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Tuberculosis in Kidney Transplant Recipients: A Nationwide Cohort in a Low Tuberculosis Incidence Country

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Background. World Health Organization recommends tuberculosis (TB) preventive treatment for risk groups such as patients preparing for organ transplantation. Pretransplant screening or treatment of latent TB infection has not been routine practice in Finland. **Methods.** In this nationwide registry study, we assessed the risk of TB among kidney transplant recipients compared to the general population. TB cases were identified by data linkage of the national infectious disease and the national transplant registries between 1995 and 2019. Standardized incidence ratios were calculated with adjustment for age, sex, and annual TB dynamics. **Results.** A total of 4101 kidney transplants in 3900 recipients with a follow-up of 37 652 patient-years were included. Eighteen TB cases were detected. Patients diagnosed with TB were older (median age 64 y, interquartile range 56–66) at transplantation than those without TB (median 51 y, interquartile range 41–60, $P < 0.001$). The standardized incidence ratio of TB was 6.9 among kidney transplant recipients compared to general population during the whole study period 1995–2019 but decreased from 12.5 in 1995–2007 to 3.2 in 2008–2019. The standardized incidence ratio was 44.2 during the first year after transplantation. Significant differences in 5-y graft losses were not detected between TB patients and those without TB. **Conclusions.** The standardized incidence ratio of TB in kidney transplant recipients has decreased over the years, but these patients remain at risk of TB, especially during the first posttransplant year. Cost-benefit analysis is required to address feasibility of latent TB infection screening among transplant candidates in countries with low incidence of TB.

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End-stage kidney failure is associated with increased risk of severe infections, including tuberculosis (TB).[1] Even though kidney transplantation is associated with improved survival in these patients, risk of certain infections is even more increased because of medication-induced immunosuppression to prevent transplant rejection.[2,3] Kidney transplant recipients appear to be at high risk for TB.[4-7] The World Health Organization advices to consider screening of latent TB infection (LTBI) with interferon-gamma release assays (IGRA) in patients with kidney failure or kidney transplantation,

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Because of legal restrictions, individual level data are not available. Aggregate-level data can be received from the authors upon reasonable request. Similar data can be applied for from the Finnish Social and Health Data Permit Authority Findata.

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depending on the local epidemiology and capacity of the health system.[8]

Finland is a high-income country with a low incidence (<10 per 100 000) of TB since 2001. Screening for TB is systematically performed only in risk groups such as asylum seekers and refugees.[9] LTBI screening and treatment has been routine practice in contact investigations. Also, people with human immunodeficiency virus (HIV) and patients starting on tumor necrosis factor-alpha blockers are screened. In Finland, routine screening and treatment for LTBI were not recommended in patients with end-stage kidney disease or kidney transplantation during the study period, but extension of screening to these patients is currently in consideration.

With the current nationwide register study, we aim to determine the risk of TB after kidney transplantation and to identify synergistic risk factors.

MATERIALS AND METHODS

Study Population

All adult patients who received a kidney transplant between January 1, 1995, and December 31, 2017, in Helsinki University Hospital (HUS) were included in this study. HUS is the only transplant center in Finland, and no transplants are performed elsewhere in Finland. Follow-up was calculated as patient-years, separately for each calendar year, starting from the day of transplantation and continued until death, graft loss, or December 31, 2019. In the case of retransplantation within the study time period, all years spent with a functioning transplant were included in the follow-up. Transplant-related data were extracted from the Finnish Transplant Registry, which is a legally obliged follow-up register maintained by the HUS (data extracted in March 2020).

Complete baseline transplant data were available for all patients. Mortality data and data on graft losses are continuously reported to the registry by the local nephrology centers and confirmed from other national registries. In case, cause of death was not available from transplantation registry, this was obtained from the official National Cause-of-Death Register at Statistics Finland.

Data Linkage

Data from patients registered in the Finnish Transplant Registry were linked with data on all TB cases from January 1, 1995, to December 31, 2019, from the National Infectious Diseases Register of Finnish Institute for Health and Welfare. Reporting of TB to this registry is mandatory by law based on the Communicable Diseases Act and Decree. The patients' personal identity code, unique to all Finnish citizens and permanent residents and used in all registries, was used for database linkage.

