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Clinical-epidemiological characterization of tuberculosis/diabetes comorbidity: integrative review

Caracterização clínico-epidemiológica da comorbidade tuberculose/diabetes mellitus: revisão integrativa

Caracterización clínico-epidemiológica de la comorbilidad tuberculosis/diabetes: revisión integradora

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ABSTRACT
Objective: to summarize the scientific evidence from sociodemographic characteristics, epidemiological indicators of morbidity, and clinical manifestations of cases of tuberculosis associated with diabetes mellitus. **Method:** this integrative review searched for literature in the Scopus, Latin American and Caribbean Health Sciences Literature, and Medical Literature Analysis and Retrieval System Online databases, and in the National Library of Medicine, Virtual Health Library Brazil and Scientific Electronic Library Online portals. The final sample comprised of sixteen studies. **Results:** the high prevalence of diabetes was found to contribute to the increase in tuberculosis cases. Patients with comorbidity tended to be older, female and with lower family income. Diabetes affects the severity of pulmonary tuberculosis adversely, causing more severe symptoms. **Conclusion:** the evidence found has the potential to guide health interventions and enable more effective health actions to be implemented.
Descriptors: Epidemiology; Tuberculosis; Diabetes Mellitus; Comorbidity.

RESUMO
Objetivo: sintetizar as evidências científicas acerca de características sociodemográficas, indicadores epidemiológicos de morbidade e manifestações clínicas dos casos associados de tuberculose e diabetes mellitus. **Método:** revisão integrativa da literatura com buscas realizadas nas bases Scopus, Literatura Latino Americana e do Caribe em Ciências da Saúde, *Medical Literature Analysis and Retrieval System Online* e nos portais *National Library of Medicine*, Biblioteca Virtual em Saúde Brasil e *Scientific Eletronic Library Online*, sendo a amostra final foi composta por dezesseis estudos. **Resultados:** observou-se que a alta prevalência de diabetes contribui para o aumento dos casos de tuberculose. Os pacientes com a comorbidade tendem a apresentar idade avançada, serem do sexo feminino e possuírem renda familiar mais baixa. O diabetes afeta negativamente a gravidade da tuberculose pulmonar, provocando sintomas mais graves. **Conclusão:** as evidências apontadas têm potencial para guiar as intervenções em saúde e possibilitam a implementação de ações de saúde mais efetivas.
Descritores: Epidemiologia; Tuberculose; Diabetes Mellitus; Comorbidade.

RESUMEN
Objetivo: resumir la evidencia científica a partir de características sociodemográficas, indicadores epidemiológicos de morbilidad y manifestaciones clínicas de los casos de tuberculosis asociados a diabetes mellitus. **Método:** esta revisión integradora buscó literatura en las bases de datos Scopus, Latin American and Caribbean Health Sciences Literature y Medical Literature Analysis and Retrieval System Online, y en los portales National Library of Medicine, Virtual Health Library Brasil y Scientific Electronic Library Online. La muestra final estuvo compuesta por dieciséis estudios. **Resultados:** se encontró que la alta prevalencia de diabetes contribuyó al aumento de casos de tuberculosis. Los pacientes con comorbilidad tendían a ser mayores, mujeres y con menores ingresos familiares. La diabetes afecta negativamente la gravedad de la tuberculosis pulmonar, provocando síntomas más graves. **Conclusión:** la evidencia encontrada tiene el potencial de orientar las intervenciones de salud y permitir la implementación de acciones de salud más efectivas.
Descriptores: Epidemología; Tuberculosis; Diabetes Mellitus; Comorbilidad.

INTRODUCTION

The epidemiological panorama of tuberculosis (TB) is impacting in terms of public health, since data from the World Health Organization (WHO), in 2017, revealed the existence of 10 million people with TB and 1.6 million deaths, in addition to one third of the population being infected and presenting a 10% chance of developing the disease throughout life[1].

The greatest risk of illness from TB is in the first two years after the first infection, but the latency period can extend to decades and some factors related to the immune system can increase the risk of illness, among them: human immunodeficiency virus (HIV) infection, immunosuppressive diseases or treatments, age (under 2 years old or over 60 years old), and diabetes mellitus (DM)[2].

