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Factors associated with tuberculosis in a population of diabetics: A case-control study

Marcelle Lemos Leal (http://orcid.org/0000-0001-7878-6654) [1]
Ethel Leonor Nóia Maciel (https://orcid.org/0000-0003-4826-3355) [1]
Nágela Valadão Cade (http://orcid.org/0000-0001-6073-504X) [1]

Abstract *This study analyzed the factors associated with tuberculosis in diabetics seen at health units of Vitória, ES, Brazil. This is a case-control study of 45 cases of diabetics seen in the 30 units of the municipality and reported in the SINAN with a diagnosis of tuberculosis in the 2007-2013 period and 90 cases of diabetic controls. We used data from the SINAN, the Health Information System of Vitória, and the Central Municipal Laboratory, as well a structured interview. Bivariate and multivariate analyses were performed, using logistic regression with the significant variables ($p < 0.05$). The case group presented a higher frequency of health-damaging life habits as compared to the control group, such as compulsive drinking ($p < 0.001$) and tobacco smoking ($p = 0.060$), as well as worse biochemical parameters, such as fasting blood sugar ($p < 0.001$) and glycosylated hemoglobin ($p = 0.034$). Regular drinking (OR 6.612, CI 2,151-20.330), previous contact with people with tuberculosis (OR 4.418, CI 1.678-11.631), and fasting blood sugar (OR 1.017, CI 1.007-1.026) were associated with tuberculosis in diabetics. The study reveals that poorer lifestyle habits and glycemic control and previous contact with active tuberculosis increase the chance of diabetics developing tuberculosis.*

Key words *Diabetes mellitus, Tuberculosis, Case-control studies, Epidemiology*

[1] Programa de Pós-Graduação em Saúde Coletiva, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo. Av. Marechal Campos 1468, Maruípe. 29040-091 Vitória ES Brasil. marcelle.leal@outlook.com

Introduction

The prevalence of chronic non-communicable diseases has increased more rapidly than infectious and parasitic diseases have receded, especially in low- and middle-income countries, where there is still an overlap of these diseases due to the incomplete epidemiological transition[1].

The important association between diabetes mellitus (DM) and tuberculosis (TB) has been reported in several epidemiological studies. In 2007 and 2008, two systematic reviews addressed the overall risk of TB in diabetics. Cohorts showed that people with DM are three times more likely than the general population to become ill for TB, and in case-control studies the chance of TB occurring in diabetics ranged from 1.2 to 7.8 times[2,3].

The pathogenesis of the association between DM and TB is quite complex. It is unclear if DM increases susceptibility to TB infection or if it triggers the development of TB that was previously latent. There is evidence that DM, particularly when poorly controlled, increases the risk of infections, including respiratory infections[4].

Some studies have found that DM predated TB for a mean period of four years, which may have impaired the innate and adaptive immune response against *Mycobacterium tuberculosis*, favoring latent TB infection and subsequent disease development in this population. Also, the influence of the cumulative effect of risk factors, such as smoking, drinking and other drug use[5,6].

In Brazil, between 2001 and 2011, 990,017 cases of TB were reported and 36,920 (3.73%) of these individuals reported having DM. While global incident cases of TB declined slightly, the proportion of diabetics among TB cases increased progressively from 380/100,000/year in 2001 to 6,150/100,000/year in 2011[7].

Vitória, the capital of the state of Espírito Santo, Brazil, has 8.1% of people aged 18 years or over living with DM, being the sixth highest prevalence in the country[8]. At the same time, it is one of the nine priority municipalities for national TB control, with an incidence rate of 49/100 thousand inhabitants and a mortality rate of 1.8/100 thousand inhabitants[9].

This scenario of overlapping two epidemics – of DM as a chronic disease and TB as an infectious-contagious disease – has triggered discussions and studies about the interaction between these diseases, considering that the current DM epidemic can lead to a resurgence of TB in endemic regions, especially in urban areas, potentially leading to a global dissemination risk with serious implications for TB control[10].

