Tuberculosis burden in stage 5 chronic kidney disease patients undergoing dialysis therapy at Livingstone Hospital, Port Elizabeth, South Africa

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Background. Tuberculosis (TB) is currently the leading cause of death from a single infectious agent worldwide. Patients who receive dialysis are particularly vulnerable to TB infection owing to immune dysfunction. Nonetheless, there is a paucity of incidence data on dialysis patients infected with TB in high-burden countries, such as South Africa (SA).
Objectives. To determine the incidence of TB in prevalent chronic kidney disease stage 5 (CKD-5D) patients on dialysis at a single centre in Eastern Cape Province, SA, and to identify the risk factors associated with TB infection.
Methods. We conducted a retrospective cohort study of all consenting CKD-5D patients between April 2010 and March 2014 at Livingstone Hospital Renal Unit, Port Elizabeth, the Eastern Cape. TB was defined as definite or probable according to World Health Organization (WHO) criteria, and the cohort was split into those who developed TB (TB+) and those who did not (TB−).
Results. One hundred and eleven patients were enrolled – predominantly black Africans (73%) and women (53%); the mean age (standard deviation (SD)) was 42 (9.8) years. The prevalence of HIV infection was 11%, all patients were receiving antiretroviral treatment and all had suppressed viral loads. Sixty-eight patients were on haemodialysis and 43 on peritoneal dialysis. Nineteen patients were diagnosed with 20 episodes of TB; 14 cases were pulmonary TB and 6 cases extrapulmonary TB. Of the patients with TB, 2 were HIV-infected, 7 (35%) were definite TB cases and 13 (65%) were probable cases. The calculated incidence rate was 4 505/100 000 patient years. Only informal housing (30% in TB+ v. 12% in TB−; *p*=0.042) and a history of hospitalisation (90% v. 76%, respectively; *p*=0.042) were significantly associated with a diagnosis of TB.
Conclusions. Dialysis patients in the Eastern Cape region of SA are at extremely high risk of acquiring TB, with an incidence rate 4.1 times that of the local population and >5 times that of the general SA population. Only informal housing and a history of hospitalisation were identified as positive risk factors for TB in this young population with a low HIV prevalence. Isoniazid prophylaxis in this high-risk group might be of benefit, but further studies are required to inform such treatment.

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Tuberculosis (TB), caused by the organism *Mycobacterium tuberculosis*, remains a major global health burden and is responsible for ill health among millions of people each year. It is currently the leading cause of death as a result of a single infectious agent worldwide.[1] South Africa (SA) has a reported TB incidence of 567/100 000 cases per year.[1] The reported incidence of TB in the Nelson Mandela Bay district, Eastern Cape Province, SA, is 1 009/100 000 cases per year,[2] which is much higher than the national average. In the Eastern Cape, it is reported to be the leading cause of death in persons 25 - 64 years of age.[2] Unfortunately SA, where the treatment cure rate is 82%, is failing at a national level to reach the proposed World Health Organization (WHO) target of 90%.[1]

Patients who receive dialysis are particularly vulnerable to active TB infection compared with the general population, due to immune dysfunction induced by their uraemic state.[3-5] In other low- and middle-income countries (LMICs), the incidence of TB among prevalent dialysis patients is 6.9 - 52.5 times higher than in the general population, depending on regional factors and background prevalence.[6-8] Other factors that might contribute to decreased immunity are malnutrition, vitamin D deficiency and hyperparathyroidism.[9]

There is a paucity of data regarding the incidence of TB in SA dialysis patients, where the background population prevalence is among the highest in the world. We are aware of only one published single-centre SA study by Tamayo-Isla *et al.*,[10] conducted in Polokwane, Limpopo Province, SA, where the authors describe a high mortality rate associated with TB peritonitis in continuous ambulatory peritoneal dialysis (CAPD) patients.

Objectives

To determine the incidence of TB in chronic kidney disease stage 5 (CKD-5D) patients receiving dialysis at a single centre in the Eastern

Cape, SA, and to identify modifiable and non-modifiable risk factors associated with TB.

Methods

Study design
We conducted a retrospective cohort study of all consenting prevalent CKD-5D patients between April 2010 and March 2014 in the Livingstone Hospital Renal Unit in the Eastern Cape. A total of 111 consenting prevalent dialysis patients were enrolled in the study during the 4-year period; no patient had TB at enrolment.

