Published in final edited form as:

J Nephrol. 2021 October ; 34(5): 1521–1529. doi:10.1007/s40620-021-00994-3.

Erectile dysfunction and coronary artery calcification in incident dialysis patients

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Abstract

Purpose—Erectile dysfunction, which has been associated with mortality in the general population, is common in individuals on hemodialysis. Our aim was to determine the relationship between erectile dysfunction, coronary artery calcification and mortality in incident hemodialysis patients.

Materials and methods—A prospective cohort of incident adult dialysis patients with no history of coronary artery disease underwent coronary artery calcification measurement by ECG-triggered multi-slice computed tomography (MSCT) scan at baseline and at least 12 months later. Erectile dysfunction was determined using the 15-item validated International Index of Erectile Function (IIEF-15) questionnaire.

Results—Erectile dysfunction was prevalent in 83% of patients, with 43% classified as severe erectile dysfunction, 22.4% as moderate erectile dysfunction, and 17.2% as mild erectile dysfunction. The median (IQR) coronary artery calcification score was 43.4 (0.25–353.8) for those with erectile dysfunction and 0 (0–0) for those without erectile dysfunction ($p = 0.007$). More than half (55.6%) of the patients with erectile dysfunction experienced progression of coronary artery calcification compared to 14.3% of patients without erectile dysfunction ($p = 0.05$). Mortality was 21% during an average follow-up of 5.2 (1.3) years. Twenty-three percent of patients with erectile dysfunction died compared to 10% of people without erectile dysfunction ($p = 0.4$). Erectile dysfunction was not significantly associated with mortality [HR 1.2 (1.3), $p = 0.87$].

Conclusions—Erectile dysfunction is common in individuals who start dialysis. It is significantly associated with an increased coronary artery calcification score, however, it is not associated with increased mortality in incident dialysis patients with no history of coronary artery disease.

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Author contributions NR and SER: met the ICMJE criteria for authorship. Research idea and study design: SER; data acquisition: SER; data analysis/interpretation: SER, NR; statistical analysis: SER, NR supervision or mentorship: SER. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest All authors declare no potential conflicts of interest.

Informed consent Informed consent has been obtained from the patients.

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Graphical Abstract

Keywords

Erectile dysfunction; Coronary artery calcification; Dialysis

Introduction

Erectile dysfunction, defined as the inability to attain erection sufficient enough to permit sexual intercourse, is prevalent among men on dialysis [1]. In individuals with kidney failure, erectile dysfunction is likely multifactorial and may include an imbalance in the hypothalamic–pituitary–gonadal axis, hyperprolactinemia, diabetic neuropathy and acceleration of atherosclerosis [2]. We previously reported that older age, diabetes and non use of ACE inhibitors have been associated with a higher prevalence of erectile dysfunction [1]. Hypertension, diabetes, atherosclerosis and coronary artery disease, which are common in individuals on hemodialysis, have also been associated with erectile dysfunction [3]. In the general population, 75% of individuals with erectile dysfunction have coronary artery disease [4].

Coronary artery calcification is associated with atherosclerotic plaques and serves as a risk marker for coronary artery disease [5]. It has been found to predict individuals at high-risk for cardiovascular disease and mortality in dialysis patients [6], and its progression has been associated with mortality in subjects with kidney failure [7]. Coronary artery calcification was found in 37.5% of individuals who were being evaluated for suspected arteriogenic erectile dysfunction [8] the severity of which has been associated with higher coronary artery calcification score [9].

Erectile dysfunction predicts mortality in the general population likely through its association with cardiovascular disease risk factors [10]. Several studies have highlighted the importance of cardiovascular screening of individuals with erectile dysfunction to prevent cardiovascular risk and mortality [11].

Our aim was to determine the relationship between erectile dysfunction, coronary artery calcification and mortality in incident dialysis patients with no prior coronary events.