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DM stands out as a metabolic disease of multi-factorial origin, characterized by high blood glucose levels, in addition to weakening the individuals' immune system, leaving them more susceptible to infections. And, like TB, it is also a Public Health[3] priority, being associated with several complications such as stroke, cardiovascular disease, kidney failure, and chronic wound[4]. Specifically in the year 2019, it was estimated that there were 463 million people worldwide with DM and approximately 4.2 million deaths worldwide were attributed to this disease[5].

It is noted that people with DM are nearly three times more likely to develop active TB and, even when they undergo appropriate treatment, there is an increased risk of reinfection or death[2,6]. It is also added that the spatial distribution of this comorbidity in the world can be explained by sociodemographic and economic factors because there is a strong relationship between diseases and social conditions and health determinants[7,8]. Furthermore, the current evidence suggests that, in addition to individual and social risk factors, ecological, geographic, climatic and socioeconomic factors increase the prevalence of comorbidity[6,8].

In this perspective, the information about sociodemographic, clinical characteristics and epidemiological indicators of morbidity (incidence and prevalence) of the associated cases of TB and DM allows understanding its dynamics in space and space-time and the associations with the local characteristics[9], indicating areas and populations susceptible to its occurrence.

It is emphasized that such information can contribute for the health professionals and services to promote better control of the comorbidity, as they serve as an instrument to assist in the management and planning of health strategies aimed at the control and prevention of diseases[10]. Thus, the need to update and expand knowledge is evident, through the analysis of the literature and the inclusion of studies that show the TB/DM association.

The aim of the present study was to synthesize the evidence about sociodemographic characteristics, epidemiological indicators of morbidity and clinical manifestations and the associated cases of TB and DM.

METHOD

This is an integrative review, a method that aims to provide a comprehensive view on a given theme, in order to better understand a worrying phenomenon[11]. For its elaboration, these stages were followed: elaboration of the research question, search for data in the literature, data evaluation, data analysis, and presentation of results.

To guide data collection, the PICo strategy (Population or problem, Interest and Context) was used. The Problem (P) covered TB/DM comorbidity; the Interest (I), sociodemographic characteristics, epidemiological indicators of morbidity, and clinical manifestations; and the Context (Co) referred to the studies conducted worldwide[12]. Thus, the following guiding question was established: "What scientific evidence is available in the literature on sociodemographic characteristics, epidemiological indicators of morbidity, and clinical manifestations of the TB/DM comorbidity in the world?"

The literature search took place in August 2020 in the Scopus, Latin American and Caribbean Health Sciences Literature (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE) databases through the Brazilian Virtual Health Library (*Biblioteca Virtual em Saúde*, BVS) portal and the Scientific Electronic Library Online (SciELO). The following Descriptors in Health Sciences (*Descritores em Ciências da Saúde*, DeCS) were used: "*Tuberculose*", "*Diabetes Mellitus*", "*Epidemiologia*", and "*Sinais e Sintomas*". Their English counterparts from the Medical Subject Headings (MeSH) of the National Library were also crossed: "Tuberculosis", "Diabetes Mellitus", "Epidemiology", and "Signs and Symptoms". The descriptors were combined using the Boolean operators AND and OR. The crossings were performed as follows: *("Tuberculosis*" AND *"Diabetes Mellitus"*) AND ("*Epidemiology*" OR "*Signs and Symptoms*").

For the selection of studies, the following inclusion criteria were adopted: original scientific articles, available free of charge in full, in Portuguese, English or Spanish, without time limits. Editorials, letters to the editor, abstracts, expert opinion, reviews, books, book chapters, theses and dissertations were excluded.

The studies were pre-selected by means of a thorough reading of the titles and abstracts to identify those that were related to the guiding question of the review and to the inclusion and exclusion criteria adopted. The search strategy was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13].

For the analysis and extraction of the data, a validated instrument was used, which includes the data related to the identification of the article, place of the study, methodological characteristics, and evaluation of scientific rigor[14].

