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Original Article

Factors Predisposing to Active Tuberculosis in Dialysis Patients

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Abstract

Background. The aim of our study was to identify risk factors for developing active tuberculosis in regular haemodialysis patients (Dps).
Methods. A 36-month follow-up of 272 Dps, in S/W Greece, where all new cases of active TB were detected. Eligible Dps were tested with tuberculin (Mantoux skin test), in a 2-step manner.
Specific Relative Risks (RR) for TB was calculated considering subjects from the general population as a reference group at the end of the studied period. The independent effect of age, BMI, diabetes, tuberculin reactivity, healed tuberculosis evidences on chest X-ray and dialysis stage was determined using Cox's proportional hazard model.
Results. Dps presented a multi-fold higher RR for TB [74.5(95% [CI] 58.65-113.6, P <0.001)] as compared to the aged matched background population. Elderly Dps (Adjusted/RR 25.3, P<0.02), diabetics (Adj/RR 25.3, P<0.03), underweighted (Adj/RR 72.3, P<0.001*)*, tuberculin responders (Adj/RR *41.4, P<0.03),* Dps with fibrotic residuals on chest x-ray (Adj./RR 82.3*, P<0.03*) and those treated for <12 months (Adj/RR 110.0, P<0.001), presented significantly higher specific RRs for TB even after allowing for the effect of the other studied risk factors.
Conclusion. TST positivity, the existence of predisposing risk factors and/or chest X-ray findings, will guide the diagnosis of latent TB infection and the selection of those DPs who warrant preventive chemoprophylaxis. To optimize the benefit the later would be commenced upon entering a chronic dialysis program.

Keywords: tuberculosis, dialysis, risk factors, tuberculin reactivity, dialysis stage, chest X-ray, Body mass index, diabetes mellitus

Introduction

Haemodialysis patients are at increased risk for developing tuberculosis (TB) due to impaired cellular immunity in chronic renal failure [1]. The frequent hospital contacts, the older age and the use of immunosuppressive drugs are other factors involved in the higher prevalence of TB reported in these patients. Furthermore, as symptomatology is often insidious and non specific, whereas the localization is often extrapulmonary, TB in dialyzed patients presents a number of diagnostic challenges [2, 3]. This makes the disease difficult to diagnose, delaying the initiation of curative treatment, a major determinant of the outcome [2-4].
That is why annual skin testing with tuberculin purified protein derivative and chemoprophylaxis for all dialyzed patients with a ≥10mm response is recommended [5]. However, as guidelines for TB prophylaxis emphasize targeted tuberculin skin testing (TST) as a means of diagnosis of latent tuberculosis infection (LTBI), they make no mention on anergic dialyzed patients.
In a recent study it was shown that the later are at increased risk for TB development and prophylaxis is justified in them too. In that study factors like advanced age, Diabetes Mellitus and a low body mass index (BMI) were associated with significant depression of the cell mediated immunity and anergy [6].
In the current study, we further assessed the impact of the above mentioned factors on the risk of developing TB. Specific risks for TB were also defined according to TST reactivity at intake, chest radiography and time on maintenance dialysis treatment. Such knowledge is particularly useful for clinical use and may facilitate targeting of preventative therapy for TB in dialyzed patients.

Patients and methods

Study design
This was a prospective, multi-center trial conducted over the course of three years in two chronic hemodialysis outpatient units affiliated with the University Hospital and a third unit in the Nephrology Department of the General State Hospital in Zakynthos. Entering the study, participants were evaluated, and active TB was ruled out by history, physical examination, chest radiography, and when indicated, bacteriological studies. Eligible patients

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were then tested with tuberculin. They were subsequently classified by: age (<49, 50-64 and >65 years old), BMI (underweight <18.5, healthy 18.5-24.9, overweight 25-29.9 and obese >30 kg/m^2), response to tuberculin skin testing (TST negative 0-4, weak positive 5-9 and positive ≥10 mm skin induration), coexistence or not of diabetes mellitus (DM), chest radiography (with evidence or not, consistent with old healed TB) and time on dialysis (short-term 0-12, mid-term 13-60 and long-term >60 months). TB prevalence and the subsequent relative risk (RR) for TB was then determined for each group separately, over a 36 month follow-up.
To identify the RR for TB in dialyzed patients accurately, on a population basis, the Prefecture's Health Service registries, where all TB cases diagnosed are mandatory reported, were also reviewed. From these, the specific rate of TB, for those of the background general population aged >25 years, was recorded [7,8]. Participants provided informed consent.

