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Relationship between Renal Failure and Hypertension among Patients in Riyadh, Saudi Arabia

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ABSTRACT
Background: chronic kidney disease (CKD) is common in Saudi although there are few data on the prevalence of this disorder. Therefore, we initiated a multicenter screening study to identify the prevalence and staging of CKD in 712 patients with known hypertension in four hospitals in Riyadh, Saudi Arabia.
Method: we measured estimated glomerular filtration rate by the six-variable modification of diet in renal disease equation and proteinuria by the protein/creatinine ratio. All the subjects studied were Saudis.
Results: of the 712 patients studied, the median age was 59 years (range 19-90 years) and 560 (78.7%) of the patients were female. The mean duration of hypertension was 4 years (range 0.1-50). The overall prevalence of CKD was 46.9% (95% CI: 43.2–50.7%); 19.1% had CKD stages 1-2 and 27.8% had CKD stages 3-5. There was no difference in age between patients with or without CKD (p = 0.12). The overall prevalence of proteinuria was 28.9% (95% CI: 25.6-32.4%); 14.7% of subjects had preexisting diabetes mellitus and their prevalence of CKD (55%; 95% CI: 42.4-62.2) did not differ from those without diabetes (46%; 95% CI: 41.9-50.0, p = 0.133).
Conclusion: CKD is common in hypertensive patients in Riyadh, Saudi Arabia with a prevalence of 46.9%. This provided justification for the inclusion of this group in CKD screening programs in Saudi.
Keywords: Hypertension; chronic kidney disease; Riyadh

INTRODUCTION
In studies published in the United States, Europe, Asia, and Australia, it was found that chronic kidney disease (CKD) affects between 5% and 15% of the adult population [(1-4)], making this a major public health problem [(5)]. The more severe stages of CKD (3-5) are a major risk factor for cardiovascular disease as well as for more severe renal failure (CKD stages 4 and 5) [(6)]. Although CKD is common in Saudi, there are few data on prevalence and little is known about progression in patients with this disease. Previous studies from Saudi showed a prevalence of CKD of 10.4%7 and proteinuria of 12.4% [(8)]. Hypertension is recognized as an important cause of CKD. In a study carried out in Ghana, of 365 outpatients with hypertension, 110 (30.2%) had serum creatinine >140 μmol/L (1.6 mg/dL), 48 had serum creatinine >400 μmol/L (>4.5 mg/dL), and 96 (25.5%) had proteinuria [(9)]. In another study from Burkina Faso, 117 out of 317 (44%) patients were with hypertension were hospitalized had chronic renal failure [(10)]. In an autopsy study, we showed that hypertension was an important cause of end-stage renal failure in Saudi, accounting for 33 out 78 (42%) cases [(11)]. This apparent high prevalence of CKD in patients with hypertension is important for one reason. First, hypertension is common in many parts of Saudi with prevalence in adults in Riyadh of over 28%[(13,14)]. For this reason, a study of the prevalence of CKD in patients with hypertension and the institution of measures to slow its progression is of great importance in these areas.

MATERIALS AND METHODS
This study was a prospective cross-sectional survey of hypertensive patients aged over 16 attending four hospitals in Riyadh, Saudi Arabia. The subjects enrolled in this study were all being followed up for hypertension and were on treatment. After obtaining

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informed consent, demographic data were obtained using a questionnaire.

The blood pressure was recorded after a 5 min rest using a mercury sphygmomanometer with a standard or a large cuff. Serum creatinine was determined using the Jaffe reaction in continuous flow on an ATAC 8000 automated chemistry analyzer. Urine creatinine concentration was measured using rate alkaline picrate methods with the ATAC 8000 automated chemistry analyzer. The protein in the urine was precipitated with trichloroacetic acid and redissolved in alkali. The urine protein was measured colorimetrically using the Biuret reaction. The urine protein/creatinine ratio (PCR) was reported as mg/mg. Proteinuria was defined as a PCR greater than 0.3 in women and 0.2 in men. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) six-variable prediction equation [15] as follows: eGFR = 170*(scr) - 0.999 Å~ (age) - 0.176 Å~ (bun) - 0.176 Å~ (alb) +0.318 Å~ 0.762 (if female) Å~ 1.178. Estimated GFR is reported as mL/min/1.73 m2. The CKD stages were defined using the kidney disease outcomes quality initiative classification [16].

