Takotsubo Cardiomyopathy and Chronic Kidney Disease: A Scoping Study


Abstract

Sympathetic nervous system hyperactivity and elevated catecholamine levels are known features of chronic kidney disease (CKD). On the other hand, CKD itself is a high risk for Cardiovascular disease (CVD) and in fact most patients with CKD die before reaching dialysis. Furthermore, Many CKD risk factors such as obesity, hypertension, diabetes are also associated with sympathetic hyperactivity. Sympathetic hyperactivity and elevated catecholamine levels also play a key role in the pathogenesis of takotsubo cardiomyopathy (TKCM). Owing to the high sympathetic tone and elevated catecholamine levels in CKD/ESRD patients, an acute stress such as infection/sepsis or surgery makes these patients highly susceptible to TKCM.

Multiple isolated case reports of TKCM in CKD/ESRD patients have been reported. We here present the first scoping study of such cases. The purpose of this review is to identify the characteristic features of ESRD/CKD who developed TKCM. Analysis of 30 cases of TKCM in CKD/ESRD primarily happens in women (87% of the cases) with a mean age of 64 ± 13 yrs (Median 63 yrs). Dyspnea (60%) was most presenting complaint, followed by chest pain (37%), fatigue (10%), lower limb edema (3%), seizures (3%) and confusion (3%).

The majority of TKCM was noted after exposure to an acute physiological or psychological stressor. Physicians should have a high clinical suspicion for TKCM amongst other differential diagnosis in CKD/ESRD patients who present with chest pain or dyspnea in the setting of acute physiological or psychological stressor.

Keywords

Chronic Kidney Disease (CKD); End Stage Renal Disease (ESRD); Hemodialysis (HD); Takotsubo Cardiomyopathy (TKCM); Stress Cardiomyopathy; Sympathetic Hyperactivity

Introduction

Sympathetic nervous system hyperactivity and elevated catecholamine levels are known features of chronic kidney disease (CKD) [1-3]. Sympathetic hyperactivity is an independent risk factor for the development of atherosclerosis, heart failure and arrhythmias [4, 5]. Elevated catecholamine levels in patients with hemodialysis is associated with increased...
risk of cardiovascular events and all cause mortality [6]. CKD patients are the “highest risk group” for cardiovascular disease [7]. Also CKD risk factors such as obesity, diabetes, and hypertension are independently associated with sympathetic hyperactivity [8-10]. Sympathetic overactivity and elevated catecholamines are known to play key role in the pathogenesis of takotsubo cardiomyopathy (TKCM) (also known as stress cardiomyopathy) which is characterized by reversible acute left ventricular dysfunction [7, 11].

Methods

On January 30th, 2018, a literature search of pubmed, google scholar, CINAHL, Cochrane CENTRAL and Web of Science databases was conducted using the key words “stress cardiomyopathy, takotsubo cardiomyopathy, CKD, end stage renal disease (ESRD)” to identify cases of TCM related to CKD and ESRD. A total of 30 cases in English literature were identified (Table 1) [11-32]. Cited references of the case reports were also reviewed to identify additional cases. Demographic data, vitals, troponin levels, electrocardiography (ECG), echocardiography (Echo) and angiography findings were analyzed.

Results

A total of 30 cases of TCM associated with CKD/ESRD were identified. The mean age at presentation was 64 ± 13 yrs (Median 63 yrs). 87% of the cases were reported in females and 13% in males. Dyspnea (60%) was most presenting complaint, followed by chest pain (37%), fatigue (10%), lower limb edema (3%), seizures (3%) and confusion (3%). Hypertension was prevalent in 53% of cases, diabetes in 40%, atrial fibrillation in 17%, hyperlipidemia in 10%, smoking in 4%, history of coronary artery disease in 3%, history of TKCM in 3% and asthma in 3%. 60% of the patients were noted to have ESRD. 16 cases reported number of years on hemodialysis (HD). Mean years on HD was 3.4 ± 3.2 yrs (median 3 yrs). 74% of cases reported another stressor that possibly led to TCM. Heart rate was reported in 16 cases, mean heart rate was 89.65 ± 25.81. Systolic and diastolic blood pressures were reported in 13 cases, mean being 124± 38 and 74 ± 23 respectively. ECG findings were reported in all 30 cases with ST-segment elevation in 50%, T wave inversion in 50%, Q waves in 10%, ST-segment depression in 7%, atrial fibrillation in 7%, QTc prolongation 7%, left anterior fascicular block (LAFB) in 7%, right bundle branch block (BBB) in 7%, new onset left BBB in 3%, sinus tachycardia in 3%, sinus bradycardia in 3.33% and nonspecific ST-T changes in 3%. Troponin levels were reported in 28 of whom 93% of cases had elevated levels. All 30 cases reported echo findings 100% had wall motion abnormalities, reduced ejection fraction (EF) was reported in 50% and apical ballooning with wall motion abnormality in 57%. Coronary angiography was reported in 20 cases of whom 85 % had normal coronaries, non-obstructive CAD was noted in 10% and CAD in 5%. Death was not reported in any case (Table 2).