Given these issues, this study was designed to analyze the factors associated with the development of TB in patients with DM in care at the health units of the municipality of Vitória, ES, Brazil.

Methods

Study population

This is a case-control study carried out with all the diabetics seen at the 30 municipal health units of Vitória, ES, Brazil, aged 18 years or older, and who signed the Free and Informed Consent Form. Those who were institutionalized, deprived of their liberty or lacked lucidity to respond to the interview were excluded.

Selection of cases and controls

The case group consisted of all diabetics using oral or parenteral hypoglycemic medication and seen at the health units of the municipality of Vitória, ES, who at some point had a history of TB diagnosis and were notified at the *Sistema de Informação de Agravos de Notificação* (SINAN – Information System for Notifiable Diseases) in the 2007-2013 period. It is noteworthy that all the individuals listed in SINAN with TB were investigated for the diagnosis of DM and were using hypoglycemic medication and insulin.

The control group consisted of all diabetics using oral or parenteral hypoglycemic medication, seen at the health units of the municipality of Vitória, ES, with no TB record in SINAN and no self-report of TB when interviewed for data collection.

Gender and age variables were matched between cases and controls because they are two possible confounders in this study, considering that DM is more common in people over 40, whereas TB affects younger people. Moreover, gender and age influence adherence to DM treatment and consequently glycemic control[11,12]. For age, a variation of up to five years was allowed between the two groups – case and control.

Regarding the number of controls per case, a 2:1 ratio was adopted, considering the small number of diabetics with TB reported in SINAN from 2007 to 2013. BioEstat 5.3 software was used for the drawing of the controls.

Instruments and procedures

To obtain the secondary data we used the electronic medical records of the health information system of Vitória *Rede Bem Estar* (RBE) for identification data, the *Sistema de Gerenciamento da Assistência Farmacêutica* (Pharmacy Assistance Management System – SISFAR) to select those in use of oral or parenteral hypoglycemic agents, the SINAN to identify those who developed TB, and the Central Laboratory of the Municipal Health Department (SEMUS), from which we extracted information on the results of fasting blood sugar and glycosylated hemoglobin (HbA1c).

The primary data were collected through structured interviews of the cases and controls conducted by the researcher from September to December 2015. The study variables were grouped as socioeconomic and demographic (age, sex, race/color, schooling and economic status; clinical characteristics of DM (time of diagnosis, complication of DM, use of oral and parenteral hypoglycemic agents, fasting blood sugar, and HbA1c), characteristic of TB (exposure), and comorbidities.

Critério Brasil was used for the socioeconomic classification proposed by ABEP. The classification was based on a scoring system with the following items: schooling of the head of the family, number of durable goods available at home, and access to public services (piped water and paved street). After summation, the cut-off point of *Critério Brasil* determined the following socioeconomic classes: Class A (45-100 points); Class B (29-44 points); Class C (17-28 points) and Class D-E (0-16 points)[13].

Regarding life habits, as for alcohol consumption, the individuals who reported having drunk in the past or drinking currently were considered. Current drinkers were included in the categories regular intake (at least one day per week) and sporadic intake (less than one day per week or per month); and in relation to the amount ingested, they were placed in the categories drinking compulsion when twice or more daily, or no compulsion when fewer than three times a month.

Smoking is associated with poor control of diabetes, triggering increased abdominal fat, reduced insulin sensitivity, and elevated blood sugar levels, which may be related to the amount of cigarettes and the duration of smoking[11]. Questions were about smoking in the past and recently.

After completing the interviews, a nominal list with date of birth and mother's name of all interviewees was prepared for the electronic search of HbA1c and fasting blood sugar test results at the SEMUS Central Laboratory.

Statistical analysis

The chi-square test and Fisher's exact test were used to analyze the categorical variables, which tested the association between the independent variables and the maximum likelihood ratio for the exposure variable that admitted more than two categories. For the variables that did not fit the Gauss model after the Kolmogorov-Smirnov test, the Mann-Whitney test was used. For the variable age, the t-test was used for the means, since there was no departure from normality. Variables with $p < 0.100$ were included for multivariate analysis through the binary logistic regression model with the forward conditional input method.

