EFFECTS OF VOLUME OVERLOAD ON PROGRESSION OF CHRONIC KIDNEY DISEASE

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OBJECTIVES

Hypertension was an independent risk factor for renal disease progression. However, no study has evaluated the association of volume dependent hypertension versus non-volume dependent hypertension with renal outcomes. We aim to evaluate the impact of baseline systolic blood pressure (SBP) and volume status, according to an overhydration (OH) index determined by Body Composition Monitor (BCM, Fresenius Medical Care), on progression of CKD. Volume overload was defined as relative OH (OH normalized to ECW) ≥7%, corresponding to the value of the 90th percentile for the reference cohort.

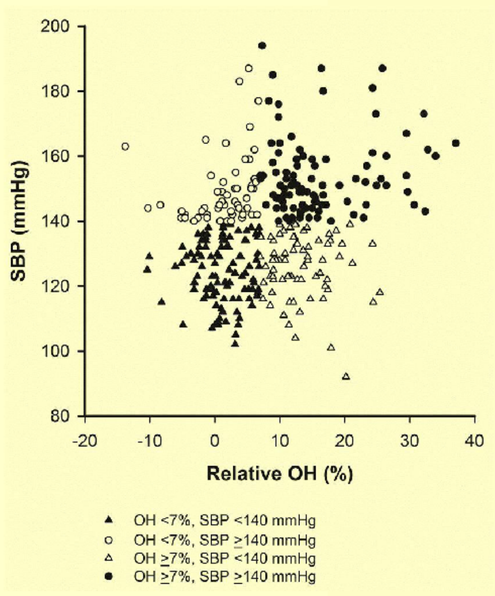
METHODS

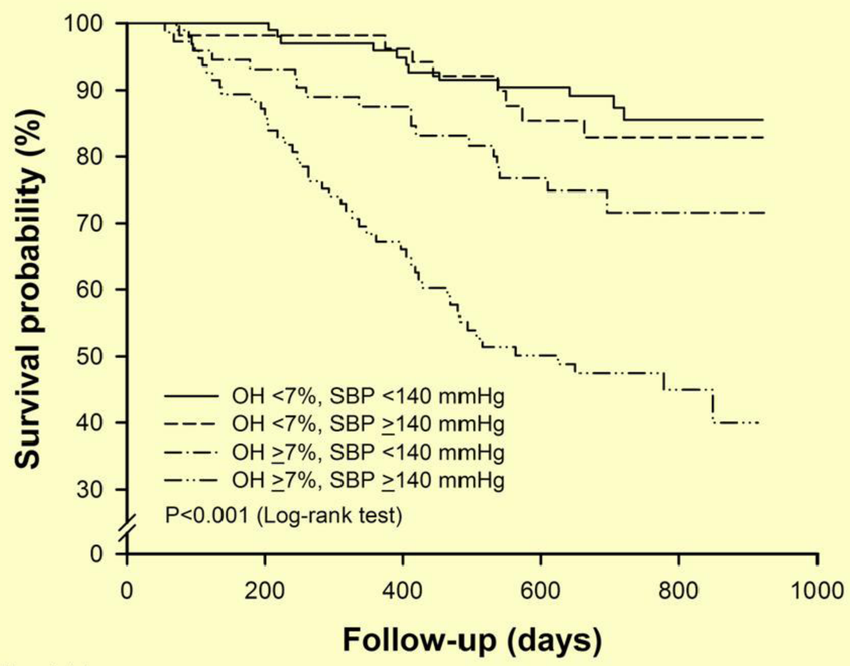
326 clinically stable stage 3–5 CKD patients were recruited from the outpatient clinics between September 1, 2011 and December 31, 2012. All patients received the integrated multidisciplinary CKD care program in Taiwan, focusing on dietary salt and protein restriction, nephrotoxin avoidance, and strict blood pressure and glycemic control. All enrolled subjects were followed up every 3 months until February 28, 2014. Participants were classified according to baseline SBP (categories: <140 or ≥140 mmHg) and OH (categories: <7 or ≥7%). Four different groups can be identified: patients who are normohydrated and normotensive (32%, Group A), who are hypertensive despite being normohydrated (17%, Group B, non-volume dependent hypertension), who are normotensive despite being volume overloaded (22%, Group C), and patients who are both volume overloaded and hypertensive (29%, Group D, volume dependent hypertension). The primary composite outcome was the first occurrence of a decline of ≥50% in the eGFR or ESRD needing chronic dialysis. Changes in the eGFR were confirmed at least 4 weeks after treatment of potentially reversible factors.