### Table 1: Summary of Results

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<th>Risk factors</th>
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<td>Hypertension 16(53%)</td>
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<td>Diabetes 12(40%)</td>
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<table>
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<th>Total Number of Cases</th>
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<td>Age in years (reported in 27 specifically)</td>
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ESRD reported: 18 patients (60%)

On hemodialysis since (reported in 13, 48.15%)

Mean 3.4 years
Median 3 years
SD 3.2 years

Other possible costressor that led to development of TCM identified in 23 (77%)

- Sepsis/infection 11 (48%)
- Emotional stress 3 (13%)
- Post Renal transplant 3 (13%)
- Drug toxicity 2 (9%)
- Seizures 1 (4%)
- Post surgical 1 (4%)
- Gastrointestinal bleeding/subarachnoid hemorrhage 1 (4%)
- Pain 1 (4%)

Heart rate reported in 16 patients

Mean 90 ± 26
Median 98

Systolic blood pressure reported in 13 patients

Mean 124 ± 38
Median 120

Diastolic blood pressure

Mean 74.23 ± 22.61
Median 70

EKG changes reported in 30 patients

- ST segment elevation 15 (50%)
- T wave inversion 15 (50%)
- Q waves 3 (10%)
- ST segment depression 2 (7%)
- Atrial Fibrillation 2 (7%)
- LAFB 2 (7%)
- RBBB 2 (7%)
- QTc prolongation 2 (7%)
- QTc prolongation 2 (6.67%)
- New LBBB 1 (3%)
- Sinus tachycardia 1 (3%)
- Sinus bradycardia 1 (3%)
- Non-specific ST-T changes 1 (3%)

Troponin levels reported in 28 patients

- Elevated levels 26 (93%)
- Normal levels 2 (7%)

Echo reported in 30 patients

- Wall motion abn 30 (100%)
- Reduced EF reported in 15 (50%)
- Apical ballooning/wall motion abn 17 (57%)

Cardiac cath reported in 20 patients

- CAD 1 (5%)
- Non-obs CAD 2 (10%)
- Normal coronaries 17 (85%)

Death reported in None

Table 2: Published Cases of TKCM in CKD/ESRD Patients, the Year of Publication and First Author’s Name have been Listed Here

2. Takemoto, et al. [12]
4. Hassan, et al. [14]
6. Numico, et al. [16]
7. Chrapko, et al. [17]
8. Mutluer, et al. [18]
Discussion

TKCM is predominantly reported in elderly women and rarely in men, who suffer emotional or physical stress. TKCK is characterized by left ventricular dysfunction, ECG changes of ST-segment elevation, deep T wave inversion, and elevated cardiac biomarkers [33]. Complete recovery of the left ventricular function has been reported in almost all cases of TKCM [34]. Sympathetic hyperactivity and increase in blood catecholamine levels are known to play a key role in the pathogenesis of TKCM. Catecholamine mediated plaque rupture and wrap around left anterior descending artery (LAD) were initially thought to contribute to pathogenesis of TKCM. However due to low plaque burden in TKCM patients and as the non-apical variants of TKCM could not be explained by wrap around TKCM these theories were disregarded [35-37]. Myocardial stunning secondary to coronary microvascular spasm induced ischemia has been attributed to apical ballooning and midventricular variety of TKCM [34-38]. This theory of TKCM derives justification further from the fact the ventricular dysfunction in TKCM is not restricted to a single coronary artery territory [34]. Coronary microvascular dysfunction secondary to neurohumoral changes has been noted in TKCM [39-42], however it is not clear if microvascular dysfunction is cause or effect of TKCM [34]. TKCM is predominantly noted in females rarely affects males [34]. Decrease in SERCA2 activity which has a key function in intracellular calcium homeostasis has been observed in TKCM [43] and in ovariectomized rats [44]. The role of estrogen deficiency on heart in stressful states is yet to be understood and may possibly explain the gender predilection in TKCM [34]. Postmenopausal estrogen levels are lower compared to estrogen levels in males and premenopausal women [45]. Animal studies have revealed the protective effect of estradiol in emotional stress induced structural changes of heart [46]. Estrogen levels are known to rise in postmenopausal women in TKCM as compared to age and gender matched postmenopausal women in acute myocardial infarction [47]. Also lack of estrogen replacement therapy is a predisposing factor development of TKCM in postmenopausal women [48].