To determine the association, the odds ratio (OR) was calculated and with a 95% confidence interval. A significance level of 5% was adopted for all applied tests and for logistic regression. Data were analyzed using the Statistical Package Social Science, version 18.0 (SPSS Inc., Chicago, USA).

Ethical considerations

This study was approved by the Ethics Committee for Research with Human Beings of the Health Sciences Center of Universidade Federal do Espírito Santo, April 29, 2015; and data collection in the primary health care units was authorized by the Technical and Professional Training School of Health "Professora Ângela Maria Campos da Silva" on June 11, 2015. The purpose of the research was explained to each interviewee, who then signed the Informed Consent Form (TCLE) to participate.

Results

From 2007 to 2013, 1,261 cases of TB were reported in SINAN, 94 of which were excluded from this study, as were two records with no patient identification and 79 cases of relapse and re-entry after abandonment, making up 1,086 patients. The records of relapse and re-entry after abandonment were excluded for eliminating duplicity of individuals. Of these, 64 had DM

according to SINAN. All patients reported in SINAN with TB with or without DM had their names verified in SISFAR and RBE of the Municipal Health Department (SEMUS), and in the end 65 cases (DM/TB) were confirmed through these three information systems. There was a loss of 152 (14%) individuals with TB in SINAN whose names were not in the municipal health information systems to confirm the diagnosis of DM.

Of these 65, there was one refusal and 19 did not meet the inclusion criteria, totaling 45 cases at the end. Ninety controls were drawn by lot.

The cases were predominantly male (62.2%).

Most cases (93.4%) were diagnosed with pulmonary TB and 97.8% were cured.

In relation to schooling, there was a predominance of people with less than four years of schooling in both groups, and one case and five controls were illiterate. More than 60% of individuals belong to socioeconomic class C, and 20% of cases and 17.4% of controls belong to classes D or E[13] (Table 1).

As compared to the controls, most of the cases involved colored people (black or brown) ($p = 0.030$) with worse living habits, since they had higher regular alcohol consumption ($p = 0.009$), drink more compulsively ($p < 0.001$) and smoke more ($p = 0.060$). Cases also had more contact with people who became ill with TB ($p = 0.001$) (Table 1).

Regarding hypoglycemic medication, insulin use, along with oral hypoglycemic, is higher among cases (51.1%) than among controls (34.4%). The control group used oral hypoglycemic (65.6%) more frequently than the case group (48.9%). Two cases and one control used only insulin (Table 1).

The median age of the cases and controls was 54 and 56 years, respectively. In the variable time of DM, the mean and median were higher in the cases than in the controls. The number of DM complications and comorbidities in both groups was similar (Table 2).

The cases presented worse glycemic control than the controls, that is, HbA1c and fasting blood sugar test results were above the reference values established by the American Diabetes Association[14]. Significant difference was observed in the variables HbA1c, HbA1c before TB, fasting blood sugar, and fasting blood sugar before and after TB (Table 2).

Of all variables with $p < 0.100$ that entered the multivariate model, regular drinking was associated with the presence of TB in diabetics, in which the odds of developing TB were 6.612 times higher; having contact with a person with TB increases by 4.418 times the chance of getting infected with *Mycobacterium tuberculosis*; and elevation of 1 mg/dl of fasting blood sugar increases the chance of TB illness by 1.017 (1.7%) (Table 3).

The covariates presence of drinking compulsion and HbA1c did not enter the model because they were highly correlated with drinking consumption and fasting blood sugar.

Although we worked with the SINAN population considered as "cases", a power test was performed *a posteriori* with the proportions of the obtained results. For the assessment of smoking and insulin use, the power of the test was less than or equal to 65%, so the number of cases and controls was not sufficient to evaluate these two exposures.

Discussion

In this study, regular drinking, previous contact with people with TB, and altered fasting blood sugar were associated with TB illness in the diabetic population.

