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Original Article

Associated Factors of Chronic Kidney Disease among Hyponatraemic Elderly Patients Attending a Primary Care Clinic

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Introduction: Chronic kidney disease (CKD) emerges to be an important geriatric health issue. It may progress to end stage renal failure and affect the quality of life. However, little is known about the associated factors of CKD. So this study aimed to determine the associated factors of CKD among hyponatraemic elderly.

Methods: This is a retrospective study of hyponatraemic patients aged ≥ 60 years attending outpatient clinic in 2014. Blood test results of glucose, potassium, creatinine, medical history, blood pressure, medication and demographic data were captured from patient records. Each patient's estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI Creatinine Equation. CKD is defined as eGFR of < 60 ml/min/1.73m^2. SPSS 21 was used to do the analysis.

Results: Totally 257 patients with mean age of 72.9 ± 7.3 years were enrolled in this study. Of them 73 (28.4 %) elderly had CKD. The mean eGFR was 72.62 ± 24.14 ml/min/1.73m^2, mean BP was (135.75 ± 18/10) mmHg. Of the participants, 134 (52.1 %) were men, 151 (58.8 %) were diabetics, 247 (96.1 %) had hypertension. The independent associated factors of CKD were increasing age (OR 1.08; 95 % CI 1.03-1.13; p = 0.002), hyperglycaemia (OR 1.10; 95 % CI 1.02-1.18; p = 0.017) and the use of loop diuretics (OR 5.15; 95 % CI 1.52-17.38; p = 0.008).

Conclusion: Hyperglycaemia and loop diuretics usage are found to be significantly associated with CKD among elderly patients attending a primary care clinic. Hence every effort should be made to optimise glucose control and cautious in the usage of loop diuretics to retard the decline in renal function.

Keywords: Chronic Kidney Disease, Aged, Primary Health Care

Introduction

Chronic kidney disease (CKD) is one of the commonest health issues among the geriatrics. National Health and Nutrition Examination Survey 1999-2004 indicated that more than one third of those aged 70 or older have moderate or severe CKD (1). The elderly are susceptible to renal impairment due to age-related declines in glomerular filtration and chronic diseases such as diabetes mellitus, hypertension and glomerular disease (2).

The referral of those elderly with moderate or severe CKD to a nephrologist is often late, leading to a shorter survival on renal replacement therapy as compared with younger patients. It is important for the primary care physician to identify those elderly patients with higher risk of developing CKD for appropriate monitoring of the disease progression and early referral to a nephrologist for better quality of care to the elderly. Hence, associated factors of CKD should be

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identified to aim at improving or avoiding deterioration in renal function.

Hyponatraemia is the commonest electrolyte abnormality seen in the older patients (3). Hyponatremia is also a prognostic factor for renal replacement therapy in CKD patients treated with diuretics (4). Therefore hyponatraemic elderly patients were recruited in this study to determine the associated factors of CKD.

Methods

Study design

This was a retrospective review of medical records of patients who attended the primary care clinic at a teaching hospital in Kuala Lumpur, Malaysia from 1 January to 31 December 2014. Inclusion criteria for medical records examination were age 60 years and above with serum sodium < 135mmol/l and concomitant availability of serum glucose, potassium and creatinine results on the date of the abnormal laboratory test.

Setting

Clinic of Primary Care Medicine, Department of Primary Care Medicine, University of Malaya Medical Centre (UMMC).

Sample size and sampling method

Epi info version 7 was used to calculate the sample size. Based on the Malaysian study whereby CKD was present for 9.07 % of adult population (5). The total number of geriatric patients which attended the primary care medicine clinic, UMMC from 1st Jan 2014 to 31 st Dec 2014 was 21544, with a confidence level of 99 % and significance level set at $p < 0.05$, the estimated minimum sample needed was 217. Finally, total 257 samples were analysed.

Continuous sampling was used in this study. The list of registration number of all geriatric patients who attended the primary care clinic with renal function test done and with serum sodium < 135mmol/l was obtained from the Division of Laboratory Medicine, Department of Pathology, UMMC. Those medical records with duplicated registered number, incomplete or inaccessible data were excluded from the study. Out of 403 medical records of the elderly, 257 with inclusion criteria fulfilled were reviewed for data analysis.