Materials and methods

Study design and research population

The Dialysis Heart and Bone study (DHB) study has previously been described [12]. In summary, 102 incident adult dialysis patients were enrolled, 63 were male and completed the erectile dysfunction questionnaire. Two patients did not have a CT scan and additionally, three patients on peritoneal dialysis were excluded. Therefore this report includes the 58 men on hemodialysis who completed the erectile dysfunction questionnaire and underwent coronary artery calcification measurement. Patients were excluded if they weighed more than 159 kg (for technical reasons), were institutionalized (nursing home or prisoner), unable or unwilling to provide informed consent, had a prior history of coronary artery disease including coronary revascularization procedures, had a life expectancy of less than 2 years as judged by their primary physician, or had received an organ transplant.

A total coronary calcium score was calculated by multiplying the area of the calcification by a coefficient based on the density of the calcification as originally described by Agatston et al. [13]. Coronary artery calcification progression was evaluated as a continuous variable by calculating the difference in Agatston score between the performed CT scans divided by the time elapsed between images. We used the square root transformed difference (SQRT) method, in which coronary artery calcification progression is measured as the difference in the square root—transformed coronary artery calcification score between scans. Coronary artery calcification progression was defined as a difference of $> 2.5 \text{ mm}^3$ between scans [14]. Coronary artery calcification progression was determined in 40 subjects. In addition, we included, as progressors ($n = 3$), individuals that underwent a coronary artery procedure such as bypass grafting or percutaneous coronary intervention prior to their scheduled second scan and therefore were for technical reasons not eligible for a second scan.

Data collection

Subjects were identified by their primary nephrologist or by the investigators at each dialysis facility. All patients provided written informed consent prior to enrollment in the study, and the institutional review board approved the protocol. Detailed information regarding demographics and medical history was obtained at the baseline visit. All medications, including ACE inhibitors and HMG-CoA reductase, were recorded. Body weight and body mass index (BMI) were obtained. Laboratory values including serum creatinine, glucose, albumin, calcium, phosphorus, and intact-PTH obtained as part of each subject's routine clinical care, were extracted from the medical records. Lipid profile (HDL cholesterol, total cholesterol, and triglycerides), inflammatory markers, and markers of bone metabolism were measured for research purposes at initiation of the study.

For each subject, coronary artery calcification was measured by an ECG-triggered multi-slice computed tomography (MSCT) scan at baseline and at least twelve months later.

Erectile dysfunction was determined using a self-administered 15-item validated questionnaire, the International Index of Erectile Function (IIEF-15) which was administered during the baseline visit. IIEF has been used as a valid diagnostic tool for evaluating erectile dysfunction [15, 16] and is widely used in studies in hemodialysis patients [17–19]. The questionnaire has five components: erectile function (Q1, 2, 3, 4, 5, 15), orgasmic function (Q9, 10), sexual desire (Q11, 12), intercourse satisfaction (Q6, 7, 8) and overall satisfaction (Q13, 14). Each question carries a maximum score of 5 and refers to the month prior to completing the questionnaire. The erectile function component was used to measure the severity of erectile dysfunction. Patients with a total score of 25 or less in the erectile function component were considered to have erectile dysfunction. We categorized severity as in the original publication [20] but due to low sample size we combined both ‘mild to moderate’ and ‘moderate’ into a single moderate category, and also included several patients with scores below 6 in the severe erectile dysfunction category. The severity of erectile dysfunction was classified as none (26–30), mild (22–25), moderate (11–21), and severe (1–10). The Beck Depression Inventory was administered during the baseline visit to evaluate depression and patients with a score of 15 or greater were considered to have depression [21].