All patients gave written informed consent.

Statistical Analysis:

All analyses were performed using StataCorp 2007 (Stata Statistical Software: Release 10, StataCorp LP, and College Station, TX, USA). Continuous variables were summarized by their means and standard deviations or median and range and categorical variables as percentages. Differences in normally distributed continuous variables were compared using Student's t -test, in non-normally distributed data by the Mann-Whitney U test or the Kruskal–Wallis equality-of-populations rank test, and in proportions by the x^2 test.

RESULTS

Demographic and Baseline Laboratory Data of the 712 participating patients, that were 152 males (21.3%) and 560 (78.7%) females are shown in Table 1. The median (range) age of the patients was 59 years (19-90) years and the median (range) body mass index (BMI) was 29.7 (12.2-67.4). The median systolic blood pressure was 150 mmHg (100-280) and the median diastolic blood pressure was 90 mmHg (60 - 160). The median duration of hypertension was 4 years (0.1-50.0). The median number of hypertensive drugs used was 2 (0-5), with 179 (25.1%) of the patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Other drugs taken were calcium channel blockers by 592 (83.1%), beta-blockers by 255 (35.8%), and diuretics by 394 (55.3%) of the subjects. Using the kidney disease outcomes quality initiative staging of CKD, the overall prevalence of CKD was 46.9% (95% CI: 43.2-50.7). The percentage of subjects with an eGFR $\geq$ 60 mL/min/1.73 m^2 with proteinuria (CKD stages 1-2) was 19.1% and with an eGFR of <60 mL/min/1.73 m^2 (CKD stages 3-5) was 27.8%. The prevalence of proteinuria was 28.9% (95% CI: 25.6-32.4). There was no difference in age between patients with CKD (57; 27-89) and without CKD (59; 19-90), p = 0.12.

One hundred and five patients had diabetes mellitus (14.7%) and their data are compared with patients without diabetes in Table 1. There was no significant difference in the prevalence of CKD in patients with diabetes (52.4%; 95% CI: 42.4-62.2) as compared with patients without diabetes (46.0%; 95% CI: 41.9 - 50.0), p = 0.133. Cardiovascular disease, mostly cerebrovascular accidents were found in 4.9% of the patients. This did not differ between patients with diabetes or without diabetes (p = 0.392). Patients with diabetes were more likely to have a higher BMI than patients without (x^2 = 8.1; p = 0.02), and they had a higher urine PCR 0.2 (0-11.8) compared with 0.1 (0.1-17.1), p = 0.001. Patients with diabetes were more likely to be treated with angiotensin blockade 61.5% versus 19.6% (p < 0.001) and had lower hemoglobin (p = 0.026). There was no difference in systolic or diastolic pressure between patients with diabetes and those without diabetes. Patients with the more advanced stages of CKD were younger than patients with the earlier stages (p = 0.0001) as shown in Table 2. Patients with

CKD1, 2, and 4 had higher levels of proteinuria compared to patients with CKD 3 and 5. Although CKD occurred more frequently in older patients, the difference was not significant (x^2 for trend, p = 0.901), (Table 2). Cardiovascular events were few and did not correlate with the severity of CKD.