Data collection

Data covering six dimensions: socio-demographic data, comorbidities, blood pressure (BP), heart rate, laboratory results, and prescribed medications were captured from patients' medical records.

The formulas to calculate Estimated Glomerular Filtration Rate (eGFR) by using CKD-Epidemiology Collaboration (EPI) equation are as follows:

Calculated serum osmolality = 2Na + 2K + urea + glucose (in mmol/L) (6).

CKD-EPI equation, eGFR = 141 × min(Scr ×0.0113/k, 1) α × max (Scr × 0.0113/k, 1) -1.209 × 0.993Age × 1.018 [if female], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1 (6).

Definition of key words

CKD is defined as an estimated glomerular filtration rate (eGFR) of < 60 ml/min per 1.73m^2 The United Nations defined older persons as 60 years and above. This definition has been adopted by policy makers in Malaysia to categorize its elderly population in the local setting and the new retirement age of 60 years has been effective since 2012 (7). Hyponatraemia was defined as serum sodium of less than 135 mmol/l (8).

Ethical consideration

This study was approved by the Medical Ethics UMMC. MECID No: 20147-411. As this was a retrospective case record analysis, informed consent was not needed, and this was waived by the medical ethics committee.

Data analysis

Data analysis was conducted using SPSS version 21.0 (Chicago, IL, US). Categorical data are presented as frequencies with percentages in parentheses and analyzed using the Chi-square test. Independent t-test, Pearson Chi-square test and Fisher Exact test were employed to look for the associated factors of CKD. Variables that failed to have a significant effect ($p > 0.25$) were eliminated before developing multivariate model. Multivariate logistic analysis was done using binary logistic regression to determine the independent predictors of an incident decline in kidney function. Continuous data were plotted as histograms to determine normal distributions. Parametric data are presented as means with standard deviations. Significance was assumed where $p < 0.05$.

Results

Patients' baseline characteristics

At baseline, the mean age of our study population sample was 72.9 ± 7.3 years (ranging from 60 to 93 years old) with 134 (52.1 %) men, 151 (58.8 %) were diabetics, 247 (96.1 %) had hypertension, 177 (68.9 %) had dyslipidemia, 43 (16.7 %) had ischaemic heart disease and 31 (12.1 %) had stroke. The mean BP was 135/75 (± 18/10) mmHg and mean heart rate was 77 ± 12/min. The commonest anti-hypertensive agents use was calcium channel blocker (CCB) 147 (57.2 %), followed by angiotensin-converting enzyme inhibitor (ACEi) 104 (40.5 %) and beta-blocker 84 (32.7 %). The mean eGFR for the elderly population was 72.62 ± 24.14ml/min/1.73m^2. Seventy-three (28.4 %) patients had CKD ie an eGFR < 60 ml/min per 1.73m^2. (Table 1)

There were 32 patients (12.5 %) had CKD stage 3A, 26 (10.1 %) had CKD stage 3B, six (2.3 %) had CKD stage 4 and nine (3.5 %) had CKD stage 5.

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Table 1. Univariate analysis on associated factors of CKD (n = 257)

