



The prevalence and risk factors for latent *Mycobacterium tuberculosis* infection in patients with chronic kidney disease

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Abstract

Introduction and Objective. Active tuberculosis (TB), which develops mostly in the mechanism of latent tuberculosis infection (LTBI) activation, is a difficult and important problem among patients with chronic kidney disease (CKD). The aim of the study was to determine the prevalence of LTBI and associated risk factors in CKD patients, both undergoing dialysis and in the pre-dialysis stage.

Materials and method. The study comprised 482 subjects aged 19–98, including 294 haemodialysis, 50 peritoneal dialysis and 32 pre-dialysis patients, as well as 106 healthy controls. In order to determine LTBI, QuantiFERON Gold In-Tube Test (QFT-GIT, Cellestis Ltd, Australia) was used.

Results. Positive QFT-GIT test was obtained in 32% haemodialysis, 28.1% pre-dialysis, 12% peritoneal dialysis patients, and in 11.3% controls. By univariate logistic regression analysis, predictors of LTBI were: active smoking (OR=1.34), coronary artery disease (OR=1.32), age (OR=1.04), male gender (OR=1.42), platelet count (OR=1.00), and duration of dialysis (OR=.95). By multivariate logistic regression, independent predictors of LTBI were: age (OR=1.02), male (OR=1.81), haemodialysis procedure (OR=2.39), TB contact (OR=2.46) and platelet count (OR=.99).

Conclusions. The obtained results revealed a high prevalence of LTBI in CKD patients. Established risk factors, especially those described for the first time, such as platelet count and coronary artery disease, provided clinical support in TB diagnosis. Since a high LTBI rate in CKD patients was observed, wide use of the QFT-GIT test is recommend to control TB in this population.

Key words

dialysis, latent tuberculosis, renal insufficiency

INTRODUCTION

Patients with chronic kidney disease (CKD) are at higher risk of active tuberculosis (TB), which develops mostly in the mechanism of latent tuberculosis infection (LTBI) activation [1, 2]. It is estimated that in the group of dialysis patients the risk of TB is 10–25-fold higher compared to the general population, and the mortality rate doubles in those patients [3]. The diagnosis of TB in CKD patients is often delayed due to the high rate of extrapulmonary TB forms (approximately 50% vs 10% of general population), which makes it difficult to obtain the necessary material for a microbiological culture [4]. Furthermore, hardly specific clinical manifestation of TB might be mistaken for the symptoms of uraemia. According to the latest WHO guidelines on the management of LTBI, dialysis patients are classified to a high risk population group which should be prioritized for LTBI testing and treatment [5].

OBJECTIVE

The aim of the study was to assess the prevalence of LTBI and associated risk factors among CKD patients, both in pre-dialysis and dialysis stages, compared to healthy controls. QuantiFERON-TB Gold In-Tube Test was used to determine LTBI.

MATERIALS AND METHOD

The study comprised 482 individuals aged 19–98, consecutively enrolled between January 2012 and December 2013. Overall, there were 294 patients undergoing regular haemodialysis programmes (HD) in four centers, 50 peritoneal dialysis patients (PD) from one centre, and 32 pre-dialysis patients with chronic kidney disease (CKD) stages 1–4 (eGFR ≥ 15 mL/min/1.73m²). The control group (CG) consisted of 106 voluntary blood donors or General Practitioner (GP) patients without chronic diseases. Among PD patients, there were 31 patients (62%) on CAPD (Continuous Ambulatory Peritoneal Dialysis) and 19 (38%) on APD (Automated Peritoneal Dialysis). eGFR was calculated using MDRD formula. Individuals were enrolled in the study if they met the following inclusion criteria: 1) at least 18 years old, 2) agreement to participate in the study and signing the informed consent. The exclusion criteria were: 1) symptoms

