only 8,1% of the patients.

Atherosclerosis sets in early and progresses rapidly in patients with CKD. It usually increases the risk of cardiovascular disease and, as the severity of kidney disease increases, so does the mortality rate, according to Olechnowicz-Tietz S. et al. [17]. In our study population 27.02% were found to suffer from atherosclerosis.

Considering the cardiovascular risk, compared to the general population, patients with CKD, according to the study of Matsushita K et al. [16] have a constant increased cardiovascular events risk. Studies identified that 70% of CKD patients, and up to 80-90% of those on dialysis, are diagnosed with high blood pressure [18,19]. Considering all these data, our studies results that 91.9% of CKD subjects were suffering of/diagnosed with hypertensive disease are consistent with the data in the literature.

As shown in the study of Maric-Bilkan C. et al. [20], in the absence of diabetes, women have a considerably lower risk than men of vascular, microvascular or macrovascular diseases. The opposite trend is observed in diabetic patients: women are at higher risk for these complications. Microvascular lesions that occur in nephropathy, neuropathy, and retinopathy are more common in men. Macrovascular lesions consisting of chronic coronary heart disease, myocardial infarction, peripheral artery damage, and stroke are more common in women. To explain this, the focus has been on sex steroids, which play an important role in regulating heart function. Estrogens are generally considered hormones with cardioprotective effects, and androgens with adverse cardiac effects. But the effects of these hormones on the target organs are complex and different, and the presence of diabetes interferes with the pathophysiological mechanisms that cause vascular damage [14,18,19].

Renal comorbidities are, in part, primary kidney disease that has progressed unfavorably, with the patient reaching the stage of CKD that requires dialysis in order to survive [20]. Another part of these comorbidities is secondary, the pre-existing disease being another. This is the case with nephropathy, which develops during the course of hypertensive disease or diabetes [14]. The percentage of incidence of nephropathy of any etiology in the study population was 45.94%. It is a high percentage, which is explained by the fact that, as we have shown above, diabetes and hypertension are precursors or caused by CKD.

Our results are consistent with literature data showing that 11.2% of patients in a large group of with CKD present with kidney stones. The same study by Chuang TF. et al [21] shows that patients with kidney stones are 1.82 times more likely to develop CKD.

Secondary hyperparathyroidism is found in chronic dialysis patients, the incidence of this comorbidity being reduced by treatments with phosphorus chelators, calcium supplements and calcitriol. As shown in the study of Llach F. et al [22] there are situations when parathyroidectomy is necessary, namely when clinical signs such as persistent hypercalcemia, pruritus, metastatic calcifications appear [23]. In our study hyperparathyroidism was found in only 5,4% of the patients but out of the whole lot, 10.81% of the patients had already been treated with parathyroidectomy. The latter can cause insufficiency of many organs.

Blood characteristics such as blood group or different blood components (eg. lymphocytes) have been linked to chronic diseases or their treatments toxicity [24-27]. According to the study of Ueda N. et al. [28] hemoglobin levels below 12 g/dl for women and below 13 g/dl for men are considered anemia. Iron and erythropoietin deficiency causes anemia in patients with CKD. Hepcidin is a hormone produced by the liver in inflammation or when the body's iron deposits in the form of ferritin or hemosiderin are saturated. Hepcidin binds to and inhibits ferroportin, thereby decreasing the release of iron from the enterocyte and reticuloendothelial cells and decreases plasma iron. Inflammatory status in CKD increases hepcidin regardless of the availability of iron to the body, so it becomes necessary to administer iron, but also to reduce inflammatory phenomena [29]. It was a frequent occurence in our study as 62.5% of our patients were diagnosed with anemia.

Hepatitis B or C virus infections can cause chronic kidney damage but do not have a high incidence according to Chacko EC et al. [30]. If the infection occurs in patients with CKD, anti-infective treatment has many side effects and may worsens the prognosis. Similar results were shown in our study as only 10.81% of the patients presented with concurrent viral hepatitis and CKD.

CONCLUSIONS

Following the analysis of the information about the patients with CKD in the dialysis program from our study weight has been found to be significantly higher in men, compared to women. Albuminemia was within normal limits in all patients, significantly correlating with the body weight. Patients' comorbidities identified in our study were similar to the ones found in the current literature to be related to CKD. The most common comorbidity is high blood pressure, identified in over 90% of the subjects. Anemia is the second most common

comorbidity, occurring in almost 60% of patients. With high frequency, in over 20% of patients, we observed the presence of diabetes, atherosclerosis, ischemic coronary heart disease, nephropathy of various etiologies, autosomal dominant polycystic disease and chronic glomerulonephritis.

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