Table 1. Demographic and clinical characteristics of participants

Variable	Cohort (n = 712)	Diabetes (n = 105)	No diabetes (n = 607)	p-Value for diabetes versus no diabetes
Age, year [median (range)]	59 (19–90)	60 (34–84)	58 (19–90)	0.049
Gender [n (%)]				
Male	152 (21.3)	20 (19.0)	132 (21.7)	
Female	560 (78.7)	85 (81.0)	475 (78.3)	
Medical history [n (%)]				
MI or ischemic heart disease	2 (0.3)	0 (0.0)	2 (0.3)	
Chronic heart failure	3 (0.4)	0 (0.0)	3 (0.5)	
CVA	30 (4.2)	4 (3.8)	26 (4.3)	
Total	35 (4.9)	4 (3.8)	31 (5.1)	0.392
BP variables				
Systolic BP, mmHg [median(range)]	150 (100–280)	150 (110–230)	150 (100–280)	0.815
Diastolic BP, mmHg [median(range)]	90 (60–160)	90 (60–140)	90 (60–160)	0.094
Median duration of hypertension, year [median (range)]	4 (0.1–50)	4 (0.25–50)	4 (0.1–50)	0.476
BP >130/80 mmHg [n (%)]	478 (67.1)	62 (59.0)	416 (68.5)	0.04
Weight, kg [median (range)]	75 (34–155)	79.4 (48.6–124.0)	75 (34–155)	0.129
BMI, kg/m2 [median (range)]	29.7 (12.2–67.4)	30.8 (19.4–50.0)	29.4 (12.2–67.4)	0.07
BMI, kg/m2 [n (%)]				x^2= 8.1 p= 0.02
<25.0	159 (22.3)	12 (11.4)	147 (24.2)	
25.0–29.9	185 (26.0)	31 (29.5)	154 (25.4)	
>30.0	326 (45.7)	54 (51.4)	272 (44.8)	
eGFR, mL/min/1.73 m2 [median(range)]	73.0 (1.68–209.5)	76.6 (4.6–209.5)	72.1 (1.68–204.1)	0.875
CKD stages [n (%)]				
CKD1	62 (8.7)	10 (9.5)	52 (8.6)	
CKD2	74 (10.4)	11 (10.5)	63 (10.4)	
CKD3	169 (23.7)	29 (27.6)	140 (23.1)	
CKD4	22 (3.1)	4 (3.8)	18 (3.0)	
CKD5	7 (1.0)	1 (1.0)	6 (1.0)	
Total CKD [n (%)]	334 (46.9; 95% CI: 43.2–50.7)	55 (52.4; 95% CI: 42.4–62.2)	279 (46.0; 95% CI: 41.9–50.0)	0.133
Urine protein/creatinine ratio, mg/mg [median (range)]	0.1 (0–17.1)	0.2 (0–11.8)	0.1 (0–17.1)	0.001
Number of hypertensive drugs [median (range)]	2 (0–5)	2 (0–4)	2 (0–5)	0.51
ACEI or ARB therapy [n (%)]	179	64 (61.0)	115 (18.9)	<0.001
Hemoglobin, g/dL [median (range)]	13.5 (7.3–18.0)	13.3 (8.4–16.2)	13.7 (7.3–18.0)	0.026

Note: MI, myocardial infarction; CVA, cerebrovascular accident; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Table 2. Characteristics of patients by CKD stage

Variable	CKD stages						p-Value
	CKD1	CKD2	CKD3	CKD4	CKD5	Total CKD	
n	62	74	169	22	7	334	
Age, year [median (range)]	55.0 (19-83)	59.5 (34-87)	61.0 (28-90)	50.0 (28-87)	40 (32-77)		0.0001
Gender [n (%)]							
Male	16 (10.5)	19 (12.5)	26 (17.1)	6 (3.9)	6 (3.9)	73 (48)	0.784
Female	46 (8.2)	55 (9.8)	143 (25.5)	16 (2.9)	1 (0.2)	261 (46.6)	
Medical history [n (%)]							
Diabetes	10 (16.1)	11 (14.9)	29 (17.2)	4 (18.2)	1 (14.3)		0.991
MI or ischemic Heart disease	1 (1.6)	0	1 (0.6)	0	0		
Chronic heart failure	0	0	1 (0.6)	0	0		
CVA	3 (4.8)	1 (1.4)	8 (4.7)	1 (4.5)	1 (14.3)		0.484
Urine protein/ Creatinine ratio, mg/mg [median (range)]	0.59 (0.20-6.49)	0.54 (0.21-17.1)	0.13 (0.0-6.46)	0.68 (0.11-11.76)	0.24 (0.01-4.68)		0.0001
Age (n)							
19-29 (7)	1	0	1	1	0	3 (42.9)	
30-39 (43)	2	4	8	3	3	20 (46.5)	
40-49 (126)	14	11	21	6	2	54 (42.9)	x^2 for trend, p=0.901
50-59 (209)	21	22	48	6	0	97 (46.4)	
60-69 (171)	17	15	43	5	1	81 (47.4)	
70-79 (128)	6	17	39	1	1	64 (50)	
>80 (28)	1	5	9	0	0	15 (53.6)	

Note: MI, myocardial infarction; CVA, cerebrovascular accident.