Data Analysis

Differences between 2 groups were compared with the Mann–Whitney *U* test for continuous data and with the Fisher exact test for categorical data. Follow-up started with first kidney transplantation, and patients were censored at time of death, start of dialysis, emigration, or at end of follow-up on December 31, 2019. Cumulative incidence of TB was estimated using the Kaplan–Meier method. Incidence rate was calculated per 100 000 patient-years for each calendar year for kidney transplant recipients. Standardized incidence ratios (SIRs) were calculated to compare with TB incidence in the general population in Finland while adjusting for age, sex, and the yearly incidence rate. SIR was calculated using the indirect standardization method with the TB rates in the general population within age (20–44, 45–64, 65–74, and ≥75 y) and sex categories as the reference ("expected" versus "observed"). Age distribution of the general population was obtained from Statistics Finland, from which official population figures are publicly available for each calendar year.[10]

All statistical analysis were performed with IBM SPSS Statistics, version 25 (IBM Corporation, Somers, NY).

Ethical Statement

This study had the approval of the institutional review board of HUS Abdominal Center (HUS/333/2019) and the Finnish Institute for Health and Welfare (THL/1877/5.05.00/2019). The statistical authorities replaced the PICs by an anonymized study code after the data linkage.

The research was conducted according to the principles of Good Clinical Practice and of the World Medical Association Declaration of Helsinki.

RESULTS

Kidney Recipients

A total of 4101 kidney transplants in 3900 adult recipients were identified, accounting for a total follow-up of 37 652 patient-years. Median age at transplantation was 51 y in the whole cohort, and 1457 of 4101 (36%) were female. Three patients were HIV positive at the time of transplantation, and no new cases of HIV were detected among the study cohort during follow-up.

TB in Kidney Recipients

TB was diagnosed in 18 cases, of whom 10 (56%) were female. Incidence of TB among transplant recipients was 114 per 100 000 patient-years in 1995–2007, and 19 per 100 000 patient-years in 2008–2019 (incidence rate ratio 5.97, 95% confidence interval [CI] 2.00-21.4, P <0.001). Median age of these TB patients was 63.5 y at the time of transplantation and 64.5 y at diagnosis of TB. The median time for TB diagnosis after transplantation was 271 d(range 25–3802), and in 12 cases (67%), TB was diagnosed within 1 y after the first transplantation. Incidence of TB among transplant patients during the first posttransplant year was 306 per 100 000 patient-years, compared to 18 per 100 000 patient-years after the first posttransplant year (incidence rate ratio 17.2, 95% CI 5.98-55.9, P < 0.001).

Two patients (11%) had been treated for acute transplant rejection after transplantation and before TB diagnosis. Fourteen patients (78%) had pulmonary TB and 4 (22%) had extrapulmonary TB, and none were multidrug resistant. TB patients were less likely to have received mycophenolate, which replaced azathioprine in baseline posttransplant immunosuppressive regimens in year 2000, than non-TB kidney transplant recipients (39% versus 77%, P < 0.0001). Three of 18 TB patients were of foreign background. Because of data restrictions related to privacy concerns, migration data were not complete within the whole population of transplant recipients. One patient died within 1 y from TB diagnosis. This case had extrapulmonary TB and died at day 307 after TB diagnosis (504 d posttransplantation), with aspiration

pneumonia filed as the acute cause and kidney disease as the underlying cause of death. None of the kidney grafts were lost within 1 y from TB diagnosis. Five-y graft survival was 72% in TB patients, and 83% in kidney recipients without TB (difference not significant). Patient characteristics of TB cases and non-TB cases are presented in Table 1.