When the socioeconomic and demographic condition was evaluated, the two groups differed (case and control) only regarding race/color in the bivariate analysis. Most TB cases occurred in non-white individuals and, as demonstrated in a descriptive study of the epidemiological and operational indicators of TB control in Brazil, the occurrence of TB is higher in the non-white population, that is, among black and brown people[9]. Another study, conducted in the United States, showed that the percentage of TB cases in blacks is higher than expected. Although TB rates in black people have declined considerably over the last decade, the disparity between races still remain[15].

Socioeconomic and demographic factors engender health outcomes, as they are associated with poverty, limited access to quality health care, low schooling, unemployment, low-skilled occupations and poor feeding, housing and transportation conditions[16]. These factors may directly or indirectly increase the risk of contracting TB, which are still disparities in public health, particularly among racial and ethnic minorities.

However, in this study, it was expected that the cases would have fewer years of schooling and worse economic status, since, historically, it has been reported in the literature that TB ill-

Table 1. Bivariate analysis of socioeconomic and demographic variables, life habits and medication according to the groups. Vitória, Espírito Santo, Brazil, 2007-2013.

Variables	Case (n = 45)		Control (n = 90)		p-value
	n	%	n	%	
Race/Color					
White	7	15.6	29	33.3	0.030
Non-white	38	84.4	58	66.7	
Schooling					
< 4 years	28	62.2	47	52.2	0.459
4 to 8 years	9	20.0	19	21.1	
> 8 years	8	17.8	24	26.7	
Socioeconomic classification					
Class A/B	5	11.1	15	16.9	0.610
Class C	31	68.9	60	67.4	
Class D/E	9	20.0	14	15.7	
Alcohol consumption					
Regular intake	16	35.6	12	13.3	0.009**
Sporadic intake	2	4.4	10	11.1	
Never drank/Does not drink currently	27	60.0	68	75.6	
Presence of drinking compulsion					
Drinking compulsion	16	35.6	8	8.9	< 0.001**
No compulsion	2	4.4	14	15.6	
Never drank/Does not drink currently	27	60.0	68	75.6	
Smoking					
Used to smoke but quit	13	28.9	34	37.8	0.060
Smokes currently	15	33.3	14	15.6	
Never smoke	17	37.8	42	46.7	
Other drug use					
Yes	3	6.7	1	1.1	0.110*
No	42	93.3	88	98.9	
Contact with people with TB					
Yes	21	56.8	21	25.0	0.001
No	16	43.2	63	75.0	
Type of contact					
Family	14	66.7	13	61.9	0.420**
Friendship	3	14.3	6	28.6	
Work	4	19.0	2	9.5	
Medication for diabetes					
Oral hypoglycemic	22	48.9	59	65.6	0.062
Oral hypoglycemic and Insulin	23	51.1	31	34.4	

* Fisher's exact test. ** Maximum likelihood ratio.

ness is linked to the individual's poverty conditions[17]. Possibly, the sample universe from which the study population was extracted, that is, users of the municipal basic health units may have leveled the socioeconomic condition across the two groups. All but 70% of the two groups belonged to socioeconomic class C.

A meta-analysis study with standardized research from 14 high TB-burden countries, including Brazil, showed that the combination of smoking, alcohol and low body mass index is associated with a three to four fold increased risk of development of active TB in diabetics. The study also showed a dose-response relationship of these conditions, evidencing that lifestyle predisposes diabetics to TB and the importance of its consideration in this population[18].

Smoking, although selected for inclusion in

Table 2. Bivariate analysis and descriptive measures of clinical characteristics of diabetes mellitus according to the groups. Vitória, Espírito Santo, Brazil, 2007 to 2013.

