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Prevalence of White Coat Hypertension in Patients with Chronic Kidney Disease

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Abstract

Background: Achieving target blood pressure is important in retarding the progression of chronic kidney disease (CKD). Optimizing patient's hypertension solely based on clinic blood pressure could be harmful as it may be masked by white coat hypertension.
Objectives: This study aimed at determining the prevalence of white coat hypertension (WCHT) in patients with CKD and correlating this with their target organ damage evidenced by left ventricular hypertrophy (LVH) and carotid intima media thickness (CIMT).
Methods: A cross sectional study of 99 patients with CKD (stage 3 to 5 with eGFR Epi of < 60 mL/min/1.732) at a CKD clinic was conducted. Demographic data, routine blood investigations, and number of antihypertensive medication were recorded. Mean clinic blood pressure of the last 2 visits were taken followed by 24-hour ambulatory blood pressure monitoring (24-hour ABPM), electrocardiography, and carotid ultrasound measurement.
Results: Ninety-nine patients (42 males and 57 females) with median age of 62 (55 to 69) years old and predominantly Malays ethnicity were recruited. The prevalence of WCHT was 34.3% (34 patients), and 65.7% (65 patients) had sustained hypertension (SHT). Median eGFRs were comparable in both groups (P = 0.479). Despite comparable mean clinic blood pressure (P = 0.85), the WCHT group had significantly lower mean average systolic, daytime, and night time blood pressure when compared with the SHT group (120.82 ± 8.24 vs. 153.20 ± 18.70), (124.50 ± 9.51 vs 155 ± 18.86) , (111.97 ± 20.07 vs 146.22 ± 21.17) and diastolic (66.36 ± 85.79 vs. 82.35 ± 12.17), (68.71 ± 10.94 vs 84.11.8) , (62.68 ± 7.78 vs. 79.28 ± 12.17) respectively (P < 0.05). The trend towards significance of LVH in the WCHT compared with the SHT group (52% vs.38% (P = 0.066)) and the SHT group had a significantly higher median CIMT 0.80 mm (0.70 - 0.90) as opposed to the 0.60 mm median of the WCHT group (0.60 to 0.70) (P < 0.05). Two-thirds of SHT were non dippers.
Conclusions: White coat hypertension is prevalent in CKD. Patients with SHT had significant carotid intima thickening; LVH was detected more commonly in the WCHT group.

Keywords: Ambulatory Blood Pressure Monitoring, Carotid Intima, Chronic Kidney Disease, White Coat Hypertension

1. Background

Hypertension (HPT) is very common among patients with chronic kidney disease (CKD) with reported prevalence of as high as 80% to 90% (1); it can be the cause or the effect of CKD itself. Hypertensive nephrosclerosis was the second leading cause of CKD in Malaysia (24.2%) (2). Conversely, CKD is the most common cause of secondary HPT (3). In the USA, it has been estimated that hypertension occurs in 23.3% of non-CKD patients (4). The glomerular filtration rate (GFR) declines more rapidly in hypertensive patients after 40 years of age at the rate of 1.5 mL/min per 1.73 m^2 per year compared to 0.75 - 1.00 mL/min per 1.73 m^2 per year in non-hypertensive counterparts (5).

Achieving blood pressure (BP) control < 130/80 mmHg is crucial to reduce Cardiovascular (CV) morbidity and mortality and retard CKD progression (6-8). However, only 27% of patients with CKD achieved a BP goal of < 140/90 mmHg, and a mere 11% achieved a BP of < 130/85 mmHg (9). This could be because of several factors, such volume overload, over-activation of renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction and arterial stiffness (10). On the other hand, patients may be perceived as hypertensive because of suboptimal BP assessment or underlying 'white coat effect' on BP.

White coat hypertension (WCHT) was defined when the office BP was elevated despite a normal reading while awake or on ambulatory blood pressure monitoring (ABPM). O'Brien et al. redefined WCHT as clinic or office blood pressure of ≥ 140/90 mmHg with ABPM < 130/80

mmHg (11). The prevalence of WCHT in normotensive individuals was 13% and as high as 32% in hypertensive individuals (12). There was limited data in CKD patients with a reported prevalence of WCHT between 28% and 31.7% (13-16).