Sympathetic hyperactivity and elevated catecholamine levels are known to occur in CKD/ESRD [1-3]. Sympathetic activation in CKD is independent of volume status, decrease in number of nephrons [43] and uremia-related toxins [44] thus suggesting that the sympathetic nervous system is hyperactive in this cohort. Elevated urea and adenosine in CKD are known to cause renal sympathetic activation and thus contribute to sympathetic hyperactivity [13, 14]. Mental and physical stress undergone by ESRD patients during HD can not be easily quantifiable and this may in turn contribute to sympathetic system activation [15]. Access site complications are a frequent occurrence and infections/sepsis are the major access site complication in CKD/ESRD patients [16]. Such infection and sepsis can thus further add to burden of sympathetic hyperactivity and

9. Muratsu, et al. [19]*
10. Santoro, et al. [20]*
11. Shin, et al. [21]**
12. Fearnley, et al. [22]
13. Golębiowska, et al. [23]
15. Kamada, et al. [25]
16. Torres, et al. [26]
17. Caccetta, et al. [27]
18. Vailas, et al. [28]
21. Carrillo-Esper, et al. [31]
22. Imam, et al. [42]

* 2 cases reported, **7 cases reported
possibly contribute to propensity for TKCM. Sympathetic hyperactivity is known to play a key role in acute kidney injury (AKI). It is not clear if AKI in turn activates the sympathetic nervous system [17]. Low levels of serum antioxidants are noted in patients with CKD and their levels may be further depleted by HD. Such an imbalance between oxidants and antioxidants might trigger or propagate TKCM [18]. Presence of CKD in TKCM patients is associated with increased morbidity in hospital as compared to non-CKD patients with TCM in one study [19]. Impairment of renal function is known to happen in TKCM [20]. Also CKD risk factors such as obesity, diabetes, and hypertension are independently associated with sympathetic hyperactivity [8-10]. This is a scoping study based on the published cases hence is not without selection bias.

The mean age of presentation of TKCM is 58-77 and 58-75 years as reported in studies and about 89-90% of the cases have been reported in females [21, 22]. The mean age of the patients observed in our study was 63.85 ±12.84 years and 86.67% of the patients were females. 60% of the patients had ESRD and 43.33% of the patients were on hemodialysis. 76.67% of the cases reported an additional stressor other than CKD/ESRD, thus indicating that CKD/ESRD patients in the setting of a physical or emotional stressor are likely to develop TKCM. Sepsis (47.8%), surgery (14.39%) and emotional stress (13.04%) were the most common addition stressors. Most of the patients presented with shortness of breath and chest pain. 100% of the patient had wall motion abnormality. Death was not reported in any case.

Conclusion

CKD/ESRD patient are at “highest risk” for development of CVD [7]. Sympathetic activity and elevated catecholamines are known feature of CKD [1-3]. Sympathetic hyperactivity and elevated catecholamines are known to play key role in pathogenesis TKCM [33, 34]. Due to hyperactive sympathetic tone and elevated catecholamine levels, CKD/ESRD patients are at elevated risk for TKCM in the setting of an acute physiological or psychological stress that leads to further activation of the sympathetic system and drives the catecholamines level higher. Physicians should have heightened suspicion for TKCM in CKD/ESRD patients, especially elderly postmenopausal females who present with shortness of breath and chest pain especially when faced with an acute stressor. Further studies are required to explore the risk, pathogenesis, management and outcome of patients with TKCM in CKD/ESRD patients.

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