Variables	Group	n Case (n = 45) Control (n = 90)	Minimum	Maximum	Median	Mean	SD	p-value
Age	Case	45	24	88	54.00	55.49	11.85	0.371 *
	Control	90	25	90	56.50	57.36	11.17	
Time of diabetes mellitus in years	Case	45	1	50	9.00	13.22	10.77	0.084 **
	Control	90	1	50	8.00	10.41	9.58	
Number of complications due to diabetes mellitus	Case	45	0	5	1.00	1.00	1.07	0.236 **
	Control	90	0	4	0.00	0.83	1.07	
Number of comorbidities	Case	45	0	3	1.00	1.04	0.80	0.596 **
	Control	90	0	3	1.00	0.97	0.66	
HbA1c [1]	Case	45	4.95	14,80	8.60	8.81	2.32	0.034 **
	Control	85	5.21	13,30	7.60	7,86	1.83	
Fasting blood sugar	Case	45	91.38	444.25	174.53	195.12	77.96	<0.001 **
	Control	90	80.50	248.55	138.16	145.04	36.92	
HbA1c1 before TB	Case	22	5.70	12.69	9.58	9.43	2.06	0.002 **
	Control	85	5.21	13,30	7.60	7,86	1.83	
Fasting blood sugar before TB	Case	31	74.00	338.00	192.50	193.17	1.83	0.001 **
	Control	90	80.50	248.55	138.16	145.04	36.92	
HbA1c1 after TB	Case	39	4.95	13,30	8.17	8.36	2.30	0.363 **
	Control	85	5.21	13,30	7.60	7,86	1.83	
Fasting blood sugar after TB	Case	40	90.90	736.60	166.96	199.64	118.59	0.003 **
	Control	90	80.50	248.55	138.16	145.04	36.92	

* T-test for means. ** Mann-Whitney test. 1 HbA1c - Glycosylated hemoglobin.

Table 3. Factors associated with the presence of tuberculosis in diabetics. Vitória, Espírito Santo, Brazil, 2007 to 2013.

Variables	Multivariate analysis		
	p-value	Adjusted OR	95% CI
Drinking			
Regular intake	0.001	6.612	2,151 - 20,330
Sporadic intake	0.346	0.308	0.027 - 3.563
Never drank/ Does not drink currently	-	-	-
Contact with person with tuberculosis			
Yes	0.003	4.418	1.678 – 11.631
No	-	-	-
Fasting blood sugar (mean from	0.000	1.017	1.007 - 1.026

the logistic regression model, was established as non-significant after adjusting for confounding variables. It is reiterated that the power of the test indicated that the number of cases was insufficient for studying this variable.

On the other hand, a study in Taiwan with a cohort of diabetics showed that smoking increases twice the risk of becoming ill with TB[19], and the possible mechanisms that increase an individual's susceptibility to develop TB due to smoking include a decrease in the immune response due to the dysfunction of ciliary mechanics on the surface of the tracheobronchial mucosa, due to defects in the immunological response of macrophages, and the reduction of CD4 levels[20].

Among the factors related to diabetics' lifestyle, regular drinking is one of the factors that negatively influences adherence to drug treatment, contributing to poor glycemic control and predisposing to complications[21]. In addition, excessive alcohol users are immunologically compromised, which increases the risk of contracting TB as well as the reactivation of latent TB. Although alcohol provides calories, without nutritional support it predisposes to gastric problems,

which in turn generate inappetence, aggravating the individual's nutritional status[22]. It can be explained by suppression of monocytes' ability to produce cytokines, which directly inhibit bacterial growth and play a key role in cell communication, activation, proliferation and migration, as well as regulation of inflammation and healing mechanisms[23].

Regarding the association between having had contact with a person infected with TB and the development of TB, shown in this study, other studies reiterate these results. In a cross-sectional study, diabetics living with relatives with TB were more positive reactors (≥ 5mm) to the tuberculin test, suggestive of latent TB infection, as compared to diabetics othrwise[24]. On the other hand, a retrospective cohort showed that individuals who had contact with people with TB were six times more likely to develop TB within two years when the tuberculin skin test ≥ 5mm[25].

Regarding the clinical characteristics of DM, although the cases had a longer time of DM diagnosis and more complications resulting from irregular glycemic control, the groups were similar. The controls, however, used oral hypoglycemics more, whereas the cases, oral hypoglycemic and insulin concomitantly, which suggests the need for more than one class of medication to achieve glycemic control. Studies show that the risk of TB is three times higher in those with DM complications[19,26], and that diabetic patients with TB have a longer time of DM diagnosis and use insulin combined with oral hypoglycemic more than diabetics without TB[27]. However, in this study, these variables were similar across the groups.

