ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 06, pp.52759-52762, June, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

CARDIOVASCULAR EVENTS IN PRE-DIALYSIS AND DIALYSIS PATIENTS WITH HYPERURICEMIA

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ARTICLE INFO

Article History:
Received 03rd March, 2017
Received in revised form
30th April, 2017
Accepted 11th May, 2017
Published online 30th June, 2017

Key words:

Hyperuricemia,
Chronic Kidney Disease,
Dialysis,
Cardiovascular Diseases.

ABSTRACT

Background: Hyperuricemia in chronic kidney disease (CKD) could increase the risk of developing cardiovascular disease (CVD). It is necessary to emphasize the need to identify patients with hyperuricemia and CKD for early prevention with reducing the levels of high serum uric acid (SUA). The aim of the study was to evaluate and compare the type of cardiovascular diseases among patients with hyperuricemia in pre-dialysis CKD stages and on dialysis treatment.
Methods: We performed a retrospective study in two centers on 58 adult patients – 36 in pre-dialysis stage and 22 on chronic dialysis treatment with hyperuricemia and CVD. The pre-dialysis patients were with chronic kidney disease from second to the fourth stage. Chi-square test, independent samples T-test, and nonparametric Mann-Whitney U Test were used.
Results: We observed that atrial fibrillation (AF) was the most common finding in the two groups and it was established in 29 (80,56%) pre-dialysis and in 17 (77,27%) dialysis patients. Ischemic heart disease (IHD) was found significantly more often in a pre-dialysis group, but the dialysis patients had higher cerebrovascular disease incidence. The incidence of IHD was higher in pre-dialysis female patients, while heart blocks were with a higher rate in dialysis females. Cerebrovascular disease and heart blocks were more often in male patients on dialysis treatment. Intragroup analysis of CVD in the pre-dialysis patients according to the genders suggested a higher rate of IHD and heart blocks in males. The same analysis in hemodialysis patients indicated that the women have a higher rate of cerebrovascular disease and AF, while men were more often with IHD and heart blocks.
Conclusions: We supposed that patients with Hu, independently of the stage of CKD were with the highest incidence of AF, but there were differences in the type of CVD between the pre-dialysis and dialysis patients that were also gender specific.

Citation: Yanka Kolarska, Asen Kamenov, Biliana Vasileva, Diana Trifonova, Nencho Nenchev and Boriana Deliyska, 2017. "Cardiovascular events in pre-dialysis and dialysis patients with Hyperuricemia", *International Journal of Current Research*, 9, (06), 52759-52762.

INTRODUCTION

The incidence of gout and hyperuricemia (Hu) increased significantly in recent decades. A large group of patients was with co-morbidities such as arterial hypertension, chronic kidney disease (CKD), cardiovascular diseases (CVD), obesity, diabetes mellitus, and hyperlipidemia. Many studies confirm that the high levels of serum uric acid (SUA) are directly involved in the development of various CVD (Masanari Kuwabara Hyperuricemia, 2016; Guedes, 2014; Borghi, 2014; Feig *et al*., 2008). That might be explained by several mechanisms - proinflammatory effect, causing proliferation of smooth muscle cells, changes in the renin-angiotensin-aldosterone system, hypertension, endothelial dysfunction, oxidative stress, low levels of endothelial nitric oxide and others. A small number studies discussed the association between glomerular filtration rate, Hu, and CVD. (Puddu *et al*., 2014; Sezer *et al*., 2014) There are no sufficient data which compared the relationship between Hu, type of CVD and stage of CKD. The present study was provided to determine the difference between the type of cardiovascular injury in patients with Hu in pre-dialysis and dialysis stages of CKD.

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PATIENTS AND METHODS

Patients

The subjects were enrolled from hospitalized patients in Clinic of Nephrology at University Hospital "Queen Joanna-ISUL" and patients undergoing hemodialysis treatment at the Clinic of Nephrology and Dialysis at University Hospital "Saint Ivan Rilski". The data were collected during the period 01 June

2015 – 01 March 2016. All subjects were older than 18 years with Hu and CVD.

Data collection

The data were collected after providing a signed informed consent. They included factors (such as age, sex, history, and duration of hypertension, CKD and hemodialysis treatment), which could affect SUA levels and cardiovascular changes. The following clinical and laboratory parameters were reported: the stage of CKD calculated glomerular filtration rate by MDRD, the presence of diabetes mellitus, values of complete blood count, biochemical parameters (serum creatinine, SUA, cholesterol, electrolytes, and proteinuria). SUA levels were categorized as Hu when they were more than 416.5μmol/l. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or the usage of anti-hypertensive drugs. The incidence of CVD was evaluated such as ischemic heart disease (IHD), percutaneous coronary intervention (PCI), aortic aneurysm, valvular heart disease, cerebrovascular disease, congestive heart failure (HF), cardiac blocks, pacemaker, atrial fibrillation (AF). IHD was defined as the use of nitroglycerine, an experience of typical chest pain, and ECG changes. Stroke was defined as an event requiring hospitalization and was verified from local hospital records.