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suggestive of active TB, 2) organ transplantation in the past, 3) immunosuppressive drugs. Haemodialyzed patients underwent HD sessions lasting 3–5 hours, 3 times a week. Baseline demographic and clinical data were obtained from a standardized interview and a physical examination, both provided by a nephrologist or a GP. A review of TB symptoms, such as cough, hemoptysis, fever, night sweats, weight loss, fatigue or weakness as well as the history of TB exposure, disease and treatment was carried out. Biochemical data were obtained from the patients' medical records. All the participants were Caucasian and originated from the Lublin province in eastern Poland. All the study subjects had been previously BCG vaccinated. Written informed consent was provided from all the participants in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Bioethical Board of the Medical University in Lublin (Protocol No. KE-0254/47/2011).

In the study, the third generation QuantiFERON-TB Gold In-Tube Test (QFT-GIT, Cellestis Ltd, Carnegie, Victoria, Australia) was used. In 2007, the QFT-GIT test was approved by FDA (Food and Drug Administration, US) for common use as an aid in LTBI diagnosing. Moreover, it was suggested that the QFT-GIT diagnostic strategy provided the greatest benefits at the lowest cost [6]. The QFT-GIT test detects sensitization to Mycobacterium tuberculosis (M. tuberculosis) by measuring IFN- γ release in response to antigens highly specific to this pathogen (proteins ESAT-6, CFP-10 and TB 7.7). The results of QFT-GIT test were considered positive, indeterminate or negative according to the criteria established in the manufacturer's software.

For the purpose of the study, LTBI was defined as a positive QFT-GIT test result without prior TB disease and with a normal clinical assessment. Blood samples for QFT-GIT test assessment were taken from the venous part of the dialysis access at the beginning of HD, as well as during outpatient's clinic visit (peritoneal dialysis patients, chronic kidney disease patients), or in a blood donation centre.

Statistical analyses were performed using STATISTICA software package (version 10.0, StatSoft Inc.). All variables were tested for normality by W Shapiro-Wilk test and for homogeneity of variances by Levene's or Brown-Forsythe test. Differences between independent groups were evaluated by a χ^2 test of independence (for categorical variables), and a student's t test or ANOVA for means of continuous variables. All p values were two sided and $p < .05$ was considered to indicate statistically significant differences. To establish risk factors associated with LTBI, logistic regression analysis was performed. Firstly, using a wide range of independent variables (socio-demographic, biochemical and clinical parameters) univariate analysis was performed. Significant risk factors in univariate analysis were placed in multivariate logistic regression. In both analyses, the pre-dialysis group was the reference group for comparisons. Finally, multivariate analysis with the control group as the reference group was performed. Odds ratio (OR) and adjusted OR with 95% confidence intervals (CI) were calculated.

RESULTS

The mean ages of HD, PD, pre-dialysis and CG groups were 65.8 ± 13.6 , 51.1 ± 13.8 , 69.2 ± 16.8 and 49.7 ± 21.9 , respectively ($p = .000$). Patients in all the groups mostly originated from

urban areas: 56.8%, 60.0%, 71.9%, 71.7%, respectively ($p = .030$). Males dominated in HD and DO groups (55.4%, 58%, respectively). In the pre-dialysis and the CG group there were 46.9% and 25.7% males, respectively. The gender distribution statistically varied between groups ($p = .000$). There were no differences between groups in BMI mean value ($p = .180$) and mean dialysis duration ($p = .166$). Overall, the most common causes of kidney failure were: diabetic nephropathy, chronic glomerulonephritis and hypertensive nephropathy.