Data collection
TB was defined as definite or probable according to WHO criteria.[11] Definite TB patients were defined as those in whom TB complex was identified from a clinical specimen by culture or newer methods, including line-probe assays. Probable TB patients were those with constitutional symptoms, radiological features suggestive of TB and/or caseating granulomas on histological examination, but with no positive culture identification of TB.[11] A medical questionnaire with all the required data was used. Patient demographics, including dialysis vintage, age, gender, race (self-reported), employment status, smoking, alcohol use, history of hospitalisation for any cause during the study period but prior to enrolment, housing type and TB household contact status were recorded. Details regarding the diagnosis of TB, mean time between initiation of dialysis and diagnosis, HIV status, vitamin D level, comorbidities and medications were also recorded.

Statistical analysis
The estimated incidence was calculated as the percentage of patients who developed TB during the study period. This incidence was then converted into an incidence per 100 000 divided by 4 (for the 4 years) to give an estimated incidence per 100 000 per year of study period.

Normality was determined with the Shapiro-Wilk test. Continuous variables were expressed as mean (standard deviation (SD)), while categorical variables were presented as frequencies and percentages. Univariate analysis was performed using the independent Student's t-test, χ^2 test or Wilcoxon rank-sum test, as appropriate. All analyses were conducted using Stata 12.0 (StataCorp., USA).

Ethical approval
The study was approved by the Human Research Ethics Committee of the University of Cape Town, SA (ref. no. HREC/REF 127:2014), and permission for conducting the study was obtained from local authorities.

Results

Baseline characteristics of patients, including gender, HIV status, prior use of immunosuppressives, employment, smoking, known TB contact status and dialysis modality, are presented in Table 1. A total of 111 patients were enrolled, predominantly black Africans (73%) and women (53%); their mean age (SD) was 42.1 (9.8) years. The prevalence of HIV infection was 11%, and all patients were receiving antiretroviral treatment. Sixty-eight patients received haemodialysis and 43 peritoneal dialysis; 93% were unemployed.

The characteristics of patients with TB are shown in Table 2. Nineteen (18%) patients were diagnosed with TB over the 4-year study period, with 1 patient treated for TB on two occasions (#6 and #7, Table 2), giving a total of 20 TB cases; 14 patients had pulmonary and 6 extrapulmonary TB. Of the 20 TB patients (Fig. 1), 7 (35%) were definite TB cases and 13 (65%) had probable TB. Of the 7 definite cases, 1 patient (#5) had TB peritonitis with dialysate effluent culture positive for drug-sensitive TB; 2 patients (#7 and #11) had TB adenitis and culture-confirmed drug-sensitive TB; 1 patient (#1) had disseminated TB with a miliary pattern on a chest radiograph, a

Table 1. Baseline characteristics of TB+ and TB− dialysis patients				
Variables	Patients (*N*=111), %*	TB+ (*n*=19), %*	TB− (*n*=92), %*	*p*-value
Age, mean (years)	42	42.4	41.8	0.868
Gender				
Female	53	45	55	0.396
Employment status				
Unemployed	93	90	93	0.584
Smoking status				
≥10 pack-years	16	10	18	0.405
<10 pack-years	84	90	82	0.405
Hospitalisation	79	90	76	0.042
Housing				
Brick	85	70	88	0.042
Shack	15	30	12	0.042
Use of biomass fuel	8	5	8.7	0.582
TB contact	28	40	25	0.174
HIV status				
Positive	11	10	11	0.909
Use of immunosuppression	8	1.4	6.6	0.171
Vitamin D, nmol/L				
Deficiency and insufficiency	45.7	20.8	79.2	0.800
Dialysis modality				
Haemodialysis	61	18	82	0.898
Peritoneal dialysis	39	19	81	0.898

TB = tuberculosis; TB+ = developed TB; TB− = did not develop TB.
*Unless otherwise indicated.

