The World Journal of
MEN's HEALTH

Association between Aortic Calcification Burden and the Severity of Erectile Dysfunction in Men Undergoing Dialysis: A Cross-Sectional Study

Naoki Fujita[1] , Shingo Hatakeyama[2] , Masaki Momota[1], Yuki Tobisawa[1] , Tohru Yoneyama[3] ,
Teppei Okamoto[1] , Hayato Yamamoto[1] , Takahiro Yoneyama[3], Yasuhiro Hashimoto[1] ,
Kazuaki Yoshikawa[4], Chikara Ohyama[1,2,3]

Departments of [1]Urology, [2]Advanced Blood Purification Therapy, and [3]Advanced Transplant and Regenerative Medicine, Hirosaki University Graduate School of Medicine, Hirosaki, [4]Department of Urology, Mutsu General Hospital, Mutsu, Japan

Purpose: Accelerated atherosclerosis is a major complication in patients with end-stage renal disease and it plays an important role in the pathogenesis of erectile dysfunction (ED). However, the association between aortic calcification burden and the severity of ED remains unclear. The aim of the present study was to investigate this association in men undergoing dialysis.

Materials and Methods: This cross-sectional study included 71 men undergoing peritoneal dialysis and/or hemodialysis between July 2016 and May 2018 at Mutsu General Hospital. ED was assessed with the Sexual Health Inventory for Men (SHIM). Patients were divided into the mild/moderate (SHIM score ≥8) and severe ED groups (SHIM score ≤7). Aortic calcification index (ACI) was examined as a clinical indicator of abdominal aortic calcification. Multivariable logistic regression analysis was performed to identify the significant factors associated with severe ED.

Results: The median age of the study participants was 64 years; all had ED, with 64.8% having severe ED. In the multivariable analyses, a slight association was observed between ankle-brachial index and severe ED (odds ratio [OR], 0.058; p=0.072), whereas ACI was significantly associated with severe ED (OR, 1.022; p=0.022).

Conclusions: Aortic calcification burden was independently associated with severe ED.

Keywords: Atherosclerosis; Dialysis; End-stage renal disease; Erectile dysfunction; Vascular calcification

INTRODUCTION

Erectile dysfunction (ED) is a frequent complication in men with end-stage renal disease (ESRD), and previous studies have reported that its prevalence reaches 80% [1,2].

ED has a negative impact on the quality of life (QOL) of men with ESRD as well as in healthy men [3]. More severe ED is also associated with a lower QOL in men undergoing hemodialysis (HD) [4]. However, only 1% of men consult with their primary physician about erectile problems [5], despite ED being a potentially

treatable complication even in men undergoing dialysis [6]. Therefore, physicians are encouraged to proactively ask about patients' sexual problems to improve their QOL. Because there are currently no robust indicators for severe ED, identifying these is crucial to provide appropriate treatment and eventually improve QOL in such men. Moreover, ED is a well-known predictor of future cardiovascular events [7] and symptoms of ED precede clinically overt cardiovascular disease (CVD) by 2 to 3 years [8,9]. Thus, investigating the pathogenesis of ED is also important.

Aortic calcification is one of the markers for atherosclerosis and can be simply and quantitatively measured by computed tomography (CT) images [10,11]. Because accelerated atherosclerosis is a major complication in patients with ESRD [12], it plays an important role in the pathogenesis of ED [13,14]. Therefore, we hypothesized that aortic calcification burden might be a useful indicator for severe ED in men undergoing dialysis.

The present study aimed to investigate the association between aortic calcification burden and the severity of ED in men undergoing peritoneal dialysis (PD) and/or HD.

MATERIALS AND METHODS

1. Ethics statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the ethics review board of Mutsu General Hospital (authorization number: H28-2). All participants provided written informed consent.

2. Patient selection

This cross-sectional study assessed 186 men undergoing PD and/or HD between July 2016 and May 2018 at Mutsu General Hospital. Among the 186 men identified, 115 were excluded based on the following exclusion criteria: (1) aged 75 years or older; (2) cognitive deficiency, inability to communicate, and/or blindness; (3) insufficient baseline information; and (4) refusal to participate in this study. Finally, 71 men undergoing PD and/or HD were included (Fig. 1).