Participants
End stage renal disease patients enrolled ultimately in this study (n = 272) were aged 27-85 years, treated with dialysis for a mean of 3.9 years (range 1 week to 18.4 years). Sixty-seven patients had chest X-ray findings suggestive of old spontaneously healed TB, but all had at least two negative sputum specimens by both smear and culture. Five patients had a history of active pulmonary tuberculosis, but all had been treated adequately. Close contacts of persons with infectious tuberculosis were not identified. Patients on corticosteroids or other immunosuppressive therapy were not included in this study. We did not performed a routine assessment for HIV infection, as in our area prevalence of HIV associated TB is insignificant. As Greece is among the countries where BCG vaccination is still in use, most patients had probably been vaccinated at the age of 6 years.

Tuberculin Skin Testing (TST)
TST was carried out by the intradermal (Mantoux) method. It was administered by injecting 0.1 ml of commercially available tuberculin (PPD-Merieux, 5 U/0.1ml dose), intradermally into the anterior surface of the forearm, and was read 48-72 hours later. A second booster injection with 10 U/0.1ml dose, was given within a 10-day interval to those Dps responding with a <10 mm induration to the first test.

Chest Radiographs
Entering the study, all patients had posterior-anterior chest radiographs. The later were examined by two independed physicians and scored blindly as positive, intermediate or negative. Dense pulmonary nodules with or without visible calcifications in the hilar area or upper lobes or pleural scarring were scored as positive findings. Lesions that could not undoubtedly be attributed to old TB, however suspected, were considered as intermediate.

Statistical methods
TB prevalence was defined as the number of TB cases per a hypothetical population of 100 at risk. The relative risk (RR) for TB was defined as the ratio of TB prevalence in dialysis patients, to the prevalence of TB in the age-matched background general population. To correlate the risk for TB with the studied risk factors, *Spearman's* product moment correlation coefficient (r) was computed, a dimensionless index that ranges from -1.0 to 1.0, reflecting the extent of the relationship between data sets. The independent effect of every studied factor, on the risk of progression to clinically manifested TB, was determined using the multivariate analytical method of *Cox's* proportional hazard model [9]. Analysis of variance (*ANOVA*) was used to assess the statistical significance of differences.

Results

Prevalence and relative risk for TB development
During the 36 month follow up, 24 Dps developed active TB, a mean rate of 8.2%. All efforts were made for bacteriological and/or histological confirmation. In 4 of the cases (16.6%), lungs were the only site of involvement. Extra-pulmonary manifestations were verified in the remaining 20 cases (83.4%), with lymph nodes, pleural, pericardium, peritoneum, liver, spleen, kidneys and bones being the sites of involvement reported. During the same period, 131 cases of TB were reported to the Public Health Services' registry of Achaia. The age-specific rate of TB for those aged >25 years was 0.11%. Considering subjects from the general population as reference group, the relative risk (RR) calculated for Dps was 74.5 *(95% confidence interval [CI] 58.65-113.6, P <0.001).* The RR was substantially higher in diabetics (P =0.01), increased with increasing age *(r =0.95, P =0.006)*, decreased with increasing BMI *(r* = -

Table 1. The correlation between the Relative Risk of TB and the studied risk factors, following the univariate (r1, P1) and the multivariate analysis (r2, P2)

Characteristic	r1 value	P1 value	r2	P2
Age	0.95	0.006	0.95	0.01
BMI	-0.98	<0.001	-0.99	<0.001
Diabetes Mellitus	0.95	0.01	0.95	0.03
TST at intake	0.84	0.02	0.51	0.03
Inactive-TB evidence on chest x-ray	0.99	<0.001	0.98	<0.001
Dialysis stage in months	-0.46	<0.001	-0.58	<0.001

r: correlation coefficient**, P value:** for the differences between groups

0.98, P<0.001), and increased with increasing tuberculin reactivity at intake *(r =0.84, P =0.02)* (Table 1).