Baseline characteristic		Total n(%) (n=257)	CKD n(%) No (n=184)	CKD n(%) Yes (n=73)	P-value
Age (years)	Mean ± SD	72.9 ± 7.3	72.4 ± 7.2	74.3 ± 7.6	0.066[a]
Gender	Men	134 (52.1)	100 (54.3)	34 (46.6)	0.261[b]
	Women	123(47.9)	84 (45.7)	39 (53.4)	
Diabetes Mellitus	No	106 (41.2)	88 (47.8)	18 (24.7)	0.001[b]
	Yes	151 (58.8)	96 (52.2)	55 (75.3)	
Hypertension	No	10 (3.9)	10 (5.4)	0 (0.0)	0.067[c]
	Yes	247 (96.1)	174 (94.6)	73 (100.0)	
Dyslipidaemia	No	80 (31.1)	65 (35.3)	15 (20.5)	0.021[b]
	Yes	177 (68.9)	119 (64.7)	58 (79.5)	
Ischaemic heart disease	No	444 (43.9)	389 (87.6)	55 (12.4)	0.161[b]
	Yes	568 (56.1)	427 (75.2)	141 (24.8)	
Stroke	No	226 (87.9)	164 (89.1)	62 (84.9)	0.351[b]
	Yes	31 (12.1)	20 (10.9)	11 (15.1)	
Nephrolithiasis	No	252 (98.1)	183 (99.5)	69 (94.5)	0.024[c]
	Yes	5 (1.9)	1 (0.5)	4 (5.5)	
SBP (mmHg)	Mean ± SD	134.9 ± 17.8	134.4 ± 16.8	136.3 ± 20.3	0.456[a]
DBP (mmHg)	Mean ± SD	74.8 ± 9.4	74.7 ± 8.9	75.1 ± 10.6	0.758[a]
Sodium (mmol/L)	Mean ± SD	130.3 ± 4.1	130.4 ± 4.2	130.2 ± 3.8	0.802[a]
Potassium (mmol/L)	Mean ± SD	4.5 ± 0.7	4.4 ± 0.6	4.7 ± 0.9	0.006[a]
Glucose (mmol/L)	Mean ± SD	8.6 ± 5.0	7.7 ± 4.0	10.6 ± 6.4	0.001[a]
ACEi	No	166 (64.6)	127 (69.0)	39 (53.4)	0.018[b]
	Yes	91 (35.4)	57 (31.0)	34 (46.6)	
ARB	No	185 (72.0)	129 (70.1)	56 (76.7)	0.288[b]
	Yes	72 (28.0)	55 (29.9)	17 (23.3)	
Beta-blockers	No	173 (67.3)	126 (68.5)	47 (64.4)	0.528[b]
	Yes	84 (32.7)	58 (31.5)	26 (35.6)	
CCB	No	110 (42.8)	83 (45.1)	27 (37.0)	0.235[b]
	Yes	147 (57.2)	101 (54.9)	46(63.0)	
Thiazide diuretics	No	178 (69.3)	130 (70.7)	48 (65.8)	0.443[b]
	Yes	79 (30.7)	54 (29.3)	20 (34.2)	
Loop diuretics	No	233 (90.7)	177 (96.2)	56 (76.7)	<0.001[b]
	Yes	24 (9.3)	7 (3.8)	17 (23.3)	
Alpha-blockers	No	238 (92.6)	172 (93.5)	66 (90.4)	0.397[b]
	Yes	19 (7.4)	12 (6.5)	7 (9.6)	
Spironolactone	No	253 (98.4)	180 (97.8)	73 (100.0)	0.580[c]
	Yes	4 (1.6)	4 (2.2)	0 (0.0)	
Lipid lowering agents	No	78 (30.4)	63 (34.2)	15 (20.5)	0.031[b]
	Yes	179 (69.6)	121 (65.8)	58 (79.5)	
Metformin	No	143 (55.6)	99 (53.8)	44 (60.3)	0.346[b]
	Yes	114 (44.4)	85 (46.2)	29 (39.7)	
Sulphonylurea	No	169 (65.8)	121 (66.3)	46 (64.4)	0.770[b]
	Yes	88 (34.2)	63 (33.7)	27 (35.6)	
Acarbose	No	241 (93.8)	174 (94.6)	67 (91.8)	0.401[c]
	Yes	16 (16.0)	10 (5.4)	6 (8.2)	
DPP4i	No	249 (96.9)	177 (96.2)	72 (98.6)	0.447[c]
	Yes	8 (3.1)	7 (3.8)	1 (1.4)	
Insulin	No	216 (84.0)	166 (90.2)	50 (68.5)	<0.001[b]
	Yes	41 (16.0)	18 (9.8)	23 (31.5)	
Antiplatelet	No	158 (61.5)	122 (66.3)	36 (49.3)	0.012[b]
	Yes	99 (38.5)	62 (33.7)	37 (50.7)	

a. t-test b. Pearson chi-square c. Fisher exact test ACEi: Angiotensin converting enzyme inhibitors ARB: Angiotensin II receptor blockers CCB: Calcium channel blocker DPP4i: Dipeptidyl peptidase-4 inhibitors SBP: Systolic blood pressure DBP: Diastolic blood pressure