3. Evaluation of variables

The following variables were analyzed: age, body mass index (BMI), hypertension (HTN), dyslipidemia, diabetes mellitus (DM), CVD, depression, laboratory values, cardio-ankle vascular index (CAVI), ankle-brachial index (ABI), education level, marital status, smoking status, current habitual drinking, and medications (*i.e.*, β-blockers, calcium [Ca]-blockers, thiazide diuretics, spironolactone, methyldopa, clonidine, and antidepressants). BMI was calculated as dry weight in kilograms divided by the square of height in meters. HTN was defined as taking antihypertensive medications and/or having a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg. Dyslipidemia was defined as taking lipid lowering medications and/or having a low-density lipoprotein (LDL) cholesterol of ≥140 mg/dL, a triglyceride concentration of ≥150 mg/dL, and/or high-density lipoprotein cholesterol of <40 mg/dL. DM was defined as taking glycemic control medications and/or having a history of type 2 DM. The following variables were measured as part of routine clinical examination: CAVI, ABI, and laboratory blood test, including serum hemoglobin, creatinine, albumin,
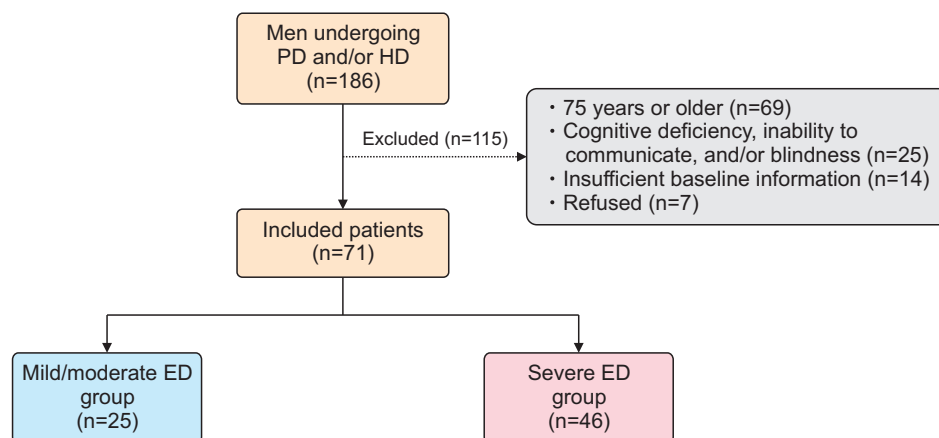

Fig. 1. Patient selection. The number of included and excluded patients is shown. PD: peritoneal dialysis, HD: hemodialysis, ED: erectile dysfunction.

Ca, inorganic phosphorus, intact parathyroid hormone (iPTH), total cholesterol, LDL cholesterol, and triglycerides. Serum total testosterone was measured for research purpose. Blood sampling was performed in the morning. Blood was drawn after 12 hours of fasting and serum was separated by centrifugation with 3,000 rpm for 5 minutes. Laboratory values except for total testosterone were measured using an enzymatic assay with an automatic analyzer (BioMajesty 6070 G; Nihon denshi, Tokyo, Japan). Serum total testosterone was measured using chemiluminescent immunoassay. Adjusted Ca levels were calculated using Payne's formula [15]. Self-reported depression was assessed using the vitality questionnaire of the Short Form 36 Health Survey. Patients who had responses to the questionnaire such as "all of the time" or "most of the time" and who were taking antidepressants were considered as having depression [16]. CAVI and ABI were measured using the VaSera VS-1500A device (Fukuda Denshi Co., Tokyo, Japan). The averages of right and left CAVI and ABI values were used for analyses.

4. Evaluation of erectile dysfunction

ED was assessed using the Sexual Health Inventory for Men (SHIM): a validated abbreviated version of the International Index of Erectile Function [17]. The SHIM scores are interpreted as follows: no ED ($\geq$22), mild ED (17–21), moderate ED (8–16), and severe ED ($\leq$7). Accordingly, men were divided into the mild/moderate (SHIM score $\geq$8) and severe ED groups (SHIM score $\leq$7) (Fig. 1).
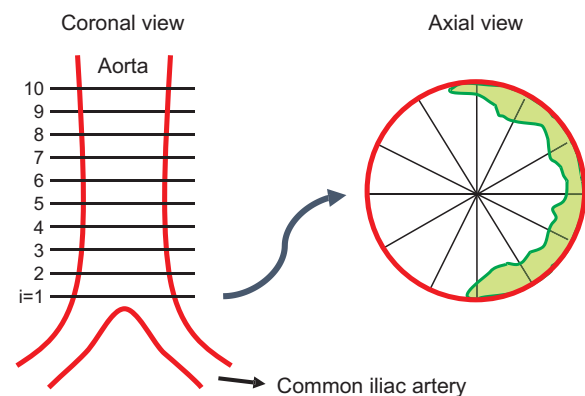
5. Measurement of aortic calcification index