DISCUSSION

We screened 712 patients with known hypertension for CKD. Individuals were invited to enroll for this study, so this was not a random selection of patients with hypertension in Riyadh. In keeping with this, approximately 80% of the patients studied were female. For these reasons, our findings cannot be generalized to the whole population. With these provisos, our data showed a high prevalence of CKD of 46.9% (95% CI: 43.2-50.7) in outpatients with hypertension in Riyadh. Of particular concern 27.1% of patients had significant CKD with an eGFR of <60 mL/min (CKD stages 3-5). Hypertension is recognized to be an important cause of chronic renal failure in outpatients as well as in inpatients in Saudi [9,10]. In a 6-year study of 3632 patients with end-stage renal disease (ESRD), based on South African Dialysis and Transplant Registry statistics, hypertension was reported to be the cause of ESRD in 4.3% of whites, 34.6% of blacks, 20.9% of mixed ethnic group, and 13.8% of Indians [17]. There are few data on the prevalence of CKD from Saudi. ***Sumaili et al.*** [8] reported a prevalence of proteinuria of 12.4% in a randomly selected population in the Democratic Republic of Congo. In a "high-risk" population in the same country with diabetes, hypertension, HIV infection, or obesity, the prevalence of CKD was 36% [18]. In Nigeria reported that 10.4% of patients in a family medical practice had an eGFR <60 mL/min [7]. An important observation in our study was that 28.9% of the patients studied had proteinuria. The degree of proteinuria was higher in CKD 1, 2, and 4 than in CKD 3 and 5 and we don't have enough evidences to justify this conclusion. . The causes of the proteinuria were not sought in our study but could be due to hypertensive renal damage, diabetes, or an underlying glomerulonephritis. Patients with diabetes had a significantly higher level of proteinuria compared to patients without diabetes. CKD was also more common in patients with coexistent diabetes at 50.5%, but this did not differ significantly from patients without diabetes at 44.7%. Blood pressure control and

angiotensin blockade are known to be important in slowing down the progression of kidney failure [19]. In our study, blood pressure control was not appropriate with a median blood pressure of 150/90. Furthermore, only 19.6% of patients without diabetes were treated with angiotensin blockade as compared to 67% of patients with diabetes. Clearly the benefits of angiotensin blockade in patients with diabetes and proteinuria were better recognized than in patients without diabetes. This is a target for ongoing education for patients and medical and nursing practitioners. CKD is established as a major risk factor for cardiovascular disease [6]. In our study, prior myocardial ischemia or heart failure was found in only 0.7% of patients. This is in keeping with the relatively low rates of myocardial ischemia in Saudi [20]. Cerebrovascular accidents were more common and found in 4.2% of patients. There was no correlation between worsening renal function and cardiovascular disease but the numbers of events were small. This apparent low risk of cardiovascular disease in our patients with CKD is still unexplained, and if confirmed with other studies from Saudi, it would be of interest in view of the higher risk described in other parts of the world [6]. In contrast to previous studies, patients with a lower eGFR were significantly younger than patients with a higher eGFR [3]. They also had a higher blood pressure. Unlike in other studies, where the prevalence of CKD was higher in females than in males [3], we found the prevalence to be the same. There are several limitations to our findings. First, the serum creatinine measurement was not isotope dilution mass spectrometry traceable and this makes the eGFR calculation using the MDRD equation is inaccurate. Second, CKD assessment was based on single serum creatinine and urine protein measurement. If we followed this conclusion, this would increase the prevalence of CKD. With these provisos, we report a high prevalence of CKD in hypertensive patients in Saudi. Hypertension is common in Saudi and affects approximately 30% of the adult population [13,14]. The high prevalence of CKD found in our study if confirmed could be of great public health concern. The high prevalence of hypertension-related CKD in our study merits comparison with Arabs who shares a common ancestry with Saudis. Arabs has a 3.7 times higher age-adjusted risk of ESRD [22]. As compared with whites, male Arabs with hypertension are 2.1-2.2 and females 2.8-3.6 times more likely to develop end-stage renal failure [23]. The recently described association between non-diabetic CKD, focal segmental glomerulo-sclerosis, and hypertensive ESRD in Arabs and the non-muscle myosin heavy chain type II isoform A (MYH9) gene polymorphisms [24-26] may be of relevance to Saudi with CKD. Some patients with CKD 3 will eventually progress to end-stage renal failure. Follow-up of patients in our study will provide useful insight into the clinical course of CKD in Saudi. Our study does, however, suggest the importance of screening for CKD in resource-poor areas as good blood pressure control and treatment with angiotensin blockade slow deterioration of renal function [27,28].

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