SIRs

TB incidence in kidney recipients was 48 of 100 000 life years at risk. This was 6.9 (95% CI 4.2-10.7; $P < 0.001$) times as high as could be expected based on age and sex-specific incidence rates of the general population in the same year. To check for any change in SIR over time, because immunosuppressive medications applied around and after transplant procedures have evolved over time, we divided the inclusion period into 2 periods of equal duration. We observed an SIR of 12.5 (95% CI 6.9-20.8; $P < 0.001$) in the period from 1995 to 2007, whereas SIR was only 3.2 (95% CI 1.2-7.1; $P < 0.03$) in the period from 2008 to 2019. SIRs are presented in Table 2.

SIR for TB incidence during the first year after transplantation was 44.2 (95% CI 24.0-75.2, $P < 0.001$), and SIR for TB incidence after the first posttransplant year was 2.57 (95% CI 1.04-5.43, $P = 0.04$).

DISCUSSION

In this nationwide register study, TB incidence in kidney transplant recipients was substantially higher (SIR 6.9, 95% CI 4.2-10.7) than in the general population of Finland in the period from 1995 to 2019, especially in the first posttransplantation year (SIR 44.2, 95% CI 24.0-75.2). However, in the second half of the study period, SIR of TB incidence approached that of the general population. The 5-y graft survival in TB patients was similar to that in non-TB kidney transplant recipients.

The number of kidney transplantations per year has risen from 166 transplantations in 1995 to 293 transplantations in 2019. Infection with HIV as a comorbidity was negligible with only 3 HIV positive kidney recipients in the cohort (0.07%). In Finland, TB incidence reduced from 12.4 of 100 000 in 1996 to 4.1 of 100 000 in 2019. The proportion of foreign-born TB cases increased from 6.5% in 1996 to 43% in 2019.[11,12]

In 2019, the majority of foreign-born TB cases were under the age of 60. Roughly one-third of TB cases in Finland are currently diagnosed in patients 75 y of age or older.[11,12] These patients may have been exposed early in life, when incidence of TB was still high in Finland. Incidence of TB-HIV coinfection remained relatively low, varying from 1 to 11 reported

TABLE 1.

Characteristics of kidney transplantations with and without TB diagnosed after transplantation.

	TB cases (n = 18)	Non-TB cases (n = 4083)	*P*
Age at transplantation, median (IQR), y	64 (56–66)	51 (41–60)	<0.001
Female sex, n (%)	10 (56)	1447 (35)	0.09
History of immigration, n (%)	3 (17)	Unknown	n.a.
Hemodialysis (vs PD) before transplantation, n (%)	12 (67)	2557 (63)	0.75
Duration of pretransplant dialysis, median (IQR), mo	22 (14–37)	19 (10–33)	0.54
Patients with delayed graft function, n (%)	5 (28)	1273 (31)	0.49
Deceased donor transplantation, n (%)	18 (100)	3946 (97)	0.43
Induction therapy, n (%)			0.55
-No induction	16 (89)	3613 (88)	
-Basiliximab	2 (11)	290 (7)	
-Antithymocyte globulin	0	180 (4)	
Cyclosporine (vs tacrolimus), n (%)	15 (83)	3026 (74)	0.37
Mycophenolate (vs azathioprine), n (%)	7 (39)	3309 (77)	<0.001
Acute rejection, n (%)	2 (11)	854 (20)	0.30
One-y graft survival, %	100	94	0.16
Five-y graft survival, %	72	83	0.16

P-values were calculated by using the Mann–Whitney *U* test for continuous data and Fisher exact test for categorical data. The log rank test was used for survival data.
IQR, interquartile range; n.a., not applicable; PD, peritoneal dialysis; TB, tuberculosis.

TABLE 2.

SIRs of TB in kidney recipients in comparison to the general population of Finland.