Aortic calcification index (ACI) was examined as a clinical indicator of abdominal aortic calcification. ACI was quantitatively measured using abdominal CT images (Revolution EVO; GE Healthcare Japan, Tokyo, Japan) by evaluating 10 slices of the aorta scanned at 10-mm intervals above the bifurcation of the common iliac arteries as previously described [18]. Each slice was divided into 12 sectors, and the numbers of sectors with calcification were counted. For example, if 8 out of 12 sectors were calcified in slice 1, this was scored as 8/12=66.7% (Fig. 2). The ACI (%) was calculated by averaging the percentage of calcification-positive sectors in slices 1–10. ACI was measured by a single investigator in a blinded manner. All abdominal CT examinations were performed as an annual routine screening

for renal cell carcinoma within 6 months before or after evaluating the SHIM score.

6. Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), and R 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). Quantitative variables were expressed as median with interquartile range. Categorical variables were compared using the Fisher exact test or chi-squared test. Quantitative variables were compared using the Mann–Whitney U-test. Correlation was analyzed using Spearman's rank correlation coefficient. The optimal cutoff value of ACI for severe ED was calculated with the receiver operating characteristic curve. Uni- and multivariable logistic regression analyses were performed to identify the significant factors associated with severe ED. Since ABI and ACI are similar indices for evaluating atherosclerosis, we included these in multivariable regression models separately. Thus, two types of multivariable regression analyses were performed. Statistical significance was set at $p < 0.05$.

$$ACI= \sum_{i=1}^{10} CP(i)/12/10 \times 100 \ (\%)$$

Fig. 2. Measurement of aortic calcification index (ACI). ACI was quantitatively measured using abdominal computed tomography images by evaluating 10 slices of the aorta scanned at 10-mm intervals above the bifurcation of the common iliac arteries. Each slice was divided into 12 sectors, and the numbers of sectors with calcification were counted. The ACI (%) was calculated by averaging the percentage of calcification-positive sectors in slices 1–10. The green area in the axial view indicates calcification. CP: calcification profile.

RESULTS

1. Patient background

The median age and dialysis duration of the study participants were 64 years and 44 months, respectively. Among the 71 patients, 8 (11.3%), 60 (84.5%), and 3 (4.2%) were undergoing PD, HD, and a combination of once-weekly HD with PD, respectively (Table 1).

Median SHIM score was 4.0. The prevalence of any level of ED was 100%. Of those, 25 (35.2%) and 46 (64.8%) patients reported mild/moderate (mild/moderate ED group) and severe ED (severe ED group), respectively

Table 1. Patient background

Variable	All (n=71)	Mild/moderate ED group (n=25)	Severe ED group (n=46)	p-value
Age, y	64 (55–66)	58 (46–65)	65 (58–67)	0.009
Body mass index, kg/m^2	23 (20–28)	25 (20–29)	23 (20–25)	0.284
Hypertension	65 (91.5)	24 (96.0)	41 (89.1)	0.414
Dyslipidemia	46 (64.8)	15 (60.0)	31 (67.4)	0.533
Diabetes mellitus	42 (59.2)	16 (64.0)	26 (56.5)	0.540
Cardiovascular disease	24 (33.8)	7 (28.0)	17 (37.0)	0.446
Depression	4 (5.6)	1 (4.0)	3 (6.5)	>0.999
Type of dialysis				0.746
PD	8 (11.3)	4 (16.0)	4 (8.7)	
HD	60 (84.5)	20 (80.0)	40 (87.0)	
Combination of PD and HD	3 (4.2)	1 (4.0)	2 (4.3)	
Duration of dialysis, mo	44 (11–86)	26 (4–74)	53 (14–102)	0.079
Medications				
β-blockers	30 (42.3)	11 (44.0)	19 (41.3)	0.826
Calcium-blockers	28 (39.4)	12 (48.0)	16 (34.8)	0.276
Thiazide diuretics	1 (1.4)	0 (0.0)	1 (2.2)	>0.999
Laboratory blood test				
Hemoglobin, g/dL	12 (11–13)	12 (11–13)	12 (10–12)	0.427
Creatinine, mg/dL	11 (9.2–13.0)	11 (9.5–13.0)	11 (8.8–13.0)	0.923
Phosphorus, mg/dL	4.6 (3.9–5.8)	5.1 (4.3–6.9)	4.2 (3.7–5.6)	0.056
Adjusted calcium, mg/dL	8.8 (8.3–9.2)	8.7 (8.2–9.1)	8.8 (8.4–9.4)	0.235
iPTH, pg/mL	125 (78–214)	147 (90–244)	106 (63–189)	0.043
Total cholesterol, mg/dL	148 (123–196)	152 (133–189)	148 (111–207)	0.805
LDL-cholesterol, mg/dL	68 (50–95)	65 (50–92)	68 (55–96)	0.466
Triglyceride, mg/dL	137 (103–173)	171 (110–174)	118 (92–141)	0.211
Testosterone, ng/dL	420 (221–561)	281 (229–523)	467 (220–581)	0.190
Smoking status				>0.999
Never	15 (21.1)	5 (20.0)	10 (21.7)	
Former	44 (62.0)	16 (64.0)	28 (60.9)	
Current	12 (16.9)	4 (16.0)	8 (17.4)	
Current habitual drinking	18 (25.4)	5 (20.0)	13 (28.3)	0.572
Post-high school education	47 (66.2)	17 (68.0)	30 (65.2)	0.813
Having current sexual partner	40 (56.3)	14 (56.0)	26 (56.5)	0.966
Cardio-ankle vascular index	9.6 (8.3–11.0)	8.7 (8.1–11.0)	9.8 (8.9–11.0)	0.088
Ankle-brachial index	1.1 (0.9–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.1)	0.087
Aortic calcification index, %	61 (28–85)	28 (10–75)	70 (37–90)	<0.001
SHIM score	4 (1–11)	14 (11–19)	2 (1–4)	<0.001