Ambulatory Blood Pressure Monitoring has been recommended by several guidelines in confirming the diagnosis of HPT when the clinic BP is > 140/90 mmHg (17). Patients with CKD and high clinic BP readings with good control on ABPM displayed better CV and renal outcomes as compared to patients with SHT (18). Furthermore, ABPM can provide more information on the early morning surge in BP as well as dipping status, both of which are increasingly recognized as cardiovascular risk factors (18).

Hypertension is a well-established predictor for cardiovascular events (3, 19). Systolic HPT highly correlates with left ventricular hypertrophy (LVH). In the elderly, systolic BP increases disproportionately to diastolic BP, resulting in a wide pulse pressure, which is a surrogate marker for arterial stiffness. Hypertension also causes carotid structural changes, such as intima media thickening and plaque (20, 21). Thickening of intima media of the common carotid artery is a useful marker in predicting vascular changes producing atherosclerosis (22).

As there is no local data available on WCHT in patients with CKD, the current study aimed at determining the prevalence of WCHT among patients with CKD and correlating this with target organ damage by measuring LVH and CIMT.

2. Methods

This was a cross sectional study on patients with CKD attending the nephrology clinic of UKMMC between November 2014 and January 2016. Inclusion criteria were being an adult patient aged > 18 and < 80 years old with CKD stages III to V (CKD EPI GFR < 60 mL/min/1.73 m^2) and with clinic BP readings of $\geq$ 140/90 mm Hg on 2 clinic visits. This study excluded patients with atrial fibrillation, patients on dialysis or those that had received renal transplantation. Recruitment was done via convenience sampling. After obtaining a written informed consent, a clinical interview, physical examination and demographic data, including age, gender, race, weight, height, comorbidities, and medications were recorded. Laboratory data from the clinic visit and clinic BP readings were recorded. All patients were subjected to 24 hours of ABPM, electrocardiogram (ECG), and ultrasound scan of common carotid artery. Chronic Kidney Disease was defined as either kidney damage or eGFR < 60 mL/min/1.73 m^2 for more than 3 months.

Clinic BP was measured during the nephrology clinic visit (8 am - 1 pm) as per guidelines (23). Next, all patients underwent 24-hour ABPM monitoring using the BPRO machine (model T6400, Healthstats), following a standard procedure (11). The researchers analyzed the mean of 24-hour daytime BP, night time systolic and diastolic BP, mean arterial BP, and pulse pressure. More than 80% technically satisfactory readings during both daytime and night time measurements were accepted as a successful recording or else they were repeated (13). The patients were then categorized to normotensive, WCHT, and Sustained Hypertension (SHT) groups (Table 1). All patients were grouped to dippers or non-dipper based on the night to day systolic blood pressure ratio (13). Patients, who exhibited a reduction of systolic or diastolic BP of > 10% during the night (10% to 20%) were categorized as normal dippers, those with > 20% reduction in night time BP were excessive dippers, < 10% in night time BP were non-dippers, and those, who had no drop in night time BP but had a paradoxical rise in BP were reverse dippers. In the current study, the normal dippers and excessive dippers were combined and regrouped as dippers, whereas the non-dippers and reverse dippers were regrouped as non-dippers. Polypharmacy is defined as the requirement of more than 3 agents (24).

Table 1. Classification of Blood Pressure

	Clinic Blood Pressure, mmHg	Daytime ABPM, mmHg
Normotensive [NOR]	< 140/90	< 130/80
White Coat HPT[WHT]	$\geq$ 140/90	< 130/80
Sustained HPT [SHT]	$\geq$ 140/90	$\geq$ 130/80

An ECG was performed and LVH was defined using the Sokolow-Lyon amplitude criteria (25, 26).