Statistical analyses

Statistical analysis of the data was performed using IBM SPSS Statistics 2000 and Microsoft Excel 2010. Categorical data were compared using chi-square test, quantitative data with a normal distribution - with paired sample t-test, or Mann-Whitney U-test when the distribution differed from normal. The data were presented as mean ± SEM; P <0,05 was a significant value accepted. Descriptive statistics (means, percentages, etc.) were used to summarize the data.

RESULTS

Fifty-eight patients from the two clinics met the criteria for Hu and CVD, 36 of them were in pre-dialysis stage CKD - from 2 to 5 stage: 12 women (33,3%) and 24 men (66,7%), mean age 68.06 ±14.2 years,22 patients were on dialysis treatment: 7 (31,8%) women and 15 men (68,2%), mean age 67.62 ± 18.4 years. Serum creatinine of pre-dialysis patients was 222,92 ± 69 mmol/l and glomerular filtration rate was 39±24ml/min/1.73 m2. Dialysis patients were with serum creatinine 684±114 mmol/l and they were on dialysis for 4.82 ± 3.1 years. They were more often with anemia and with diabetes mellitus. Proteinuria in predialysis patients was 1,47±0,8g/d. There were no significant differences between the two groups in SUA, cholesterol, electrolytes and blood pressure (Table 1 and Table 2). The type and incidence of registered cardiovascular changes are presented in Table 3. AF was most common finding in both groups. Pre-dialysis patients were with a higher incidence of IHD - 27 patients (75%), with valvular diseases established in 10 patients (27,77%), cardiac blocks in 10 patients (27,77%) and HF-9 patients (25%). Patients on dialysis treatment often had IHD - 13 patients (59,09%), valvular diseases in 7 patients (31,82%), heart blocks in 7 patients (31,82%) and cerebrovascular events in 7 patients (31,82%). We observed that IHD and pacemaker were more often in the pre-dialysis group, while the cerebrovascular disease was with a higher incidence in dialysis patients. The data was analyzed according to the sex distribution of CVD in the two groups. CVD was observed in 12 women in pre-dialysis stage and, on dialysis stage (Table 4). AF was with a higher incidence in all observed subjects, more often in dialysis patients. Eight pre-dialysis women (66,67%) were with IHD and 2 (28, 57%) from dialysis group. Heart blocks were established more often in dialysis females - 7 (31,82%) vs. 3 patients (16,67%) in the pre-dialysis stage. Cerebrovascular disease and heart blocks were often observed in males on dialysis treatment (Table 5).

Table 1. Clinical and laboratory data of the two groups

Parameter	Pre-dialysis	Dialysis patients
Anemic syndrome	21 (58,33%)	22 (100%) (p<0,01)
Diabetes mellitus	15 (41,67%)	11 (63,64%) (p<0,01)
Uric acid /mmol/l/	451,1 ± 48,2	442 ± 31 (p>0,01)
Hemoglobin /g/l/	113,36±18,4	103,9±15 (p>0,01)
Potassium /mmol/l/	4,92±1,2	5,29±0,5(p>0,01)
Sodium /mmol/l/	140,67±4	137,9±11(p>0,01)
Calcium /mmol/l/	2,23±0,1	2,1±0,2 (p>0,01)
Cholesterol /mmol/l /	5,66 ± 0,8	4,88 ± 0,4 (p<0,01)

Table 2. Blood pressure of the two groups

Parameter	Pre-dialysis	Patients on dialysis
Systolic BP (mmHg)	143,3±18,3	147,82±15,9
Diastolic BP (mmHg)	81,1 ± 12,4	79,09 ± 18,6

Table 3. Type and rate of cardiovascular changes in the two groups

Cardiovascular changes	Pre-dialysis patients		Dialysis patients
	Number (%)		Number (%/)
Valvulopathy	10 (27,78)	p>0,05	7 (31,81)
Aortic aneurysm	2 (5,55)	p>0,05	2 (9,09)
Ischemic heart disease	27 (75)	p<0,05	13 (59,09)
Cerebrovascular disease	7 (19,44)	p<0,05	7 (31,82)
Atrial fibrillation	29 (80,56)	p>0,05	17 (77,27)
Heart blocks	10 (27,78)	p>0,05	7 (31,82)
Pacemaker	5 (13,89)	p<0,05	0
PCI	6 (16.67)	p>0,05	3 (13.64)
Heart failure	9 (25)	p>0,05	5 (27.73)