Values are presented as median (interquartile range) or number (%).
ED: erectile dysfunction, PD: peritoneal dialysis, HD: hemodialysis, iPTH: intact parathyroid hormone, LDL: low-density lipoprotein, SHIM: sexual health inventory for men.

(Fig. 1). No patient received any type of treatment for ED at the time of investigation.

No significant differences in patient background were observed between both groups except for age, iPTH, and ACI (Table 1). No patients were taking spironolactone, methyldopa, or clonidine in both groups.

2. Correlation between aortic calcification index and SHIM score

Spearman's rank correlation test demonstrated a significant negative correlation between SHIM scores and ACI ($\rho=-0.304$, p=0.010; Fig. 3A) and between SHIM scores and CAVI ($\rho=-0.241$, p=0.043; Fig. 3B). On the other hand, no significant correlation was observed between SHIM scores and ABI ($\rho=0.191$, p=0.113; Fig. 3C).

3. Association between aortic calcification index and the severity of erectile dysfunction

The median ACI in all patients was 61% (Table 1, Fig. 4A). The severe ED group had significantly higher ACI than the mild/moderate ED group (Table 1, Fig. 4A; 70% *vs.* 28%, respectively, p<0.001). When we focused on only patients undergoing HD (n=57), similar result was observed (62% *vs.* 52%, respectively, p=0.022; Supplement Fig. 1).

The optimal cutoff value of ACI for severe ED was 82% (Supplement Fig. 2); patients with ACI ≥82% had significantly higher prevalence of severe ED than those with ACI <82% (46% *vs.* 8.0%, respectively, p<0.001; Fig. 4B).
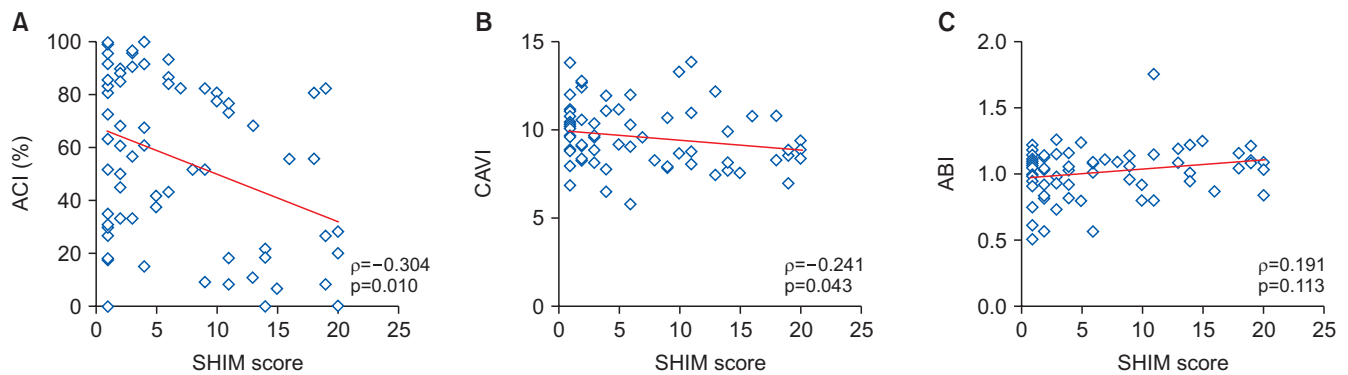