RESULTS

After a median follow up of 660 days, there were 12 primary end-point events in the Group A (11.7%), 8 in the Group B (14.5%), 18 in the Group C (24.7%), and 48 in the Group D (50.5%). Patients with volume dependent hypertension (Group D) were found to have significantly more traditional and non-traditional risk factors for CKD progression and cardiovascular disease than those of the other 3 groups. Kaplan-Meier analyses revealed a significant association between volume dependent hypertension and the primary composite outcome (log-rank *P* <0.001). By multivariate regression analysis, the risk of primary composite outcome among patients of the Group D was triple the risk among those of the Group A (adjusted hazard ratio [HR], 3.1; 95% confidence interval [CI], 1.6–6.2; *P* = 0.001). In contrast, the HR was not statistically significant for patients with non-volume dependent hypertension (Group C) compared to those of the Group A (adjusted HR, 1.0; 95% CI, 0.4–2.4; *P* = 0.955).

Characteristics	Group A (n = 103)	Group B (n = 55)	Group C (n = 73)	Group D (n = 95)	*P* Value
SBP (mmHg)	124 ± 9	149 ± 11	126 ± 10	154 ± 12	<0.001
Relative OH (%)	1.1 ± 3.7	1.4 ± 4.4	13.3 ± 4.3	16.1 ± 7.2	<0.001
Age (years)	62.5 ± 14.8	69.5 ± 11.7	67.7 ± 12.7	65.5 ± 12.5	0.008
Male sex, n (%)	74 (72)	34 (63)	54 (74)	63 (66)	0.511
DM, n (%)	26 (25)	18 (33)	49 (67)	55 (58)	<0.001
CVD, n (%)	13 (13)	8 (15)	26 (36)	28 (29)	0.001
Diuretics, n (%)	26 (25)	16 (30)	28 (38)	40 (42)	0.054
RAS blockers, n (%)	62 (60)	32 (59)	43 (59)	60 (63)	0.935
Statins, n (%)	25 (24)	11 (20)	23 (32)	26 (27)	0.506
baPWV (m/s)	14.6 ± 2.5	16.7 ± 3.8	16.0 ± 2.6	17.0 ± 2.9	<0.001
BMI (kg/m^2)	24.9 ± 4.9	26.6 ± 4.3	23.4 ± 7.5	25.3 ± 6.0	0.021
NT-proBNP (ng/L)	84 (38–219)	131 (68–492)	344 (110–988)	610 (275–1561)	<0.001
eGFR (ml/min/1.73 m^2)	32.4 ± 14.9	31.2 ± 14.2	28.3 ± 14.8	24.5 ± 14.0	<0.001
UPCR (g/g)	0.4 (0.2–0.9)	0.8 (0.3–1.6)	1.0 (0.4–2.5)	2.6 (1.0–4.9)	<0.001
Albumin (g/dL)	3.8 ± 0.3	3.7 ± 0.4	3.5 ± 0.4	3.4 ± 0.4	<0.001
IL-6 (pg/mL)	2.7 (1.5–4.2)	3.1 (1.8–5.1)	4.4 (3.1–9.1)	4.2 (2.6–7.2)	<0.001





No. at risk

Group A	OH <7%, SBP <140 mmHg: 103	103	88	73	36
Group B	OH <7%, SBP ≥140 mmHg: 55	51	48	38	17
Group C	OH ≥7%, SBP <140 mmHg: 73	68	60	41	12
Group D	OH ≥7%, SBP ≥140 mmHg: 95	79	58	39	15

CONCLUSION

Hypertension associated with volume overload is common among moderate to advanced non-dialysis CKD patients and exhibits a strong relationship with risk factors for CKD progression and cardiovascular disease. Volume dependent hypertension is associated with worse renal outcomes than non-volume dependent hypertension in hypertensive CKD patients, suggesting that volume overload may serve as an important mechanism contributing to the adverse outcomes. Further research is warranted to clarify whether the correction of volume overload would improve renal outcomes of CKD patients with hypertension.

	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Group A	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Group B	1.3 (0.5–3.1)	0.590	1.2 (0.5–3.1)	0.630	1.2 (0.5–2.9)	0.761	1.3 (0.5–3.1)	0.630
Group C	2.2 (1.1–4.7)	0.032	2.3 (1.1–4.9)	0.026	1.9 (0.9–4.2)	0.100	1.0 (0.4–2.4)	0.955
Group D	5.9 (3.1–11.1)	<0.001	5.9 (3.1–11.3)	<0.001	5.3 (2.8–10.2)	<0.001	3.1 (1.6–6.2)	0.001

Model 1 is adjusted for age and sex.
Model 2 is adjusted for Model 1 variables as well as CVD, DM, and use of angiotensin converting enzyme inhibitor/angiotensin II receptor blockers and statin.
Model 3 is adjusted for Model 2 variables as well as eGFR, UPCR cut at 0.5 g/g, LDL, IL-6, and BMI.

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