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In the study evaluation stage, scientific rigor was analyzed considering the research design of each study to identify the level of evidence, based on the evidence classification system that categorizes the studies hierarchically according to the methodological approach[15]. This choice was based on this system providing subsidies for critical evaluation of studies carried out for decision making regarding the implementation of scientific evidence in clinical practice. Thus, the articles were classified into: I– Those that presented evidence from systematic reviews or meta-analysis of relevant clinical trials; II– Evidence derived from at least one well-designed randomized controlled clinical trial; III– Well-designed clinical trials without randomization; IV– Well-designed cohort and case-control studies; V– Systematic review of descriptive and qualitative studies; VI– Evidence derived from a single descriptive or qualitative study; and VII– Opinion of authorities or report of expert committees. It is noteworthy that evidence of levels I and II are considered strong; levels III to V, moderate; and VI to VII, weak[15].

RESULTS

From the criteria established for the integrative review, 16 studies were selected, published between 2009 and 2020. The results found in the search are shown in the flowchart (Figure 1), adapted from PRISMA[13].

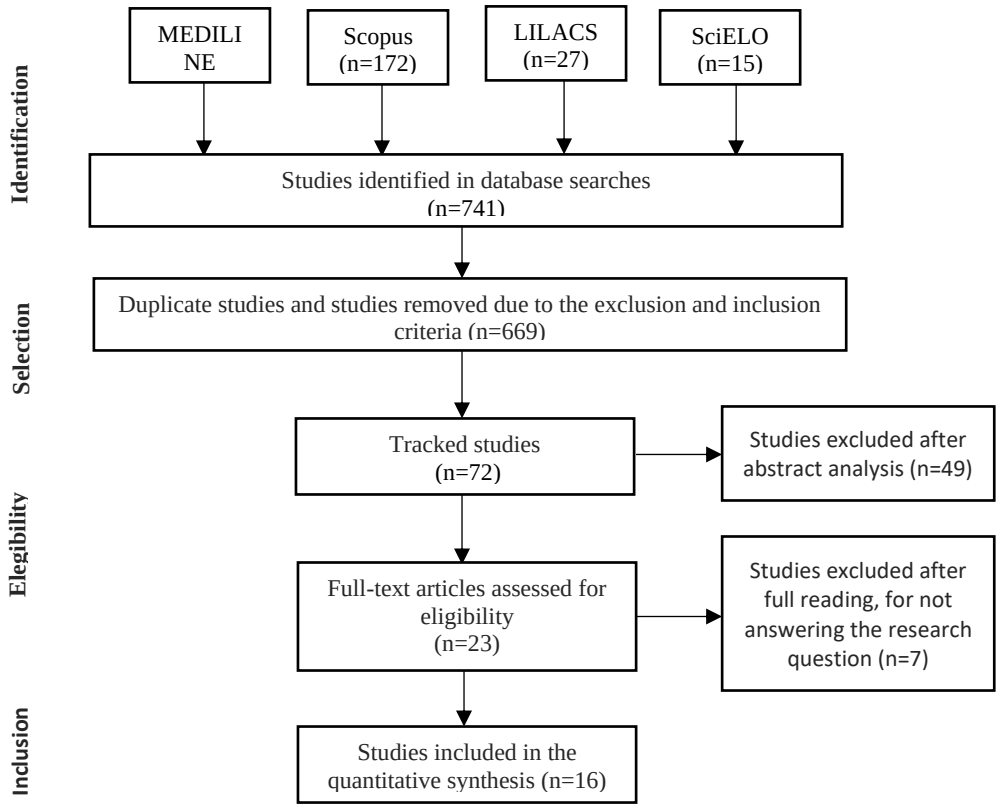

FIGURE 1: Selection of the studies found flowchart. São Luís, MA, Brazil, 2020

The absolute majority (93.7%) of the research aimed to describe and compare the clinical and epidemiological characteristics of patients with TB and DM, and only one article addressed the theme of spatial analysis.

Regarding the setting of the studies, it is noteworthy that six were carried out in Brazil[16-21], three in Mexico[22-24] and the others in India[24], Ethiopia[26], Spain[27], China[28], Chile[29] and Turkey[30], with only one analyzing estimates from several countries[31].