Period	Expected	Observed	SIR	Lower CI	Upper CI	*P*[a]
1995–2019	2.60	18	6.93	4.24	10.74	<0.001
Division 1[b]						
1995–2007	1.04	13	12.49	6.95	20.82	<0.001
2008–2019	1.56	5	3.21	1.18	7.123	0.03
Division 2[b]						
1995–2002	0.49	10	20.63	10.48	36.78	<0.001
2003–2019	2.11	8	3.79	1.76	7.19	0.001

[a]*P* value CI: 95% CI.
[b]The time period was divided into 2 different manners, division 1 into 2 equal time periods of 11 y and division 2 to account for the change in immunosuppressive regiments in 2000–2001.
CI, confidence interval; SIR, standardized incidence rate.

cases yearly on a population of approximately 5.5 million people during the study period.[11,12]

In this study, TB disease was associated with immunosuppressive regimens including azathioprine instead of mycophenolate. However, this may well be the result of confounding as overall management of kidney transplantation evolved during the long study period.[13] Early in the study period, baseline immunosuppression consisted mainly of cyclosporine and azathioprine in addition to corticosteroids. In 2000, azathioprine was replaced by mycophenolate. After 2001, tacrolimus was used instead of cyclosporine in a subgroup of patients with high immunological risk such as retransplantation or poor HLA mismatch. During the 2000s, patients with higher immunological risk also received induction with basiliximab. Since 2014, antithymocyte globulin was given to patients with known or presumed donor-specific HLA antibodies at the time of transplantation. Steroids were usually withdrawn during the second posttransplant year.

Findings from a smaller cohort from Brazil report higher incidence of TB in kidney transplant recipients on azathioprine in comparison to those on mycophenolate, but this difference was not statistically significant.[14] In contrast, in another small cohort from Turkey, kidney recipients receiving mycophenolate or tacrolimus were more likely to develop TB than those on other regimens, but neither of these differences was statistically significant.[15] In a large Spanish cohort, azathioprine was associated with lower TB incidence in univariate analysis, but not in multivariate analysis.[16] Small sample sizes, contradictory results and probable confounding hamper definite conclusions from our and previous studies with regard to the relationship between TB incidence and various immunosuppressive regimens. Regardless of the regimen, immunosuppression is most intensive during the first post transplantation year, providing one explanation for the high SIR (44.2) in the first post transplantation year, as observed in our study. Altogether, the decline in SIR of TB incidence over time indicates that overall management—such as advances in immunosuppressive and monitoring protocols—have a major impact on the risk of post transplantation TB.[13] Thereby, our findings highlight the importance of recent advances in transplantation management with respect to post transplantation TB.

Our study has some limitations. First, even though the use of SIR allowed us to adjust for age, sex, and year of diagnosis, other potential confounders such as history of immigration, could not be taken into account. Second, because of low TB incidence, the absolute number of TB cases remained low, thereby hampering the identification of synergy of risk factors. Third, even though the use of SIR allows to apply the results to populations with higher TB incidence, the decline of the SIR over time indicates that our findings cannot be directly applied to settings in which recent advances in management of transplantation are poorly integrated. Fourth, TB may have been left undiagnosed if clinically not suspected. This may be more likely in extrapulmonary TB, which accounted for 22% of TB cases in our cohort, 14% in a Spanish cohort, but for 67% of cases in a French cohort. On the other hand, strengths of our study include the long time period, and a large nationwide cohort using statutory registries with the possibility to compare annual TB incidence with the general population. It is also worth noting that pretransplant screening or treatment for LTBI was not recommended in Finland during the study period.

According to World Health Organization guidelines, risk factors such as renal failure, dialysis and organ transplant should be considered when prioritizing for LTBI screening and treatment.[8] In our cohort of 3900 kidney transplant recipients, TB was diagnosed in 18 cases. Immunosuppressive therapy negatively affects sensitivity of IGRA for TB infection, but systematic screening before transplantation could potentially have improved healthcare for those patients.[17] A study from South Korea and a retrospective study from the United States support the use of quantitative IGRA-based isoniazid treatment for TB infection in kidney transplant recipients.[18]

In conclusion, even though incidence of TB in kidney transplant recipients has decreased over the years, these patients remain at increased risk of TB in comparison to the general population, especially during the first posttransplant year. Larger cohort studies and studies from countries with higher TB incidence could address synergistic risk factors in this population. Based on our results, there is an indication to screen candidates prior to kidney transplantation for LTBI. However, a cost-benefit analysis should be performed to investigate whether this would be feasible in Finland and in other countries with low incidence of TB.

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