Statistical analysis

We initially stratified the population based on erectile dysfunction severity and evaluated differences between the groups. Means and standard deviations were used to summarize continuous variables. Medians were used to summarize those without normal distribution. Categorical variables were summarized as percent of total. We used ANOVA to assess the difference in continuous variables and tested the difference in categorical variables with a chi-squared test. We used test for trends to evaluate variables with ordinal value to determine the association between erectile dysfunction severity and coronary artery calcification score and change in score. Kaplan–Meier was used to assess mortality risk between individuals with and without erectile dysfunction. Differences in survival were analyzed using the log-rank test. A Cox proportional hazards model was used to examine the association between erectile dysfunction and all-cause mortality. Variables evaluated included age, race, comorbidities such as hypertension, diabetes mellitus, smoking, BMI, mineral metabolism and inflammatory markers. The list of variables is shown in Table 1. Variables that were associated with erectile dysfunction with a p value less than 0.1 were included in the final model as well as a priori selected variables such as baseline coronary artery calcification score. Covariates included in the regression models were selected based on the backward elimination method.

For mortality, the unadjusted hazard ratio was determined, then the hazard ratio was adjusted for various variables that were significant in the univariable Cox proportional hazards models. We performed proportional hazard models with covariate adjustment by propensity score. Covariates in this model included age, diabetes mellitus, race, ever smoker and baseline coronary artery calcification score. Results were considered statistically significant if the corresponding p value was less than or equal to 0.05. We used STATA, version 15.0 (Stata Corporation, College Station, TX, USA) to perform analysis.

Results

The mean age of patients was 48.7 (13.3) years. Sixty-six percent of the cohort were African Americans, 33% Whites and 1% others. Table 1 presents the demographic and comorbidities stratified by erectile dysfunction severity. Notably, individuals with erectile dysfunction were older and more likely to have kidney failure attributed to diabetes mellitus.

Sixty percent of patients had a regular sexual partner. Ninety percent of patients with no erectile dysfunction had a regular sexual partner as compared to 40% who had severe erectile dysfunction ($p = 0.02$). The prevalence of any erectile dysfunction was 82.8%. While 17.2% had no erectile dysfunction, 43.1% of patients reported severe erectile dysfunction, 22.4% moderate erectile dysfunction and 17.2% had mild erectile dysfunction. Ninety percent of patients without erectile dysfunction had adequate intercourse satisfaction scores (score > 10) compared to 25% of patients in the erectile dysfunction group ($p < 0.001$). Figure 1 shows the IIEF-15 total score and components stratified by erectile dysfunction. Individuals with erectile dysfunction scored lower in each IIEF-15 component. Depression was found in 20% of patients with no erectile dysfunction and in 15% of those with erectile dysfunction ($p = 0.7$).

Coronary artery calcification

We found that 34.5% of patients had no calcification. The median (IQR) coronary artery calcification score was 22.4 (0–274.6) for the cohort. Erectile dysfunction was associated with higher coronary artery calcification score. The median (IQR) coronary artery calcification score was 43.4 (0.25–353.8) for those with erectile dysfunction and 0 (0–0) for those without erectile dysfunction ($p = 0.007$). Table 2 summarizes the coronary artery calcification score at baseline and coronary artery calcification progression by presence of erectile dysfunction and erectile dysfunction severity. Erectile dysfunction severity was associated with increasing coronary artery calcification scores ($p = 0.056$). More than one-third (37.5%) of the individuals with erectile dysfunction had a coronary artery calcification score > 100 compared to 10% of those without erectile dysfunction ($p = 0.09$).

Coronary artery calcification progression

Individuals with erectile dysfunction were more likely to experience coronary artery calcification progression over time. More than half (55.6%) of the patients with erectile dysfunction experienced progression of coronary artery calcification compared to 14.3% of patients without erectile dysfunction ($p = 0.05$). Individuals with erectile dysfunction had higher annual coronary artery calcification change compared to those without erectile dysfunction [39.6 (7.8–231.6) vs 0 (0–2.7), $p = 0.009$]. However, univariable and multivariable models adjusted for age, race, ever smoking, diabetes and baseline coronary artery calcification score did not show erectile dysfunction to be significantly associated with annual coronary artery calcification change. Similar results were found with progressors. The only variable that was significant was baseline coronary artery calcification score. Figure 2 shows baseline coronary artery calcification and coronary artery calcification progression stratified by erectile dysfunction severity.