Fig. 3. Correlations between the Sexual Health Inventory for Men (SHIM) scores and aortic calcification index (ACI) (A), cardio-ankle vascular index (CAVI) (B), and ankle-brachial index (ABI) (C) were analyzed using Spearman's rank correlation coefficient.
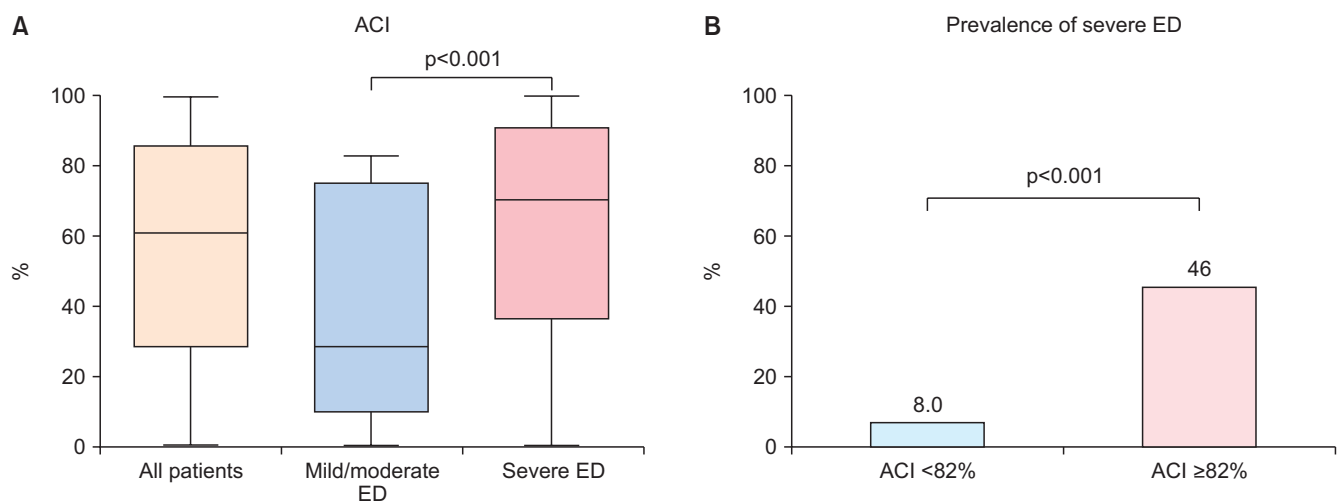

Fig. 4. Association between aortic calcification index (ACI) and the Sexual Health Inventory for Men (SHIM) score. ACI was compared between the mild/moderate and severe erectile dysfunction (ED) groups using the Mann–Whitney U-test (A). The prevalence of severe ED was compared between patients with ACI <82% and ACI ≥82% using the Fisher exact test (B).

4. Uni- and multivariable analyses for severe erectile dysfunction

In the univariable analyses, age, ABI, and ACI were significantly associated with severe ED (Table 2). In the multivariable analysis (Model 1; including ABI), a slight association was observed between ABI and severe ED (odds ratio [OR], 0.058; 95% confidence interval [CI], 0.003–1.295; p=0.072; Table 3) and only age was significantly and independently associated with severe ED (OR, 1.072; 95% CI, 1.013–1.135; p=0.016; Table 3). In the multivariable analysis (Model 2; including ACI), only ACI was significantly and independently associated with severe ED (OR, 1.022; 95% CI, 1.003–1.041; p=0.022; Table 3). When we focused on only patients undergoing HD, only ACI was associated with severe ED (OR, 1.019; 95% CI, 1.000–1.039; p=0.050; Supplement Table 1).

DISCUSSION

Although accelerated atherosclerosis is a major complication and plays an important role in the pathogenesis of ED in men undergoing dialysis [12-14,19], to the best of our knowledge, no study has investigated the impact of aortic calcification burden on the severity of ED, and this is the first study to investigate this association. We found that ACI was significantly associated with severe ED. Patients undergoing dialysis might be reticent to discuss their sexual problems with a physician and some patients perceive ED as part of the normal aging process rather than complication [14,20]. Thus, these results might be helpful for identifying and eventually treating men suffering from severe ED.