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Associated factors of CKD

Pearson Chi-square test showed that diabetes mellitus (DM), dyslipidaemia, the use of loop diuretics, ACEi, insulin, anti-platelet and lipid-lowering agents were associated with CKD ($p < 0.05$). Fisher Exact test showed that nephrolithiasis was significantly associated with CKD ($p < 0.05$). Independent t-test showed serum potassium and glucose level were associated with CKD ($p < 0.01$). (Table 1)

After multi-variate analysis, three variables were identified as the independent associated factors of CKD; increasing age, hyperglycaemia and the use of loop diuretics ($p < 0.05$). The elderly with increasing age was more to have CKD [odds ratio (95 % confidence interval) = 1.1 (1.0 to 1.1); $p < 0.01$]. Among the anti-hypertensive agents, use of loop diuretics increased the odd of CKD by five times among the elderly. [Odds ratio (95 % confidence interval) = 5.1 (1.5 to 17.4); $p < 0.01$]. Elderly patients with hyperglycaemia were more likely to have CKD [odds ratio (95 % confidence interval) = 1.1 (1.0 to 1.2); $p < 0.05$]. (Table 2)

Table 2. Multivariate analysis on associated factors of CKD (n = 257)

Independent Variable	OR	95% CI for OR		P-value
		Lower	Upper	
Age	1.076	1.028	1.126	0.002
Diabetes mellitus	0.804	0.357	1.810	0.599
Dyslipidaemia	0.771	0.191	3.101	0.714
Ischaemic heart disease	1.640	0.617	4.359	0.321
Nephrolithiasis	4.226	0.341	52.343	0.262
Potassium level (mmol/L)	1.658	0.996	2.760	0.052
Glucose level (mmol/L)	1.095	1.016	1.180	0.017
Loop diuretics	5.145	1.523	17.377	0.008
ACEi	1.264	0.620	2.579	0.519
CCB	1.558	0.791	3.067	0.200
Lipid lowering agents	0.892	0.227	3.512	0.871
Insulin	2.284	0.950	5.493	0.065
Anti-platelet	2.013	0.997	4.063	0.051

Binary Logistic regression model, Enter method was applied
Hosmer-Lemeshow test, (p = 0.993), Pearson Chi-square & sig, (p = 0.000)
Classification table (overall correctly classified percentage = 80.1) were applied to check the model fitness

Discussion

The prevalence of CKD among adults in West Malaysia was 9.07 % (5). As a limitation in my study, data on albuminuria were unavailable, and it is an important element in defining CKD. However, eGFR < 60 ml/min per 1.73 m^2 is a well-accepted definition for CKD in population–based research settings and was adopted in our study (9). The Modification of Diet in Renal Disease (MDRD) study equation is inaccurate in individuals with eGFR above 60 ml/min per 1.73m^2 or with obesity, resulting in an underestimation of GFR in patients with normal renal function. Thus, we have applied the CKD-EPI equation which has been recently shown to more accurately categorize the risk for mortality and end stage renal disease than the MDRD study equation across a broad range of populations was appllied (10).

In the univariate model, diabetes mellitus (DM), dyslipidaemia, the use of loop diuretics, ACEi, insulin, anti-platelet, lipid-lowering agents, nephrolithiasis, serum potassium and glucose had a significant association with CKD. After multivariate analysis, only three variables namely increasing age, hyperglycaemia and the use of loop diuretics emerged as the independent associated factors of CKD. Of note, the use of loop diuretics was the most important factor associated with CKD.

Ederly with increasing age had higher incidence of renal dysfunction. This findings were consistent with a population-based study in West Malaysia found that those aged 65 years and above were three times more likely to develop CKD than those younger than 65 years old (5). The Kungsholmen Swedish project indicated a significant decline of eGFR with age. The eGFR declined from 52 ml/min per 1.73 m^2 at age 75 to 27 ml/min per 1.73 m^2 at age 95 with an average rate of 1.2 ml/min per 1.73 m^2 per year (11). Those elderly patients with hyperglycaemia were more likely to have CKD. This could be explained by a study done in West Malaysia that showed patients with diabetes mellitus were 2.6 times more likely to have CKD (5).