2.1. Carotid Intima Media Thickness (CIMT)

Carotid ultrasound was performed as per the American echocardiographic guidelines (27). Both carotid arteries were scanned to determine the CIMT, using an ultrasound scanner (Siemens SONOLINE G40) with a 7 MHz linear transducer and a transducer aperture of 38 mm. The CIMT images were recorded from a distance between the first echogenic line (lumen-intima interface) and the second echogenic line (media adventitia interface). The CIMT was measured at 1 cm proximal to the start of the carotid bulb dilatation of the common carotid artery in the far wall, and the maximum CIMT value was recorded. The mean from 3 readings was taken each from both sides and then the maximum CIMT value was recorded for analysis. The ultrasound images were verified by a radiologist, who

was blinded to the cases. As there was no reference for CIMT values in the local (Asian) population, the matched age and gender CIMT value from the Carotid Atherosclerosis Progression Study (CAPS) was used (20). Carotid Intima Media Thickness values of $\geq$ 75th percentile are considered abnormally high and indicative of increased CVD risk, 25th to 75th percentile are average and are not considered to change CVD risk, whereas values $\leq$ 25th percentile are considered to have lower CVD risk.

The statistical package for social science version 20.0 (SPSS Inc. Chicago, IL) was used for data analysis. After testing for normality, the data were expressed either as mean $\pm$ SD (standard deviation) or median with IQR (inter quartile range of 25th percentile; 75th percentile) based on their normality distribution. Chi- square was used for categorical variables and Student's t-test and Mann Whitney-U test were used for continuous variables. In addition, correlation was determined either by the Pearson coefficient or the Spearman coefficient, based on data distribution. A P value of < 0.05 was considered significant.

This study received ethics approval from the research ethics committee, Universiti Kebangsaan Malaysia [study code FF-2014-341] and was supported by a grant from the UKMMC Fundamental Research Fund.

3. Results

Ninety-nine patients were enrolled with median age of 62 (IQR 55 to 69) years old with 42 (42.4%) males and 57 (57.6%) females. The racial distribution consisted of 66 (66.7%) Malays, 29 (29.3%) Chinese, and 4 (4%) Indians. Diabetes was the main aetiology of CKD (46.5%) followed by glomerulonephritis (23.3%) and hypertension. The majority of the cases were in stage III and IV CKD; 48.5% and 40.4% respectively. The median duration of hypertension was 9 (6 to 17) years with the longest duration being 33 years. Most of the patients had co-morbidities, with dyslipidaemia and diabetes mellitus being the commonest. Based on the world health organization (WHO) classification, the majority of the patients were overweight with a median body mass index (BMI) of 26 (26 - 30) kg/m^2. Twenty-six patients were smokers.

The prevalence of WCHT in the current study was 34.3% (n = 34) whereas 65.7% (n = 65) had SHT. Both groups, WCHT and SHT, had comparable laboratory parameters except for a significantly higher serum creatinine in the SHT group as shown in Table 2. Two-thirds of the patients were non dippers (66.7%).

3.1. ABPM Measurements

As expected, the WCHT group had significantly lower BP on ABPM at all times (Table 3). In addition, there were a few patients in the WCHT group, who had a systolic BP of < 100 mm Hg. All patients were on anti-HPT treatments with the median number of anti-hypertensive prescribed being 3 agents. Fourty-six (46.5%) patients required < 2 antiagents whereas the remaining 53 (53.5%) patients needed 3 agents. Of these 53 patients, the majority were in the SHT group (n = 32, 60.4%). There were 44 (44.4%) patients on Angiotensin-Converting-Enzyme (ACE) inhibitor and 22 (22.2%) were on angiotensin receptor blockade (ARB).

3.2. Left Ventricular Hypertrophy

Forty patients (40.4%) had LVH based on the ECG criteria. There was a higher prevalence of LVH in the WCHT group (18/34, 52%) compared with the SHT group (22/65 and 33.8%) with a trend towards significance (P = 0.066) (Table 4).