In the present study, we evaluated aortic calcification burden as a surrogate marker of atherosclerosis. Ideally, the condition of the internal pudendal artery should be evaluated because this artery is responsible for the arteriogenic ED [21]. However, it is difficult to evaluate atherosclerosis of the internal pudendal artery in clinical practice because of its size [22]. Another alternative site is the coronary artery. Several studies reported a negative correlation between coronary artery calcification burden and the International Index of Erectile Function 5 (IIEF-5) score without adjustment for other confounding variables in men undergoing HD [23,24].

Table 3. Multivariable analyses for severe erectile dysfunction

Model and variable	Factor	p-value	Odds ratio	95% confidence interval
Model 1				
Age	Continuous	0.016	1.072	1.013–1.135
Ankle-brachial index	Continuous	0.072	0.058	0.003–1.295
Model 2				
Age	Continuous	0.141	1.046	0.985–1.111
Aortic calcification index	Continuous	0.022	1.022	1.003–1.041

Table 2. Univariable analyses for severe erectile dysfunction

Variable	Factor	p-value	Odds ratio	95% confidence interval
Age	Continuous	0.013	1.072	1.015–1.132
Body mass index	Continuous	0.491	0.971	0.893–1.056
Hypertension	Positive	0.340	0.342	0.038–3.100
Dyslipidemia	Positive	0.534	1.378	0.502–3.783
Diabetes mellitus	Positive	0.541	0.731	0.268–1.994
Type of dialysis	PD	0.359	0.500	0.114–2.200
Duration of dialysis	Continuous	0.051	1.010	1.000–1.020
β-blockers	Taking	0.826	0.896	0.335–2.396
Calcium-blockers	Taking	0.278	0.578	0.214–1.558
Serum iPTH level	Continuous	0.161	0.997	0.992–1.001
Serum testosterone level	Continuous	0.176	1.002	0.999–1.005
Smoking status	Current	0.786	1.000	0.999–1.001
Depression	Positive	0.663	1.674	0.165–17.00
Cardio-ankle vascular index	Continuous	0.257	1.183	0.885–1.581
Ankle-brachial index	Continuous	0.049	0.045	0.002–0.987
Aortic calcification index	Continuous	0.003	1.027	1.009–1.045

PD: peritoneal dialysis, iPTH: intact parathyroid hormone.

However, it is also difficult to measure its calcification burden due to the facility restriction [22]. On the other hand, aortic calcification burden can be easily and quantitatively measured by general CT images [18]. It takes only 1 to 2 minutes to analyze a single subject. Because atherosclerosis theoretically affects all arteries at the same time to the same extent [25], it is reasonable to measure aortic calcification burden as a surrogate marker of atherosclerosis of penile arteries. Other non-invasive surrogate markers of arteriosclerosis include the CAVI, ABI, and intima-media thickness (IMT) of carotid arteries. Stolic and Bukumiric [26] reported a negative correlation between the IMT of carotid arteries and IIEF-5 score in men undergoing HD. However, because they could not adjust for other confounding variables, the conclusion was not definitive. Regarding CAVI and ABI, these indices were not selected as independent factors associated with severe ED in the present study (Table 2, 3). Moreover, it was reported that accurate ABI values might not be obtained in cases with high arterial calcification burden [27]. Therefore, aortic calcification burden might be a better surrogate marker of atherosclerosis of the penile arteries, considering its correlation with the severity of ED, ease of measurement, and non-invasiveness. However, to our knowledge, no study has demonstrated the correlation between aortic calcification burden and penile artery calcification burden. Further studies are needed to address this issue.

Although it is well-known that the pathogenesis of ED in men undergoing dialysis is multifactorial [2,5,28-30], it remains unclear which factor has the greatest contribution to the severity of ED. Collaborative Depression and Sexual Dysfunction in Hemodialysis Working Group [1] conducted a multinational cross-sectional study with relatively larger sample size to identify correlates for severe ED in men undergoing HD. Age, HTN, DM, depression, endocrine abnormalities, and unmarried status were found to be significantly associated with severe ED in a multivariable model. However, they did not evaluate atherosclerosis, which may play a crucial role in the pathogenesis of ED in men undergoing dialysis [13,14]. Although many possible factors (*i.e.*, age, HTN, dyslipidemia, DM, anemia, mineral metabolism disorders, depression, serum testosterone level, smoking status, habitual drinking, marital status, and medications) were analyzed in the present study, only age and aortic calcification burden

were significantly associated with severe ED. Those results suggest that arteriogenic factors might contribute more to severe ED than other factors in men undergoing dialysis.