Table 2. Demographics and clinical characteristics of TB patients

Patient	Gender	Age, years	Race	Time on dialysis, months*	HIV status	Dialysis modality	TB infection	Definite/probable
1	Female	52	Black	4	Negative	HD	Bone marrow	Definite
2	Female	44	Black	63	Negative	HD	Pleural effusion	Probable
3	Female	39	Black	3	Positive	HD	Pleural effusion	Probable
4	Female	35	Mixed	0	Negative	PD	Pleural effusion	Probable
5	Male	34	Black	16	Negative	PD	Peritoneal fluid	Definite
6	Female	59	Black	12	Negative	HD	Pulmonary	Probable
7	Female	59	Black	12	Negative	HD	TB adenitis	Definite
8	Male	38	Black	56	Positive	HD	Pleural effusion	Probable
9	Female	53	Black	38	Negative	HD	Pulmonary	Definite
10	Female	50	Mixed	50	Negative	PD	TB pericarditis	Probable
11	Male	34	Mixed	72	Negative	PD	TB adenitis	Definite
12	Male	45	Black	35	Negative	HD	Pleural effusion	Definite
13	Male	56	Black	32	Negative	HD	Pulmonary	Definite
14	Male	43	Black	19	Negative	PD	Pleural effusion	Probable
15	Male	31	Black	2	Negative	PD	TB pericarditis	Probable
16	Male	28	Mixed	13	Negative	PD	Miliary	Probable
17	Female	41	Mixed	44	Negative	HD	Pleural effusion	Probable
18	Male	35	Black	37	Negative	HD	Pleural effusion	Probable
19	Male	38	Black	59	Negative	HD	Pleural effusion	Probable
20	Male	41	Black	49	Negative	PD	Pleural effusion	Probable

TB = tuberculosis; HD = haemodialysis; PD = peritoneal dialysis.
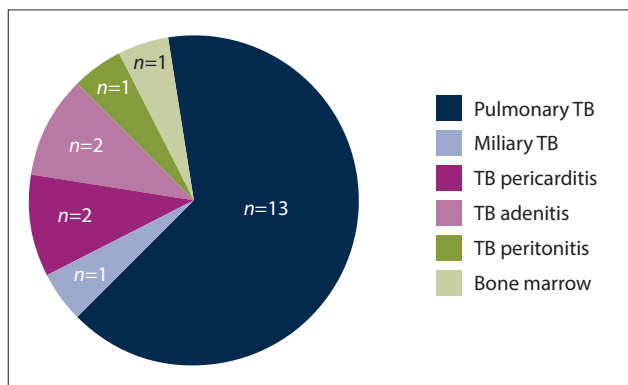*Duration of dialysis before TB diagnosis.

Fig. 1. TB-positive cases: spread of TB diagnosis. (TB = tuberculosis.)

Fig. 2. Tuberculosis incidence in the study population compared with the local, regional and national incidence in 2015.[12,13]

bone marrow biopsy showing caseating granulomas and a mycolytic blood culture that confirmed drug-sensitive TB; 1 patient (#9) had drug-resistant TB (multidrug-resistant TB (MDR-TB)) on culture; 1 (#12) had pulmonary TB with positive acid-fast bacilli on sputum microscopy (culture was not available), and 1 (#13) had pulmonary TB (suggestive chest radiograph) and was positive for drug-sensitive TB on sputum culture.

Of the 13 probable TB patients, 10 were diagnosed based on clinical features and lymphocytic pleural effusion and 2 had pericardial effusions with stranding on echocardiography. A pericardial tap in both patients revealed a lymphocyte-predominant picture, while 1 patient had a miliary pattern on chest radiography but a negative culture. The incidence of TB infection is shown in Fig. 2.

Discussion

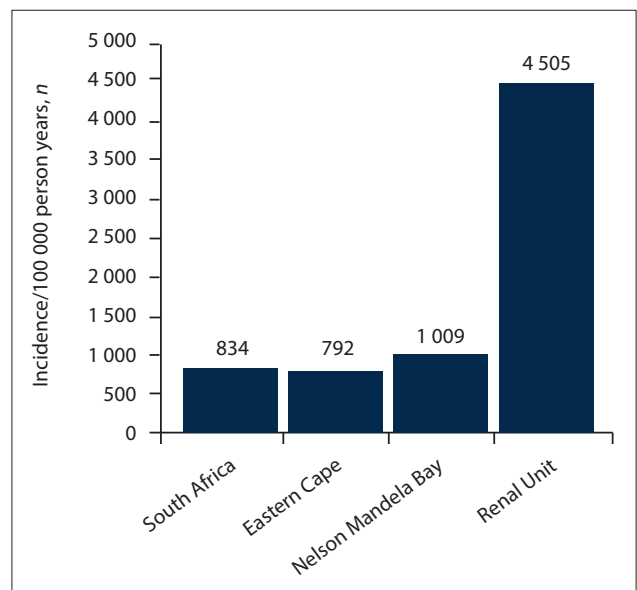This single-centre retrospective cohort study revealed an extra-ordinarily high incidence of TB in dialysis patients in the Eastern Cape, with a calculated incidence 4.1 times that of the local population and >5 times that reported in the general population for the country as a whole (Fig. 2). While such a relative risk is consistent with that described in dialysis cohorts from other countries,[8] the absolute risk to our TB patients is extremely high given the very high background prevalence of TB in SA (~1 in 5 over a 5-year period). The patients are predominantly young and HIV-negative, reflecting the selection bias in the SA public sector dialysis programme that favours those with less comorbidity. Moosa and Kidd[14] have previously reported on