Findings of the tuberculin skin testing

Upon entering the study, the prevalence of a positive Mantoux skin test (≥10mm) was 18.9% for the first and 22.7% (n=62) for the second test. Twenty-seven patients (9.9%) demonstrated a weak-positive response. A negative response to TST was recorded in 183 patients (67.2%). Among them 2 patients had history of old treated pulmonary TB and 32 had chest radiographs suggestive of spontaneously healed old TB. Seventeen patients with negative TSTs at intake developed active TB. Thirteen of them (13/17) had negative TSTs even when the active disease developed.

Association of chest X-ray with risk for TB

From the 67 patients with findings suggestive of old-healed TB in chest radiographs, upon entering the study, 10 (14.9%) developed active mainly extrapulmonary TB. Even after allowing for the remaining risk factors, patients with old-healed TB residuals on chest radiographs demonstrated an almost three-fold higher risk for developing active TB as compared to patients without such evidences in chest radiographs *(P <0.001)*.

There was no significant correlation between TST positivity and chest radiography results (lesions were described in: 27 (43.5%) patients with positive, 8 patients (29.6%) with week-positive and 32 patients (17.4%) with negative TST). Using both screening methods 102 patients (37.5%) were identified as having been infected with M. Tuberculosis.

Findings of the multivariate analysis

As most of the studied risk factors are interrelated, a multivariate analysis was undertaken to confirm the associations observed. The estimated adjusted RRs (Adj.RR) were appreciably smaller than the respective RRs, due to the high correlation between the studied factors.

The Adj.RR for TB remained significantly higher in diabetics *(P =0.03)* and an increasing trend with age was still demonstrated *(r =0.95, P =0.01)*. Underweight Dps presented a significantly higher Adj.RR for TB as compared to overweight and/or obese patients. The Adj.risk for TB decreased steadily *(r = -0.99, P < 0.001),* with increasing BMI from 72.3 *(95% confidence interval [CI] 65.2-79.8)* in underweight patients, to 23.1 *(95% confidence interval [CI] 18.4-28.2)* in obese patients (Table 2).

Table 2. The risk for tuberculosis in dialysis patients during the 36-month study period, by age, Body Mass Index (BMI), incidence of Diabetes Mellitus, tuberculin skin testing at onset, old-TB evidences on chest radiographs and time on dialysis following the Cox regression for multivariate analysis

Characteristic	Adj RR	95% CI	P value
Age			
≤ 49	16.2	11.7-20.6	0.001
50-69	22.8	20.6-24.9	0.001
≥ 70	25.3	20.4-28.4	0.01
BMI			
< 18	72.3	65.2-79.8	<0.001
18-25	36.8	28.3-44.5	<0.001
25-30	28.4	22.1-34.3	<0.001
>30	23.1	18.4-28.2	<0.001
Diabetes Mellitus			
Yes	25.3	20.4-28.4	
No	19.2	17.2-21.1	0.03
TST at intake (mm)			
0-4	24.5	22.5-26.5	<0.001
5-9	8.4	3.1-13.6	<0.001
≥10	41.4	37.9-44.8	<0.001
Inactive-TB evidence on chest x-ray			
Yes	82.3	51.3-95.5	
No	21.3	19.8-22.8	<0.001
Time on Dialysis in months			
0-12	110.0	97.4-135.3	<0.001
13-60	9.3	5.2- 14.6	<0.001
≥60	41.3	31.3-56.8	<0.001

BMI: Body Mass Index, **TST**: Tuberculin Skin Testing, A**dj RR:** adjusted relative risk after allowing for the effect of the other characteristics**, CI**: Wald 95% Confidence Interval, **P value:** for the differences between groups

The Adj.RR for the 0-4 mm PPD-S group *(24.5, 95% confidence interval [CI] 22.5-26.5)*, remained significantly lower in comparison to the respective value for the ≥10mm group *(41.4, 95% confidence interval [CI] 37.9-44.8, P<0.001)*. However, the Adj.RR for the 5-9mm group was significantly lower than the respective value for the 0-4mm group *(P<0.001)*, resulting finally in a weaker not grated correlation *(r = 0.51)* between tuberculin sensitivity and the risk for developing TB. (Tables 1,2).