3.3. Carotid Intima Media Thickness

The overall median CIMT was 0.70 (0.70 to 0.80) mm. The median CIMT in the WCHT group was 0.60 (0.60 to 0.70) vs 0.80 mm (0.70 to 0.90) in the SHT group (P < 0.01). A total of 26 patients were found to have thickened CIMT, of which 25 were in the SHT group (Table 5). Half of the patients with thickened CIMT had concomitant LVH. Age correlated with CIMT in the overall population (r^2 = 0.198, P = 0.049). As the majority of patients, who had thickened CIMT, were in the SHT group, the research further subanalyzed the SHT group to look at significant predictors for the development of CIMT thickening. This study demonstrated that age (r^2 = 0.342, P = 0.005) was the only significant predictor. Based on logistic regression, the independent factors associated with greater risk of obtaining thickened CIMT were pre-existing IHD and age. The probability of having thickened CIMT was 14.3% (P = 0.001, CI 95%) higher with IHD. The probability of having thickened CIMT was increased by 22.6% (P = 0.025; CI 95%) by every one year increment of age. On multiple linear stepwise regressions, both variables were still significant P < 0.025, (R^2 = 0.051, adjusted R^2 = 0.041).

4. Discussion

Achieving BP target remains a challenge to physicians either due to resistant HPT in CKD or due to the effect of WCHT. Effective treatment ameliorates the harmful effects of uncontrolled HPT and provides renal and CV protection (3-5). However, poor awareness and non-adherence are 2 well-known factors for suboptimal BP control (28). Furthermore, the high prevalence of WCHT among the CKD population leads to misclassification of true BP (13, 14). This study found that the prevalence of WCHT in the CKD cohort

Table 2. Characteristics of Sample in the Two Groups[a]

Characteristics	WCHT (n = 34)	SHT (n = 65)	P Value
Age, y	65.50 (58-69)	62 (52-68)	0.131[b]
Gender			0.143[c]
Male	11 (32.4)	31 (47.7)	
Female	23 (67.6)	34 (52.3)	
BMI, kg/m^2	27.50 (23.75 - 33)	25 (22.50 - 30.00)	0.087[b]
Smoking status			0.159[c]
Smokers	6 (17.6)	20 (30.8)	
Non smokers	28 (82.4)	45 (69.2)	
Diabetes Mellitus	23 (67.6)	39 (60)	0.455[c]
Dyslipidemia	29 (85.3)	56 (86.2)	0.907[d]
IHD	3 (8.8)	13 (20)	0.151[c]
CVA	4 (11.8)	9 (13.8)	0.769[d]
CKD Stages			0.157[d]
Stage III	21 (61.8)	27 (41.5)	
Stage IV	10 (29.4)	30 (46.2)	
Stage V	3 (8.8)	8 (12.3)	
Renal Function Test			
Urea, mmol/L	10.41 ± 4.27	11.17 ± 4.33	0.404[e]
Creatinine, μmol/L	174.00 (144.25 - 195.00)	194.00 (137.00 - 141.00)	0.038[b]
Fasting Serum Lipid			
Triglyceride, mmol/L	1.68 (1.26 - 2.85)	2.03(1.46 - 2.77)	0.290[b]
Total Cholesterol, mmol/L	5.12 (4.33 - 6.13)	5.21(4.40 - 5.87)	0.897[b]
LDL, mmol/L	2.62 (2.07 - 3.52)	3.01(2.15 - 3.51)	0.808[b]
HDL, mmol/L	1.21 (0.98 - 1.47)	1.14(0.91- 1.46)	0.255[b]
CKD-EPI GFR, mL/min/1.73 m^2	32.39 ± 11.15	30.52 ± 13.03	0.479[e]

Abbreviations: BMI, body mass index; CKP EPI GFR, chronic kidney disease Epidemiology collaboration glomerular filtration rate; CKD, Chronic Kidney Disease; CVA, cerebrovascular accident; HbA1c, Haemoglobin A1c; HDL, high density lipoprotein; IHD, Ischemic heart disease; LDL, low density lipoprotein Urine PCI, urine protein-creatinine index.
[a]Values are expressed s mean ± SD/median (IQR) or No. (%).
[b]Mann-Whitney U Test.
[c]Pearson Chi Square.
[d]Likelihood ratio.
[e]T-test.

was 34.3%, which is in agreement with the reported literature on both CKD and general populations (9, 13-16).