Vascular calcification has been historically classified as (1) tunica intima calcification associated with atherosclerosis and (2) tunica media calcification mediated by a phenotypic change of vascular smooth muscle cells into bone forming cells and associated with disturbances in the metabolism of Ca, phosphorus, and vitamin D [31]. Tunica media calcification is particularly common in patients with ESRD [32,33]. Although we evaluated aortic calcification burden using CT images in the present study, CT is not sensitive enough to identify the exact location of calcification. Thus, we could not evaluate the association between the location of calcification and the severity of ED. Further study is needed to address this issue.

The present study has several limitations. First, the cross-sectional study design does not allow the determination of cause-and-effect associations. Second, a relatively small number of men were enrolled, and the number of men undergoing PD was also small. Third, we did not evaluate the imbalance in the hypothalamic–pituitary–gonadal axis, hyperprolactinemia, and zinc deficiency, which might increase the prevalence of ED in men undergoing dialysis [13,34]. Fourth, only a single examiner was tasked to measure all ACIs and the inter-observer agreement was not evaluated. Fifth, there were time lags between CT scan and ED evaluation using the SHIM. Therefore, the actual aortic calcification burden might be changed at the time of investigation. Finally, we could not compare the aortic calcification burden between patients with and without ED because all patients had ED. Despite these limitations, the present study demonstrated a negative impact of aortic calcification burden on the severity of ED in men undergoing dialysis.

CONCLUSIONS

Aortic calcification burden was independently associated with severe ED. This result might be helpful for clinicians to identify and eventually treat men suffering from severe ED.

The World Journal of
MEN's HEALTH

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: NF. Data curation: NF, MM. Validation: SH, YT, TO, HY, Takahiro Yoneyama, YH, KY, CO. Formal analysis: NF. Funding acquisition: SH, Tohru Yoneyama, CO. Investigation: NF. Methodology: NF. Project administration: NF. Supervision: SH, CO. Writing – original draft: NF. Writing – review & editing: all authors.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.210230.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time due to legal and ethical reasons.

REFERENCES

1. Collaborative Depression and Sexual Dysfunction in Hemodialysis Working Group; Vecchio M, Palmer S, De Berardis G, Craig J, Johnson D, et al. Prevalence and correlates of erectile dysfunction in men on chronic haemodialysis: a multinational cross-sectional study. Nephrol Dial Transplant 2012;27:2479-88.
2. Rosas SE, Joffe M, Franklin E, Strom BL, Kotzker W, Brensinger C, et al. Prevalence and determinants of erectile dysfunction in hemodialysis patients. Kidney Int 2001;59:2259-66.
3. Lew-Starowicz M, Gellert R. The sexuality and quality of life of hemodialyzed patients--ASED multicenter study. J Sex Med 2009;6:1062-71.
4. Fernandes GV, dos Santos RR, Soares W, de Lima LG, de Macêdo BS, da Fonte JE, et al. The impact of erectile dysfunction on the quality of life of men undergoing hemodialysis and its association with depression. J Sex Med 2010;7:4003-

10.
5. Arslan D, Aslan G, Sifil A, Cavdar C, Celebi I, Gamsari T, et al. Sexual dysfunction in male patients on hemodialysis: assessment with the International Index of Erectile Function (IIEF). Int J Impot Res 2002;14:539-42.
6. Türk S, Karalezli G, Tonbul HZ, Yildiz M, Altintepe L, Yildiz A, et al. Erectile dysfunction and the effects of sildenafil treatment in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2001;16:1818-22.
7. Uddin SMI, Mirbolouk M, Dardari Z, Feldman DI, Cainzos-Achirica M, DeFilippis AP, et al. Erectile dysfunction as an independent predictor of future cardiovascular events: the multi-ethnic study of atherosclerosis. Circulation 2018;138:540-2.
8. Tanaka Y, Bundy JD, Allen NB, Uddin SMI, Feldman DI, Michos ED, et al. Association of erectile dysfunction with incident atrial fibrillation: the multi-ethnic study of atherosclerosis (MESA). Am J Med 2020;133:613-20.e1.
9. Gowani Z, Uddin SMI, Mirbolouk M, Ayyaz D, Billups KL, Miner M, et al. Vascular erectile dysfunction and subclinical cardiovascular disease. Curr Sex Health Rep 2017;9:305-12.
10. Albanese I, Khan K, Barratt B, Al-Kindi H, Schwertani A. Atherosclerotic calcification: Wnt is the hint. J Am Heart Assoc 2018;7:e007356.
11. Kälsch H, Lehmann N, Moebus S, Hoffmann B, Stang A, Jöckel KH, et al. Aortic calcification onset and progression: association with the development of coronary atherosclerosis. J Am Heart Assoc 2017;6:e005093.
12. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974;290:697-701.
13. Kaufman JM, Hatzichristou DG, Mulhall JP, Fitch WP, Goldstein I. Impotence and chronic renal failure: a study of the hemodynamic pathophysiology. J Urol 1994;151:612-8.
14. Bellinghieri G, Savica V, Santoro D. Vascular erectile dysfunction in chronic renal failure. Semin Nephrol 2006;26:42-5.
15. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J 1973;4:643-6.
16. Soma O, Hatakeyama S, Imai A, Matsumoto T, Hamano I, Fujita N, et al. Relationship between frailty and lower urinary tract symptoms among community-dwelling adults. Low Urin Tract Symptoms 2020;12:128-36.
17. Ramanathan R, Mulhall J, Rao S, Leung R, Martinez Salamanca JI, Mandhani A, et al. Predictive correlation between the International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM): implications for calculat-