As for the level of evidence, seven (43.7%) were classified as level IV, five of which were retrospective cohort studies and two of prospective cohort, and 9 (56.25%) were classified as level VI, involving most studies of a cross-sectional nature, demonstrating that the eligible studies were classified with moderate and weak evidence.

Considering the epidemiological indicators of morbidity, the studies revealed that some regions of the world with a high prevalence of DM had a higher incidence of TB[18,20,21,26,27,29-31]. The prevalence of TB among the patients with DM was higher than in the general population[18,26,31] and one study pointed out that the patients with DM were more likely to have TB[18].

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In the case of the sociodemographic characteristics of the cases, comorbidity was associated with advanced age[16-22,24-27,30], female gender[16-18,24-26,29] and low family income[18,25].

Regarding the clinical aspects, comorbid patients had more severe symptoms than those without DM, the following being more frequent: cough, sputum, hemoptysis, fever, fatigue, night sweats, weakness, diarrhea, headache, leg pain, and malaise[18,19]. In addition, they were more likely to have cavity patterns on chest X-ray, smear-positivity[17,19,21,22,27-28,30], delay in sputum conversion[19-22], treatment failure[16,24,26] and greater chance of developing multidrug-resistant tuberculosis (MDR-TB)[16].

It was also evidenced that there is spatial aggregation of patients with DM/TB around the health center where they received care[23]. Figures 2 and 3 highlight the authors, countries where the studies were carried out, and levels of evidence, as well as the objectives and main findings in the selected studies.

Authors / Place	Level of Evidence	Population (N) and/or Sample (n)	Objectives	Main Findings
Evangelista et al, Brazil, 2020[16]	IV	Cases notified to the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificações*, SINAN) (N=709,429).	To know the clinical-epidemiological situation of the reported cases of TB/DM by age group in Brazil.	TB/DM comorbidity was found in 6.0% of the cases, mainly in men aged 18 to 59 years old, although adolescent and older women have a greater chance of having TB/DM. An increase in MDR-TB was observed in all age groups among the patients with TBDM.
Abreu et al, Brazil, 2020[17]	IV	Tuberculosis and diabetes cases reported in the national databases of Sinan and Hiperdia (N=338,825)	To analyze the sociodemographic profile and the characteristics of the diagnosis and treatment of tuberculosis cases with and without diabetes in Brazil.	Comorbidity was found in 7.2% of the cases. There was an association with females, aged 40–59 and ≥ 60 years old, and a smear positive result.
Leal et al, Brazil, 2017[18]	VI	Individuals undergoing treatment for tuberculosis in Salvador (n=323).	To describe and compare the clinical and epidemiological characteristics of patients with TB, with and without diabetes.	The prevalence of comorbidity was 14.6%, this group was older, had a higher schooling level and a lower family income. The patients had slow wound healing, fatigue, body aches and a longer mean duration of fever and other symptoms.
Gil-Santana et al, Brazil, 2016[19]	IV	TB cases treated at the IBT (N=408).	To compare the clinical presentation and outcomes of TB in diabetic and non-diabetic patients treated at primary care reference centers in a highly endemic area of TB in Brazil.	The DM patients were older, had a higher frequency of coughing, night sweating, hemoptysis and malaise and a higher frequency of smear-positivity. The greater severity of TB was associated with the TB-diabetes comorbidity.
Reis-Santos et al, Brazil, 2014[20]	VI	TB cases reported to the SINAN (N = 990,017).	To evaluate the sociodemographic and clinical factors that can influence the result of TB in patients with DM.	The chance of death was greater for individuals aged 60 years old, institutionalized in shelters, alcoholics, HIV/AIDS, pulmonary and extrapulmonary TB, with an unknown type of treatment.
Reis-Santos et al, Brazil, 2013[21]	VI	TB cases reported to the SINAN (N = 84,691).	To evaluate the sociodemographic and clinical differences in TB patients with and without DM.	The individuals with TB/DM were older, had an initial smear positive test and were more likely to die from TB, less likely to have been institutionalized, more likely to develop extra-pulmonary TB and return to TB treatment after abandonment.