Mortality

Twelve (21%) patients died during an average follow-up of 5.2 (1.3) years. Eleven (23%) patients with erectile dysfunction died compared to 1 (10%) among those without erectile dysfunction ($p = 0.4$). In individuals with calcification at baseline and erectile dysfunction, 32% died compared to 0% among those without erectile dysfunction ($p = 0.3$). In individuals without calcification at baseline and erectile dysfunction, 6% died compared to 12.5% among those without erectile dysfunction ($p = 0.6$). Figure 3 shows Kaplan-Meier curve stratified by erectile dysfunction. Using a proportional hazard model with covariate adjustment by propensity score that included age, diabetes mellitus, race, ever smoker and baseline coronary artery calcification (log), erectile dysfunction was not significantly associated with mortality [HR 1.2 (1.3), $p = 0.87$].

Discussion

We evaluated the relationship between erectile dysfunction, coronary artery calcification and mortality in incident dialysis patients without prior coronary events. We found a high prevalence (83%) of erectile dysfunction in incident dialysis patients with no history of coronary artery disease including 43% of patients reporting severe erectile dysfunction. Patients with erectile dysfunction had a higher coronary artery calcification score and higher annual coronary artery calcification progression. However, we were unable to find any difference in mortality between individuals with and without erectile dysfunction.

The overall prevalence of erectile dysfunction and erectile dysfunction severity in this incident cohort is similar to what has been described in long-term dialysis patients [1, 22]. Prior studies have shown the association between increased coronary artery calcification and incident cardiovascular events [5]. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, an association between high coronary artery calcification score and erectile dysfunction was reported in similar magnitude as found in our study. In this study, coronary artery calcification > 100 was 36.4% for patients with erectile dysfunction as compared to 17.2% in patients with no symptoms ($p < 0.001$) which is similar to findings from our study. These associations likely stem from the common risk factors and pathophysiology at the vascular level in both coronary artery disease and erectile dysfunction. Endothelial dysfunction, which leads to impaired vasodilatation, is the likely link between erectile dysfunction and vascular disease [23]. It was also hypothesized that the small penile arteries are more susceptible to progressive occlusive disease than the larger coronary arteries [24] and can predict coronary artery disease. In a study of 200 patients with suspected arteriogenic erectile dysfunction, 90.5% of the patients had obstruction of erection-related arteries and 37.5% had coronary artery calcification [8].

We have previously shown that erectile dysfunction is prevalent in individuals with long term hemodialysis [1] and drawn attention to the negative effects on their quality of life [25]. Individuals with erectile dysfunction had significantly lower quality of life mean scores [25], and the physical component scores of the SF-12 also showed a statistically significant decline as the severity of erectile dysfunction increased. It has been proposed that erectile dysfunction in the general population should be treated as a coronary artery

disease risk equivalent given the strong association with coronary artery calcification similar to peripheral artery disease and diabetes [26].

Our finding that coronary artery calcification score increased as the severity of erectile dysfunction increased is similar to data reported in studies of non-dialysis individuals. Chiurlia et al. in a cohort of 143 Italian individuals (70 erectile dysfunction vs 73 no erectile dysfunction with no history of coronary artery disease) showed that 41.4% of those with erectile dysfunction had a coronary artery calcification score above the 75th percentile compared with 19.1% of the control group ($p = 0.004$) (among erectile dysfunction patients) and stated that erectile dysfunction can be an early warning sign for coronary atherosclerosis [27]. Inci et al. in a study of 35 male individuals on hemodialysis (12–232 months) showed that coronary artery calcification score was significantly higher among individuals with severe erectile dysfunction ($p = 0.03$) [22].