the rationing of dialysis treatment in SA – patients are screened and accepted onto the dialysis programme based on favourable medical and socioeconomic criteria. Known TB risk factors that we assessed included age, employment status, smoking, alcohol use, average number of days admitted to hospital per year, housing type, TB contact status, HIV status and vitamin D levels.[15,16] However, of these risk factors, only informal housing and a history of hospitalisation were significantly associated with a diagnosis of TB ($p \leq 0.05$). In SA, informal housing (shack dwelling) is associated with overcrowding and unhygienic conditions, which would favour the transmission of TB in the community. While a history of hospitalisation may represent a more compromised cohort prone to TB, lack of adequate isolation facilities in our hospital during the study period may have contributed to nosocomial transmission of TB, although this is speculative.

Interestingly, HIV was not predictive of TB, but this is possibly confounded by the use of isoniazid (INH) chemoprophylaxis therapy in this group according to national guidelines and the low overall prevalence of HIV in our unit (11%). Moreover, all HIV patients on dialysis had undetectable viral loads and relatively preserved CD4+ counts as per dialysis selection criteria discussed above. A higher number of patients with TB had a history of a known TB contact (40% v. 25%), but this was not statistically significant ($p=0.174$). The combined vitamin D deficiency/insufficiency prevalence for our cohort was 45.7% and was not shown to be a significant risk factor for the development of TB. However, vitamin D levels were not measured at the time of TB diagnosis, as the test has not always been available at our study centre.

In our study, the incidence of extrapulmonary TB was very high (30%) and is consistent with reports from previous studies of CKD patients.[8,11,17-20] The increased tendency for extrapulmonary TB in CKD patients is thought to be due to impaired cellular immunity.[19] In dialysis patients, TB symptoms are often nonspecific and difficult to distinguish from uraemic symptoms, which can result in delayed diagnosis.[8,19] This may also facilitate transmission to other patients, particularly in haemodialysis units, where patients spend much time in close proximity to each other. Of the 20 TB patients, 7 (35%) were definite cases, with positive microscopy or culture. Tamayo-Isla et al.,[10] in their retrospective TB peritonitis study in SA, reported that TB was isolated in 75% of their cohort. In our cohort, 13/20 (65%) patients with TB were culture negative, reflecting the difficulty of definitive TB diagnosis in dialysis patients.

INH chemoprophylaxis in HIV-positive patients has been found to be efficacious in a number of large-scale randomised controlled trials, with up to a 74% reduction in TB incidence in select groups displaying a positive tuberculin skin test.[21] There are clear guidelines for this population, but data on INH chemoprophylaxis in CKD patients are lacking. A few randomised clinical trials have assessed INH chemoprophylaxis in both pre- and post-transplant patients and demonstrated its benefit to such patients for up to 1 year.[22-24] Further large randomised clinical studies in the dialysis setting are required to help inform best practice regarding when to commence INH chemoprophylaxis and the most efficacious duration of therapy.

Study limitations and strengths
There were some limitations to the study. Because of its retrospective nature, we were unable to include dialysis patients who had died during the study period, as their health records were unavailable. We also could not make assumptions regarding hospitalisation as a risk factor for TB, as we could not prove causality. Details regarding the reason for admission, length of stay and timing in relation to onset of TB were not available.

Study strengths include use of a single laboratory with standardised methodology, as well as availability of accurate clinical notes for determination of the diagnosis. While the overall numbers are relatively low for this cohort, a further strength of this study is that it included all living patients on dialysis in the public sector for the entire western part of the Eastern Cape and is therefore inclusive.

Conclusions
Dialysis patients in the Eastern Cape are at extremely high risk for TB, with a calculated incidence of 4 505/100 000 population per year. There is a need for improved healthcare structures, including the provision of adequate isolation facilities for TB patients in our hospital and renal unit to reduce transmission. Further research on outcomes and response to TB treatment of CKD patients in SA is required. Whether INH prophylaxis is a reasonable option for TB prevention in this population, remains unknown and should be the subject of further study.

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