Both the WCHT and SHT group were similar in demographics and in terms of CKD staging despite the SHT group having a higher serum creatinine. However, there was a significant discrepancy between ABPM and clinic BP in both WCHT and SHT groups with a minimum difference of 20 to 30/10 to 20 mm Hg. This effect was pronounced in the WCHT group proving that clinic BP always overestimates the true BP as demonstrated in other studies (13, 15). The degree of reduction on ABPM at night time went down over the threshold limits of hypoperfusion (SBP of < 100 mmHg) in the WCHT group. Therefore, intensification of anti-hypertension based on clinic BP would potentially predispose patients to ischemia-induced worsening of renal and CV outcomes (29).

The current study also showed that the patients with CKD were older with co-morbidities, such as ischaemic heart disease (IHD) or stroke. Diabetes mellitus remains the most common cause of CKD, in agreement with the registry of this study (2, 30).

The SHT group required more anti HPT medications

Table 3. Blood Pressure in the Two Groups[a]

Characteristics, mmHg	WCHT (n = 34)	SHT (n = 65)	P Value
Clinic			
Systolic	162.09 ± 20.47	161.34 ± 14.88	0.85[b]
Diastolic	80.21 ± 7.80	81.18 ± 9.72	0.61[b]
Pulse pressure	81.88 ± 19.92	80.15 ± 16.25	0.64
ABPM			
Systolic	120.82 ± 8.24	153.20 ± 18.70	< 0.001[b]
Diastolic	66.36 ± 85.79	82.35 ± 12.17	< 0.001[b]
Pulse pressure	54.47 ± 9.21	70.84 ± 19.35	< 0.001[b]
Day time			
Systolic	124.50 ± 9.516	155.55 ± 18.86	< 0.001[b]
Diastolic	68.71 ± 10.94	84.46 ± 11.88	< 0.001[b]
Pulse pressure	54.79 ± 10.08	71.09 ± 18.73	< 0.001[b]
Night time			
Systolic	111.97 ± 20.07	146.22 ± 21.17	< 0.001[b]
Diastolic	62.68 ± 7.78	79.28 ± 12.17	< 0.001[b]
Pulse pressure	49.29 ± 18.11	66.94 ± 18.96	< 0.001[b]
Dipping, %			
Dippers	7.43 ± 6.99	5.84 ± 6.68	0.272[b]
Non Dippers	9 (26.5)	15 (23.1)	
Extreme Dippers	21(61.8)	45 (69.2)	0.710[c]
	4 (11.8)	5 (7.7)	

Abbreviations: SHT, sustained hypertension; WCHT, white coat hypertension.
[a]Values are expressed s mean ± SD or No. (%).
[b]T-test.
[c]Likelihood ratio.

Table 4. Clinical Characteristics of Patients with Left Ventricular Hypertrophy[a]

	WCHT (n = 18)	SHT (n = 22)	P Value
Age, y	63.83 ± 9.14	63.82 ± 11.48	0.996[b]
Gender			0.019[c]
Male	4 (22.2)	13 (59)	
Female	14 (77.8)	9 (41)	
BMI, kg/m²	28.98 ± 4.66	25.18 ± 3.96	0.008[b]
Smoker			0.265[d]
Yes	3(16.7)	7 (31.8)	
No	15 (83.3)	15 (68.2)	
Duration of HPT, y	15 (6.00 - 21.25)	12 (9.00 - 20.00)	0.697[c]
Diabetes Mellitus	14 (77.7)	15 (68.1)	0.496[d]
Dyslipidemia	16 (18.8)	20 (90.9))	0.833[d]
IHD	2 (11.1)	9 (40.9)	0.030[d]
CVA	2 (11.1)	6 (27.3)	0.192
CKD-EPI GFR, mL/min/1.73 m²	38.54 ± 12.72	29.56 ± 5.64	0.039[c]

Abbreviations: BMI, body mass index; CVA, cerebrovascular accident; CKP EPI GFR, chronic kidney disease epidemiology collaboration glomerular filtration rate; IHD, ischemic heart disease.
[a]Values are expressed s mean ± SD/median (IQR) or No. (%).
[b]T-test.
[c]Mann-Whitney U Test.
[d]Likelihood ratio.

perhaps due to their advancement of CKD (31). This study also found that two-thirds of the SHT group were non dippers with a more severe degree of CKD and in keeping with others (8). Multiple factors may contribute to the resistant HPT and loss of dipping in CKD. The renin angiotensine aldosterone system (RAAS) activation, sodium hypersensitivity and baroreflex impairment lead to sympathetic activation and autonomic neuropathy resulting in an increase in extracellular volume, which causes disruption of normal circadian pattern of BP and resistant HPT (32). Furthermore, the endothelial dysfunction could also contribute to the loss of nocturnal dip in BP (10). Hence, the majority of the patients of this study were either on ACE-inhibitor and/or ARB groups as their anti-hypertensive agents.