Another variable that showed an association between DM and TB was altered fasting blood sugar. As fasting blood glucose increases by 1 mg/dl, there is a 1.017-fold increase in the chance of diabetics developing TB. An observational study identified that the DM and TB group showed significantly higher levels of HbA1c and postprandial blood sugar, which indicates worse glycemic control compared to diabetics without TB. Fasting blood sugar was also higher in the group with TB, but without a significant difference between the groups[27].

An *in vitro* study to investigate the association between *Mycobacterium tuberculosis* and monocytes in diabetics' and non-diabetics' blood without a history of TB has shown that diabetics have higher HbA1c (> 6.5%) and fasting glucose (≥126 mg/dl) levels. In addition, the identification of *Mycobacterium* by monocytes is weaker in diabetics favoring bacterial replication[28].

One of the justifications for increased susceptibility to TB would be the dysfunctional innate and adaptive immune response in diabetics related to the cumulative effect of chronic hyperglycemia, similar to what occurs in other diabetic complications[29,30].

For the higher HbA1c levels (≥ 8.5%), the contribution of fasting blood sugar is preponderant. Both are complementary and very important for assessing glycemic control during treatment, providing different information on glucose levels[15].

This is the first case-control study, according to a literature review, that considers fasting blood sugar and Hb1Ac measured more than once over the years, despite the irregularity of this glycemic control in the periodicity of its verification. Another important aspect in this study is the relationship of data from three information systems – SINAN, RBE and SISFAR – which allowed a better classification of cases and controls.

Limitations of this study consist of a possible memory bias, since exposure is easier to remember by the cases when illness is prior to data collection, and losses of individuals with TB enrolled in SINAN who could not be confirmed as for the DM diagnosis. Possibly some patients with TB resided in another municipality and received treatment in Vitória, ES, while others had to use the private health network for the treatment of DM or there were inconsistencies in health information systems, a fact that could be mitigated by the use of a protocol for confirmation or diagnosis of DM, such as the one already established between TB and AIDS programs.

This study shows that the lifestyle expressed by regular drinking, previous contact with a person with TB, and elevated fasting blood sugar are factors associated with TB in diabetics. Because the habit of drinking regularly increases diabetics' chance of contracting TB, rapid interventions and specific services are essential for a comprehensive and continued care and attention to people with needs resulting from alcohol and other drug use. In this sense, it is important to implement integrative and health promotion policies that support diabetics and their families in the search for coping strategies and adherence to treatment, since the consequences of alcohol use place drinking as at least a supplementary factor or mediator between health problems, such as DM and TB comorbidity. Previous contact with people with TB was associated with TB infection, which makes this type of diabetic monitoring important, that is, the screening of latent infection and respiratory symptoms. These measures

could diagnose TB cases early and disrupt the disease transmission cycle. Fasting blood sugar, a differential factor in this study, presented a discrete odds ratio, but showed that dysfunction of the cellular immunity in diabetics, triggered by poor glycemic control, is the best explanation for the development of active TB in this population. This finding reiterates the importance of monitoring the variability of glycemic levels in diabetics, considering the regularity of the periodic exams that are part of the clinical guidelines for the treatment of DM. These results reinforce the complexity of DM and TB comorbidity, since this association involves three aspects – lifestyle, TB exposure and clinical characteristics of DM. We thus highlight the need for integration between TB and DM programs as well as intensification of health promoting actions.

Collaborations

ML Leal carried out the conception and design of the study, data collection analysis and interpretation, and writing of the article; she is responsible for the accuracy and integrity of any part of the work. ELN Maciel contributed with data analysis and interpretation and in the relevant critical review of the intellectual content. NV Cade participated in the conception and design of the study and contributed in data analysis and interpretation and critical-intellectual review of the article.

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