Erectile dysfunction has been associated with mortality in the general population but we are the first to report the association of erectile dysfunction with mortality in individuals on dialysis. Araujo et al. reported that erectile dysfunction was associated with a 26% increased risk of mortality after adjusting for comorbidities (HR 1.26 95% CI 1.01–1.57) in 1709 men with a mean follow-up of 15.2 years [28]. Chung et al. in a study of 1436 Chinese men with a median follow-up of 11.5 years reported that erectile dysfunction was significantly associated with mortality ($N = 320$, HR 1.63, 95% CI 1.20–2.23) after adjusting for comorbidities [29]. These studies highlight the importance of screening patients with erectile dysfunction for cardiovascular disease. Banks et al. reported that the severity of erectile dysfunction increased the risk of cardiovascular disease and death [30]. The findings of this study provided a gradient of cardiovascular disease risk with increasing severity of erectile dysfunction and the need for cardiovascular disease risk assessment for men with erectile dysfunction. Among men without previous cardiovascular disease, the relative risk for all-cause mortality increased with erectile dysfunction severity. But only severe erectile dysfunction was significantly associated with all-cause mortality after adjusting for comorbidities. Loprinzi et al. in a study of 557 men with erectile dysfunction showed a 70% increased risk of premature all-cause mortality compared to men without erectile dysfunction (HR 1.70; 95% CI 1.01–2.85; $p = 0.04$) [11]. In the VITAL study cohort of 31,296 men who completed the questionnaire, 7762 men had erectile dysfunction and there were 486 cardiovascular deaths over a 7.8 year follow-up [31]. They showed that erectile dysfunction was not independently associated with an elevated risk of cardiovascular death after adjustment for known risk factors for cardiovascular disease (diabetes, treatment for hypertension or hyperlipidemia, family history of myocardial infarction/stroke, BMI, and exercise). (HR 0.93, 95% CI 0.76, 1.15). This cohort differs from others due to the large size and because the majority of patients (92%) were white. While the effect size we found is similar to these studies, our results were not statistically significant.

Depression is common in dialysis patients [32]. In our study, only 15% of patients had depression. We found only 20% of patients with no erectile dysfunction to have depression and 15% patients with erectile dysfunction to have depression. Our cohort was 20 years younger than the national average and significant cardiovascular morbidities were excluded.

Though beta-blockers are a frequent cause of erectile dysfunction, there was no difference in beta-blocker use by erectile dysfunction severity in our study. The majority of the beta-blocker users were on metoprolol.

While our study has many strengths, such as the use of a well characterized, multiracial cohort with serial measurements of coronary artery calcification and the prospective participation of the incident dialysis cohort without coronary artery disease history, we have to acknowledge several limitations. Our well-characterized cohort is relatively small. The erectile dysfunction assessment and medication lists were self-reported. Although anemia has been associated with erectile dysfunction in this population, we did not determine hemoglobin levels in our cohort. The observational nature of this study could have introduced unknown and unmeasured confounders. Finally, we used all-cause mortality as the primary outcome, as cause of death was not always available.

Erectile dysfunction is common in individuals on dialysis and its severity is associated with the presence of coronary artery calcification. The presence of particularly severe erectile dysfunction should alert the practitioner about the need for an evaluation of cardiovascular disease.

Acknowledgements

This work was supported by NIH Grants R21 HL 086971. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. Funding sources had no involvement in study design, data collection, analysis, and interpretation, writing of the report, or decision to submit the paper for publication. We would like to thank the research coordinators and patients involved in this study.

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Fig. 1.
Box plot of IIEF-15 components stratified by erectile dysfunction. All $p < 0.05$

Fig. 2.

Box plot of baseline coronary artery calcification and coronary artery calcification progression stratified by erectile dysfunction severity. * $p < 0.05$