Significant differences were observed between groups in the proportion of positive QFT-GIT test results ($p = .000$). The percentage of positive QFT-GIT test results was higher in the HD group (32%, 94/294) than in the PD (12%, 6/50) ($p = .004$) and in the CG group (11.3%, 12/106) ($p = .000$). Positive QFT-GIT test was observed more often in the pre-dialysis group (28.1%, 9/32) than in the CG group ($p = .020$). No statistical differences were found in the proportion of positive QFT-GIT test results between pre-dialysis and HD patients ($p = .656$), pre-dialysis and PD patients ($p = 0.065$), nor between patients at different stages of the pre-dialysis phase, assessed by serum creatinine concentration ($p = .916$) (data not shown in Tables). In total, 7 indeterminate results were found: 6 (2%) in the HD group and 1 (2%) in the PD group. Because of the limited number of indeterminate results, they were excluded from further statistical analysis.

Table 1 shows comparison between groups of patients with QFT-GIT positive (QFT-GIT+) and QFT-GIT negative (QFT-GIT-) test results. QFT-GIT(+) patients were older, more frequently male and active smokers. In the QFT-GIT(+) group, coronary disease cases were significantly more frequent. Diabetes mellitus, arterial hypertension, stroke and alcoholism were reported more often in the QFT-GIT(+) group, but the observed differences were not statistically significant. QFT-GIT(+) patients presented lower platelet count. The QFT-GIT(+) result was not associated with nutrition parameters (BMI, serum albumin level, total cholesterol level), as well as C-reactive protein level, white and red blood cells parameters.

By univariate logistic regression analysis, predictors of LTBI were: active smoking, coexisting coronary artery disease, age, male, platelet count and the duration of dialysis. By multivariate logistic regression analysis, independent predictors of LTBI were: platelet count, male, TB contact, haemodialysis procedure and age (Tab. 2 and 3).

DISCUSSION

In the presented study on a large population of patients with CKD, both receiving dialysis (HD or PD) and in the pre-dialysis stage, a high prevalence of LTBI was found. A percentage of QFT-GIT(+) results in HD patients was threefold higher compared to the both PD and CG groups. HD procedure was an independent risk factor for LTBI in multivariate logistic regression analysis, when the CG group was the reference group for comparisons. Previous studies on HD population provided consistent results (a range of positive QFT-GIT test from 21% – 40%) [7]. The lower prevalence of LTBI in PD patients could result from technical dissimilarities between the 2 methods of dialysis. PD procedure required less frequent visits in health centres such as HD units. Thus, the exposure to M. tuberculosis and the risk for iatrogenic infections among PD patients could be reduced. However, since we reported

Table 1. Comparison of comorbidities, biochemical and socio-demographic parameters between groups with positive and negative QFT-GIT test results

Variables	QFT-GIT test result		P value (χ^2 or t-student test)
	Positive N=121	Negative N=354	
Age (years)	67.8±11.5	58.3±18.8	.000
Gender (female/male) - %	38/62	55.8/44.2	.003
TB contact - %	19.2	13	.167
TB treatment in the past, %	4.3	4.7	.876
Place of residence (urban/rural), %	58.7/41.3	61.9/38.1	.340
Coronary artery disease, %	44	31.2	.001
Diabetes mellitus, %	36.7	28.1	.206
Arterial hypertension, %	79.8	69.9	.097
Respiratory tract diseases, %	22.9	25.8	.687
Stroke in anamnesis, %	9.2	4.6	.188
Cancer in anamnesis, %	4.6	8.1	.371
Hepatitis B or C, %	6.4	8.8	.624
Alcoholism, %	11	7	.314
Active smokers, %	31.2	20.2	.024
CRP (mg/L)	20.4±41.1	19.6±33.3	.679
Albumin (g/dL)	3.9±0.4	3.8±0.5	.170
BMI (kg/m ²)	26.7±6.7	25.3±5.1	.516
Total cholesterol (mg/dL)	176.3±42.4	178.3±52.1	.252
Erythropoietin demand (IU/week)	13463.8 ± 12356.2	14828.9 ± 12924.9	.503
Iron (µg/dL)	67.0±30.8	65.6±35.8	.452
Ferritin (ng/mL)	446.2±408.2	442.4±397.2	.275
HGB (g/dL)	10.9±1.3	10.7±1.5	.295
WBC (x10 ⁹ /L)	6.6±1.9	6.9±2.6	.819
NEU (x10 ⁹ /L)	4.3±1.9	4.9±2.5	.158
LYM (x10 ⁹ /L)	1.5±0.6	1.3±0.6	.124
PLT (x10 ⁹ /L)	213.8±59.0	246.6±89.8	.020