ing a derived SHIM for clinical use. J Sex Med 2007;4:1336-44.

18. Tsushima M, Terayama Y, Momose A, Funyu T, Ohyama C, Hada R. Carotid intima media thickness and aortic calcification index closely relate to cerebro- and cardiovascular disorders in hemodialysis patients. Int J Urol 2008;15:48-51; discussion 51-2.

19. Lue TF. Erectile dysfunction. N Engl J Med 2000;342:1802-13.

20. Nassir A. Sexual function in male patients undergoing treatment for renal failure: a prospective view. J Sex Med 2009;6:3407-14.

21. Pereira JA, Bilhim T, Rio Tinto H, Fernandes L, Martins Pisco J, Goyri-O'Neill J. Radiologic anatomy of arteriogenic erectile dysfunction: a systematized approach. Acta Med Port 2013;26:219-25.

22. Matsuura T, Abe T, Onoda M, Ikarashi D, Sugimura J, Komaki T, et al. Pelvic artery calcification score is a marker of vascular calcification in male hemodialysis patients. Ther Apher Dial 2018;22:509-13.

23. Roy N, Rosas SE. Erectile dysfunction and coronary artery calcification in incident dialysis patients. J Nephrol 2021;34:1521-9.

24. Inci K, Hazirolan T, Aki FT, Oruc O, Tombul T, Tasar C, et al. Coronary artery calcifications in hemodialysis patients and their correlation with the prevalence of erectile dysfunction. Transplant Proc 2008;40:77-80.

25. Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, et al. Common grounds for erectile dysfunction and coronary artery disease. Curr Opin Urol 2004;14:361-5.

26. Stolic RV, Bukumiric ZM. Intima-media thickness of carotid arteries and erectile dysfunction in hemodialysis patients. Hemodial Int 2010;14:510-4.

27. Ohtake T, Oka M, Ikee R, Mochida Y, Ishioka K, Moriya H, et al. Impact of lower limbs' arterial calcification on the prevalence and severity of PAD in patients on hemodialysis. J Vasc Surg 2011;53:676-83.

28. Bommer J, Ritz E, del Pozo E, Bommer G. Improved sexual function in male haemodialysis patients on bromocriptine. Lancet 1979;2:496-7.

29. Chopp RT, Mendez R. Sexual function and hormonal abnormalities in uremic men on chronic dialysis and after renal transplantation. Fertil Steril 1978;29:661-6.

30. Massry SG, Goldstein DA, Procci WR, Kletzky OA. Impotence in patients with uremia: a possible role for parathyroid hormone. Nephron 1977;19:305-10.

31. Coll B, Betriu A, Martínez-Alonso M, Amoedo ML, Arcidiacono MV, Borras M, et al. Large artery calcification on dialysis patients is located in the intima and related to atherosclerosis. Clin J Am Soc Nephrol 2011;6:303-10.

32. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, et al. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int 2002;61:638-47.

33. Ballanti P, Silvestrini G, Pisanò S, De Paolis P, Di Giulio S, Mantella D, et al. Medial artery calcification of uremic patients: a histological, histochemical and ultrastructural study. Histol Histopathol 2011;26:191-200.

34. Suzuki E, Nishimatsu H, Oba S, Takahashi M, Homma Y. Chronic kidney disease and erectile dysfunction. World J Nephrol 2014;3:220-9.