Association of dialysis stage with risk for TB

Patients undergoing dialysis for a shorter than 12 months period presented a significantly higher risk for TB, as compared to patients treated for a longer period *(P<0.001)*. The lowest risk was recorded in patients treated for 13 to 60 months. A significant increase in the risk for TB was noticed in patients treated for more than 60 months *(P< 0.001)*. However, even in this group patients, the risk for TB remained significantly lower as compared to the risk recorded in those dialyzed for less than 12 months *(P<0.001)*.

Discussion

Worldwide TB infection in dialyzed patients ranges from 5-25% and a 6.9-52.5-fold risk of TB is reported as compared to the general population [3]. These findings were verified in the current study too. Ideally, we would have liked to have recorded the prevalence of TB among those of the general population that had cardiovascular disease, diabetes mellitus or positive TST and calculate the relative risk for TB based upon this. Unfortunately, this was not possible due to lack of the necessary data from the general population. However, the main trends concerning the relative risk for TB, could hardly been biased by this limitation.

Advanced age, diabetes mellitus and low BMI were already known factors of immunological imbalance and development of tuberculosis in the general population [10-15]. In this study, they were proved to be predisposing factors to active TB development in Dps too.

Elderly patients (>70 years), presented two times higher risk for TB as compared to their younger counterparts. Diabetics had an almost two times higher risk for TB than non-diabetics. In addition, underweighted dialysis patients presented more than six times higher risk for TB than obese patients, independently of their initial tuberculin reactivity and even after allowing for the effect of the remaining studied risk factors.

Most authors agree that to provide substantial protection against TB, chemoprophylaxis should be commenced in all dialysis patients with a positive TST [5]. However, as the diagnostic utility of TST is unclear in such an anergic population, there are many considerations concerning the selection of those patients that have to be protected [6]. In the general population, TST remains the most satisfactory tool for diagnosing TB infection, and initial tuberculin sensitivity was well associated with the incidence of TB [16]. In the current study, dialysis patients presented a weaker association between initial tuberculin sensitivity and the subsequent risk for TB. A substantial proportion of the patients that developed TB, had a negative TST upon entering the study (14/24) and/or when active disease was developed (8/24). Obviously, as anergy influenced tuberculin reactivity, TST underestimated the prevalence of TB infection among our patients.

In dialysis patients, a negative TST has a comparatively low prognostic and diagnostic importance. However, as patients with positive TSTs presented increased risk for developing TB, a positive TST should never be underestimated.

It was for the first time in this study that was obtained specific relative risks for the association between time upon entering a regular dialysis program and TB development. A significantly higher prevalence and risk of TB was recorded, in those patients dialysed for a shorter than 12 month period. Kaufman *et al*. offered a convenient explanation of the above [17]. There is a higher prevalence of anegy in patients at onset dialysis treatment, associated with low-protein diet and related to abnormally low values of serum total protein and total lymphocyte count.

These observations allow us to propose that to provide substantial protection against TB in dialysis patients chemoprophylaxis should be commenced upon entering a chronic dialysis program.

Persons with abnormalities on chest radiographs consistent with prior, healed TB have a high risk for progression to active TB (2.0-13.6 per 1000 person-years of observation) Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for future progression to active TB [18,19]. Dialysis patients with radiographic evidences of healed TB demonstrated an even higher risk of developing active TB, independently of their response to TST, even after allowing for the effect of the remaining risk factors. The weak correlation between chest radiography and TST positivity recorded in the current, as well as in previous studies, verifies the role of chest X-ray in detecting TB infection in dialysis patients [20].

Commencing chemoprophylaxis in all patients with evidences of healed TB on chest X-rays, independently of their response to TST, upon entering a chronic dialysis program, would improve the control and prevention of TB in this high risk population.

Conclusions

Our findings verified the high risk for developing TB reported in dialyzed patients. Advanced age, DM and low BMI are independent factors, predisposing to developing of TB. We have to consider them, evaluating dialysis patients for TB. The existence of any of the above factors supports the decision to treat when definitive diagnosis of clinical manifest TB is not possible, although there is strong presumptive evidence.

Uremic patients are at increased risk for developing TB, upon entering a chronic dialysis program, and this is the most appropriate period for screening and commencing preventive therapy against TB in this vulnerable population. TST positivity and the existence of predisposing risk factors in combination with the chest X-ray findings, will guide the diagnosis of latent TB infection and the selection of those patients who warrant preventive chemoprophylaxis.

Conflict of interest statement. None declared.

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