p<0.05 – statistical significance; TB – tuberculosis; CRP – C-reactive protein; HGB – haemoglobin; WBC – white blood cells; NEU – neutrophils; LYM – lymphocytes; MONO – monocytes; EOS – eosinophils; BAS O-, basophils; PLT – platelets; IU – International Unit

old age as an independent risk factor for LTBI, the lower age of PD patients could be the reason for lower LTBI prevalence in this group. Contrary to the current findings, some authors have reported a similar rate of LTBI in HD and PD patients [8, which challenges the theory of M. tuberculosis airborne transmission in HD room. In the current study, the prevalence of LTBI was similar in the HD and the pre-dialysis group. There were also no differences in LTBI rate between pre-dialysis and PD patients. Moreover, the positive QFT-GIT test result was not associated with the creatinine concentration in the pre-dialysis group. Thus, the current study supports the theory of high LTBI risk since the early stages of CKD.

By univariate logistic regression, predictors of LTBI included active smoking, old age, male, and the dialysis duration. Similar observations have been reported in previous studies [9]. In a literature review, the described risk factors were also associated with the development of active TB [10]. The present study revealed a significantly higher incidence of coronary artery disease (CAD) in the QFT-GIT(+) group compared to QFT-GIT(-) patients. The presented finding of increased risk of cardiovascular disease (CVD) among

Table 2. Results of uni- and multivariate logistic regression analyses of risk factors for LTBI (Pre-dialysis CKD group as a reference group for comparisons)

Variables	Univariate			Multivariate		
	OR	95%CI	P value	Adjusted OR	95%CI	P value
Age (years)	1.04	1.02-1.05	.001	1.02	1.00-1.05	.021
Duration of dialysis (years)	.95	.90-1.00	.046	.95	.89-1.02	.172
Ferritin (ng/mL)	.94	1.00-1.00	.936			
Total cholesterol (mg/dL)	1.00	1.00-1.00	.737			
Iron (µg/dL)	1.00	.99-1.01	.736			
Albumin (g/dL)	1.09	.68-1.75	.711			
HGB (g/dL)	1.13	.97-1.33	.120			
PLT (x10 ⁹ /L)	1.00	.99-1.00	.001	.99	.99-.99	.011
WBC (x10 ⁹ /L)	.94	.85-1.04	.212			
NEU (x10 ⁹ /L)	.88	.78-1.00	.052	.89	.77-1.03	.147
LYM (x10 ⁹ /L)	1.45	.98-2.16	.064	1.58	1.00-2.51	.050
CRP (mg/L)	1.00	.99-1.01	.869			
Gender (male)	1.42	1.16-1.78	.001	1.47	.80-2.63	.185
Diabetes mellitus	1.22	.96-1.55	.102			
Coronary artery disease	1.32	1.05-1.66	.018	1.53	.87-2.69	.137
Arterial hypertension	1.31	1.00-1.71	.052	1.93	.98-3.78	.056
Respiratory tract disease	.93	.71-1.20	.566			
Stroke in anamnesis	1.45	.94-2.23	.098			
Living place (urban areas)	1.35	.81-2.22	.238			
Hepatitis B or C	.84	.54-1.30	.439			
Alcoholism	1.28	.88-1.89	.201			
Active smoking	1.34	1.04-1.73	.024	1.85	.99-3.46	.054

p<0.05 – statistical significance; OR – odds ratio; CI – confidence interval; HGB – haemoglobin; PLT – platelets; WBC – white blood cells; NE – neutrophils; LYM – lymphocytes; CRP – C reactive protein