Table 4. CVD in women in the two groups

Cardiovascular changes	Pre-dialysis women		Dialysis women
	Number (%)		Number (%/)
Valvulopathy	3 (25)	p>0,05	2 (28,57)
Aortic aneurysm	0	p>0,05	1 (14,28)
Ischemic heart disease	8 (66,67)	p<0,01	2 (28, 57)
Cerebrovascular disease	4 (33,33)	p>0,05	3 (42,86)
Atrial fibrillation	10 (83,33)	P<0,05	7 (100)
Heart blocks	3 (16,67)	p<0,05	7 (31,82)
Pacemaker	2 (16,67)	p>0,05	0
PCI	3 (25)	P>0,05	0
Heart failure	3 (25)	p>0,05	2 (28.52)

Table 5. CVD in men in the two groups

Cardiovascular changes	Pre-dialysis men		Dialysis men
	Number (%)		Number (%/)
Valvulopathy	7 (29,17)	p>0,05	5 (33,33)
Aortic aneurysm	2 (8,33)	p>0,05	1 (6,67)
Ischemic heart disease	19 (79,17)	p>0,05	11(73, 33)
Cerebrovascular disease	3 (12,5)	p<0,05	4 (26,67)
Atrial fibrillation	19 (79,17)	P>0,05	10 (66,67)
Heart blocks	7 (29,17)	p<0,05	7 (46,67)
Pacemaker	3 (12,5)	p<0,05	0
PCI	3 (12,5)	p<0,05	3 (20)
Heart failure	6 (25)	p>0,05	3 (20)

Intragroup analysis of CVD in pre-dialysis patients according to the genders supposed higher rate of IHD in male – 19 patients (79,17%) vs. 8 female (66,67%) and heart blocks in 7 male (29,17%) vs. 3 (16,67%) female. The same analysis in hemodialysis patients proved that the women had a higher rate of cerebrovascular disease – 3 patients (42,86%) vs. 4 males (26,67%) and AF – 7 females (100%) vs. 10 male (66,67%). Men were more often with IHD and heart blocks than women.

DISCUSSION

In the recent years, the interest of the relationship between CVD and high levels of SUA has been increasing. The data of our study suggested some differences of cardiovascular changes in patients with Hu in pre-dialysis and dialysis stage of CKD. Many studies indicated the association between Hu, and AF. According to our data, this type of CVD was with the highest incidence independently of the stage of CKD and had some, distribution predominantly in females. Some studies suggested a strong association between SUA levels and CVD in women, but they did not analyze the data according to the stage of CKD (Kivity *et al*., 2013). Other papers established that baseline SUA was associated with an increasing risk for future AF in both genders (Nyrnes *et al*., 2014). Hu was related with, development of cardiac hypertrophy in women with CKD (Yoshitomi *et al*., 2014). Higher levels of SUA might also increase the risk of chronic heart diseases and all-cause mortality (Zuo *et al*., 2016; Fang and Alderman, 2000). We did not find a significant difference in the incidence of HF between pre-dialysis and dialysis patients and between the genders. There was some evidence that elevation of SUA declines the kidney function, especially in women (Akasaka *et al*., 2014). Cardiovascular risk increased in women at an even lower value of SUA compared to men and requires more attention. Some studies suggested that higher SUA levels might contribute to cerebral infarction and Hu increases the risk of stroke. Other authors suggested that UA was also a risk factor for coronary and cerebrovascular changes, especially in patients with hypertension, metabolic syndrome, and kidney disease (Kim *et al*., 2009; Li *et al*., 2014; Falsetti *et al*., 2017; Li *et al*., 2015; Norvik *et al*., 2017). We observed the relatively higher incidence of cerebrovascular disease in dialysis patients, especially in men. IHD were most often in pre-dialysis patients mainly in males. Some studies observed that Hu was associated with increased risk of HF and poor prognosis in patients after myocardial infarction. They supposed that SUA is a low-cost available biomarker, that could improve risk stratification of patients with complicated myocardial infarction (Shimizu *et al*., 2015; von Lueder *et al*., 2015). CKD and the anemic syndrome might cause left ventricular hypertrophy. The majority of our patients were with various stages of impaired renal function, anemia syndrome, and diabetes mellitus. We supposed that this co-morbidity in association with Hu increased the incidence of CVD.

This study reported differences in the type of damage of the cardiovascular system in all patients – pre-dialysis and on dialysis treatment. It is known that uric acid levels increase cardiovascular and every other type of mortality. The patients in a pre-dialysis stage have an increased risk of cardiovascular disease, which, with traditional and non-traditional risk factors. We could summarize that hyperuricemia should be added, as an important risk factor for cardiovascular pathology. We supposed that patients with Hu, and with different degree of renal failure independently of the stage of CKD were with the highest incidence of AF but there is some difference in the type of CVD between pre-dialysis and dialysis stage of CKD and some of them also gender specific.

Acknowledgements

None to declare.

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