The prevalence of LVH among patients with CKD has been reported as approximately 40%, which is similar to the current study (33). Interestingly, more patients with LVH were found in the WCHT group as opposed to the SHT group, and were predominantly obese females. It could be suggested that LVH is related to obesity as the odds of developing LVH was reported to be 4.62 times higher in overweight patients compared with those of normal weight and this effect was doubled for obese compared to overweight subjects (34, 35). De Simone et al. demonstrated that left ventricular mass increased independent of BP in obese normotensive females (36).

Carotid intima media thickness is a well-established index of systemic atherosclerosis that correlates with the incidence and prevalence of coronary heart disease in the CKD population (37, 38). Brzosko et al. found that dialysis patients with thickened CIMT had a significantly higher incidence of IHD (39). These findings were similar to the current study, except that in the present study the cohort of patients with CKD were not on dialysis. However, atherosclerosis started as early as CKD stage II (40). The patients with thickened CIMT in the current study also had LVH, which has been well described in both the general population and dialysis population. The SHT group also had a significantly thicker median CIMT compared to the WCHT group, consistent with previous literatures (41-43). The patients with thickened CIMT were also dyslipidaemic (92%) and two-thirds of them were diabetic There was a signifi-

Table 5. Blood Pressure and Pulse Pressure in Both Thickened and Non-Thickened Carotid Intima Media Thickness Groups

Blood Pressure, mmHg	Thick (n = 26)	Non Thick (n = 73)	P Value
Clinic			
Systolic	168.27 ± 16.12	159.22 ± 16.64	0.18 e
Diastolic	82.81 ± 9.58	80.15 ± 8.86	0.202 e
Pulse pressure	85.46 ± 18.42	79.10 ± 17.00	0.110 e
ABPM			
Systolic	153.88 ± 22.35	137.88 ± 20.62	0.001 e
Diastolic	82.58 ± 11.86	74.82 ± 13.47	0.011 e
Pulse pressure	71.31 ± 18.81	63.05 ± 17.71	0.048 e
Daytime			
Systolic	157.23 ± 21.46	140.49 ± 20.54	0.001 e
Diastolic	84.27 ± 12.27	77.19 ± 13.84	0.023 e
Pulse pressure	72.96 ± 17.91	63.30 ± 17.17	0.017 e
Night time			
Systolic	146.35 ± 25.63	130.32 ± 25.64	0.007 e
Diastolic	78.69 ± 12.96	71.75 ± 131.81	0.023 e
Pulse pressure	67.65 ± 19.27	58.47 ± 20.39	0.048 e

cant correlation between thickening of the CIMT and ageing, consistent with previous reports (40). Both univariate and multivariate analysis demonstrated that age and pre-existing IHD were 2 independent predictors of thickened CIMT. The age association and atherosclerosis occurred probably due to prolonged exposure to risk factors, such as hypertension, oxidative stress, dyslipidaemia and hyperglycemia, amongst others. Age-related physiological changes, such as increased adiposity and change in sex hormones, affect lipids profile and could also play a role in atherosclerosis formation.

4.1. Conclusions

In conclusion, ABPM should be considered routinely in patients with HPT. Furthermore, WCHT should not be perceived as "benign" however, attention should be addressed to patients with SHT as they have worst CV outcome.

The main limitation of the current study was that LVH assessment was done by ECG rather than echocardiography. Recruiting patients with underlying IHD and CVA may confound the findings in the thickened CIMT group, where the association might be due to complications rather than prediction of subclinical atherosclerosis among patients with CKD.

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