Table 3. Results of multivariate logistic regression analysis of risk factors for LTBI (Control group as a reference group for comparisons)

Variables	Multivariate		
	Adjusted OR	95% CI	P value
Age (years)	1.03	1.01–1.04	.000
Gender (male)	1.81	1.14–2.85	.012
Place of residence (rural areas)	1.11	.70–1.75	.679
TB contact	2.46	1.31–4.62	.005
TB treatment	.69	.22–2.15	.527
Pre-dialysis stage of CKD	1.99	.70–5.66	.193
Hemodialysis procedure	2.39	1.19–4.80	.014
Peritoneal dialysis procedure	1.18	.39–3.56	.758

p<0.05 – statistical significance; OR – odds ratio; CI – confidence interval; TB – tuberculosis; CKD – chronic kidney disease. Biochemical parameters were not evaluated in the control group

people with M. tuberculosis infection is consistent with recent studies [11, 12, 13]. The main underlying process in CAD (Coronary Artery Disease) is atherosclerosis, which is currently considered an inflammatory disease [14]. It is suspected that many pathogens, including M. tuberculosis,

could be involved in the formation of atherosclerotic plaque [15]. Although, the presence of *M. tuberculosis* DNA in the plaque has not yet been confirmed, the constitution of the *M. tuberculosis*'s cell wall, rich in phosphatidylinositol of procoagulant properties, allows assumption of the atherogenic potential of this pathogen [16, 17]. Interestingly, the immune response to the mycobacterial heat shock protein (HSP65) was considered a factor in the pathogenesis of atherosclerosis. By immunizing with mycobacterial HSP65, Zhang et al. were able to induce arteriosclerotic lesions in normocholesterolemic rabbits [18]. Similar results were obtained by Grundtman et al. [19].

Overall, the results obtained in the presented study are promising, although they should be interpreted with caution. Firstly, the current knowledge does not allow to conclude whether experiments on atherosclerosis in active TB can be related to the LTBI. Secondly, in this study, CAD was a predictor of LTBI only in univariate analysis, and confounding factors, e.g. age, cannot be excluded. Nevertheless, in-depth research on the role of *M. tuberculosis* in atherogenesis is needed, particularly with regard to the high prevalence of LTBI and increased cardiovascular mortality in CKD patients.

Limitations of the study. The study has some limitations. First, despite several advantages over TST, particularly in the immuno-compromised and BCG vaccinated populations, QFT-GIT is not a 'gold standard' for LTBI diagnosis [20]. Additionally, the assessment of accuracy of QFT-GIT test is impaired by the lack of any confirmatory test. Furthermore, the positive QFT-GIT test result does not alter the LTBI and culture-negative active TB. Since the extrapulmonary and oligosymptomatic character of active TB in the CKD population is prevalent, active TB cases among the QFT-GIT(+) group cannot be excluded. Thus, it is suspected that the lower platelet count in the QFT-GIT(+) group observed in this study could result from the presence of active TB cases with associated thrombocytopenia in this group. This is convincing evidence that all patients with positive QFT-GIT test result should be medically evaluated for the active TB disease according to the guidelines on the management of LTBI in CKD patients [21, 22]. Hence, the authors have arranged a continuation of their study to perform more extensive TB diagnostic evaluation in QFT-GIT(+) patients. Furthermore, a longitudinal study is scheduled to determine how many QFT-GIT(+) patients will ultimately develop active TB.

CONCLUSIONS

In the present study on a large population of patients with CKD, both those receiving dialysis and the in pre-dialysis stage, a high prevalence of LTBI was found. New risk factors for LTBI were evaluated. Since a high LTBI rate in CKD patients was observed, using widely QFT-GIT test to control TB status in this population is recommended. The obtained findings have important implications for the epidemiology, diagnosis and control of TB in CKD patients. The study has added to knowledge about TB and restriction the global spread of the disease in the future.

Declaration of conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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