Fig. 3.
Kaplan–Meier curve stratified by erectile dysfunction. $p = 0.4$

Table 1

Demographic and comorbidities stratified by erectile dysfunction severity

Characteristics	No ED (N = 10)	Mild ED (N = 10)	Moderate ED (N = 13)	Severe ED (N = 25)	p value
Age (years) ^a	39.7 (12.1)	51.2 (14.2)	46.5 (13.4)	52.5 (12.0)	0.06
African American (%)	50	70	76.9	64	0.77
HTN (%)	80	100	100	100	0.03
DM (%)	10	60	30.8	60	0.03
Smoker (%)	40	70	53.9	48	0.56
BMI ^a	29.9 (5.4)	28.9 (6.2)	28.6 (5.4)	29.7 (5.8)	0.91
Regular sexual partner (%)	90	80	61.5	40	0.02
Cause of ESRD					
DM (%)	0	30	30.8	52	0.12
HTN (%)	60	40	84.6	80	0.12
Creatinine (mg/dl) ^a	7.6 (2.3)	6.3 (2.1)	5.9 (2.6)	6.7 (2.2)	0.36
Albumin (g/dl) ^a	3.7 (0.5)	3.5 (0.5)	3.4 (0.7)	3.3 (0.6)	0.29
Calcium (mg/dl) ^a	9.1 (0.5)	9.0 (1.3)	8.5 (1.1)	8.7 (1.1)	0.52
Phosphorus (mg/dl) ^a	4.8 (0.9)	4.2 (1.3)	4.4 (1.5)	4.6 (1.5)	0.79
Vitamin D (ng/ml) ^a	31.1 (11.4)	26.7 (11.6)	23.4 (11.8)	31.4 (16.4)	0.36
PTH (pg/ml) ^a	170.4 (130.6)	298.4 (305.8)	255.9 (141.2)	233.5 (144.1)	0.48
hsCRP (mg/l) ^a	8.4 (6.3)	11.4 (17.5)	9.4 (9.9)	22.7 (55.2)	0.65
IL-6 (pg/ml) ^a	3.8 (3.7)	4.4 (4.8)	4.4 (4.3)	4.1 (3.0)	0.98
TNF alpha (pg/ml) ^a	3.9 (2.4)	4.4 (1.5)	4.8 (3.8)	7.1 (8.8)	0.45
FGF—23 (Ru/ml) ^a	3050.2 (2718.7)	4033.5 (5737.2)	1721.3 (1898.0)	2204.2 (3437.4)	0.43
Total cholesterol (mg/dl) ^a	173.7 (44.9)	171.7 (26.6)	158.8 (37.6)	158.8 (43.7)	0.68
LDL (mg/dl) ^a	168.4 (49.9)	154.2 (34.5)	144.8 (39.7)	143.0 (35.4)	0.37
Medications					
Beta blockers (%)	50	80	61.5	68	0.58

Characteristics	No ED (N = 10)	Mild ED (N = 10)	Moderate ED (N = 13)	Severe ED (N = 25)	p value
ACE/ARBs (%)	62.5	50	53.9	60	0.93
Diuretics (%)	25	50	38.5	52	0.55
CCBs (%)	62.5	90	61.5	60	0.37
Nitrates (%)	0	30	15.4	16	0.39
Alpha blockers (%)	25	30	30.7	16	0.70
Statins (%)	10	60	23.1	44	0.07
Aspirin (%)	37.5	40	0	44	0.04

Due to missing values, total may not always equal 58

^aMean (SD)

Table 2

Association of diabetes mellitus, erectile dysfunction and severity of erectile dysfunction with baseline coronary artery calcification score and annual coronary artery calcification score change

	Baseline Agatston Score	Median (IQR)	N	p value	Annual CAC change	Median (IQR)	N	p value
Diabetes								
<i>No DM</i>	0 (0–107.8)		32	0.003	2.3 (0–48.6)		20	0.002
<i>DM</i>	59.8 (10.4–452)		26		151.4 (18.1–328.1)		20	
ED								
<i>None</i>	0 (0–0)		10	0.007	0 (0–2.7)		7	0.009
<i>Any ED</i>	43.4 (0.25–353.8)		48		39.6 (7.8–231.6)		33	
ED severity								
<i>Mild</i>	35.6 (0.5–458.9)		10	0.056	167.8 (16.9–1137.4)		8	0.14
<i>Moderate</i>	53.6 (0–310.1)		13		23.5 (0–95.1)		10	
<i>Severe</i>	33.1 (0.6–204.6)		25		62.1 (2.4–231.6)		15	