Estrogen hormone reduced proteinuria and glomerular fibrosis after experimental renal damage in different animal models render slower progression of renal injury in female animals than in their male littermates (12). My study populations were elderly and women were mostly post-menopausal, lack of estrogen as the protective factor for the development of CKD, contributing to no gender predominance of CKD. This finding is different from the reduction of

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end points in NIDDM with the Angiotensin II receptor antagonist Losartan (RENAAL) study in which CKD was commoner among men. This is because the participants in the RENAAL study were aged 31 to 70 years and pre-menopausal women were included (13).

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends that renin-angiotensin system blockade and thiazide diuretics should be used in hypertensive patients with CKD stages 1 to 3; and loop diuretics in those with CKD stages 4 and 5 (14). Thiazides diuretics are ineffective in patients with more advanced CKD because of less sodium being delivered to the distal tubule and therefore less thiazide diuretic action in the distal tubule (15). Contradictory to the recommended use of diuretics in CKD patients, I found that the use of loop diuretics but not thiazide diuretics was an independent predictor of incident CKD. This finding was supported by a study by Khan et al. at the Hospital University Sains Malaysia, that the use of diuretics was associated with adverse renal outcomes indicated by decline in eGFR and increasing risk of renal replacement therapy initiation (16). Data analysis of The Third National Health and Nutrition Examination Survey, NHANES III, reported that increase creatinine level was positively associated with diuretic prescriptions (17). Both thiazide and loop diuretics contribute to hypokalemia and volume loss. Hypokalemia leads to renal hypertrophy and tubulointerstitial fibrosis (18). Volume loss that results in prolonged vasoconstriction leads to tubular dysfunction and necrosis (19).

For those with inevitably diuretics requirement to relieve the uremia or fluid overload, lowest dose of diuretics should be used to avoid or retard the eGFR decline. The dosage of loop diuretic reduction in subjects with underlying renal dysfunction is safe and associated with an improvement in eGFR (20). Loop diuretic activates renin via multiple mechanisms and there was a trend for decreased renin with loop diuretic reduction. Reduced renin activation following loop diuretic reduction may in part account for the increase in GFR (21). Therefore, we need to be cautious when prescribe loop diuretic to our patients. Adequate electrolytes with creatinine monitoring should be done to prevent untreated hyponatraemia, hypokalaemia and eGFR decline. Besides, we need to counsel patients to follow a low-sodium diet to allow for a lower dose of loop diuretic is effective (22).

UK Prospective Diabetes Study (UKPDS) showed that elevated SBP increases the risk for development of nephropathy in diabetics, while 13 % reduction in micro-vascular complications including nephropathy for every 10 mmHg decreased in SBP (23). Patients with impaired renal function also seem to have higher SBP levels than individuals with normal renal function (24). My study showed that BP was not associated with CKD. This is because the mean BP was well controlled and almost similar between the non-CKD and CKD groups.

Conclusion

In our study, hyperglycaemia and loop diuretic usage were significant modifiable risks factors associated with CKD among the elderly. One in four elderly who were on loop diuretics had CKD. This finding is especially important because of high prevalence of diabetes mellitus and rampant use of diuretics in Malaysia. Effort should be made to optimize the glycaemic control and cautious in the usage of loop diuretic in order to slow down the decline of renal function in geriatrics.

Strengths and limitations of this study

This study has provided important messages to clinicians with regard to the adverse effect of loop diuretics to renal function as it has substantial clinical implication to the elderly.

This study was conducted in a single centre, thus could not be generalized.

This study involved retrospective record review; hence poor documentation could affect the result of the study.

Conflict of interest

No conflict of interest is declared.

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Authors' contribution

Chai Li Tay conceived and conducted the study and all data collection, involved in the data analysis, interpretation of results and writing of this manuscript.

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