IBIT = Brazilian Institute for Tuberculosis Research (*Instituto Brasileiro para Investigação da Tuberculose*) in Salvador; SINAN = Notifiable Diseases Information System (*Notifiable Diseases Information System*); MDR-TB = Multidrug-Resistant Tuberculosis.
FIGURE 2: Distribution of the national articles included in the review. São Luís, MA, Brazil, 2020

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Authors / Place	Level of Evidence	Population (N) and/or Sample (n)	Objectives	Main Findings
Jiménez-Corona et al, Mexico, 2012[22]	IV	Individuals with tuberculosis in southern Mexico (n=1262)	To determine the clinical consequences of pulmonary tuberculosis (PTB) among patients with DM.	The prevalence of DM was 29.63%. Comorbid patients had more severe clinical manifestations such as: cavities of any size on chest X-ray, delayed sputum conversion, greater probability of treatment failure, recurrence and relapse.
Blanco-Guillot et al, Mexico, 2018[23]	IV	Individuals with pulmonary TB registered in the National Tuberculosis Registry (n=1105).	To test the hypothesis that DM and PTB occur in spatial and molecular aggregations.	Molecular grouping and spatial aggregation of patients with DM and TB were identified.
Delgado-Sánchez et al, Mexico, 2015[24]	VI	Pulmonary TB cases contained in the National Tuberculosis Registry (N=181,378).	To describe the clinical conditions of pulmonary TB associated and not associated with DM and the compilation of treatment outcomes in patients with and without DM.	The incidence values of pulmonary TB associated with DM increased, in contrast to the rates of pulmonary TB without DM, which decreased. TB/DM patients were more likely to be women, older adults, residents of the urban region, and were more likely to experience therapeutic failure.
Pande et al, India, 2019[25]	IV	Hospitalized adults diagnosed with pulmonary TB (PTB) or extrapulmonary TB	To estimate the prevalence of DM in adult hospitalized TB patients and to evaluate the factors associated with a higher prevalence of DM among TB patients.	The overall prevalence of DM among the TB patients was 25.3%. TB patients over the age of 41 were more likely to have DM. Women were less likely to have DM than male TB patients.
Workneh et al, Ethiopia, 2016[26]	VI	Newly diagnosed TB patients attending a treatment clinic (n=1314).	To determine the prevalence and analyze the factors associated with the TB and DM comorbidity in the Southeastern Amhara region, Ethiopia.	The prevalence of DM was estimated at 8.3% among the TB patients. The factors associated with the TB-DM comorbidity were female gender, age over 41 years old, pulmonary TB and a family history of DM.
Moreno-Martínez el al, Spain, 2015[27]	VI	Cases diagnosed with active TB detected by the Tuberculosis Prevention and Control Program (N=5,849).	To analyze the prevalence of DM and its associated factors in adults with TB in a large city of an industrialized country.	The prevalence values varied between 4.0% and 7.2%. The factors associated with TB/DM were the following: born in Spain, age over 40 and cavity patterns on chest X-ray.
Hongguan et al, China, 2014[28]	IV	Individuals with pulmonary TB enrolled in the Beijing TB control program (n=1,126).	To explore the impact of DM on the clinical presentation and in the treatment outcome for pulmonary tuberculosis (PTB) in China.	DM was associated with a higher proportion of smear-positivity, a higher proportion of lung cavities and the following symptoms: cough, sputum, hemoptysis, night sweats and weakness.
Herrera et al, Chile, 2013[29]	VI	Tuberculosis cases reported in the National Tuberculosis Registry of a metropolitan region (N=821).	To determine the prevalence of DM among the TB cases diagnosed in 2012 in the metropolitan area of Santiago, Chile, and to estimate the association of these two diseases.	The prevalence of DM was 15.6%. The estimated incidence rate of TB among the diabetic population is 1.7 times higher than in the general population of the region.
Tatar et al, Turkey, 2009[30]	VI	TB cases registered in the Esrefpasa Tuberculosis Dispensary in Izmir, Turkey (N=1,063).	To evaluate the characteristics of TB in diabetics in the region.	The prevalence was 7.3% of TB in patients with DM. Cavity formation and atypical localization were more commonly found in diabetics, in addition to longer treatment duration and drug resistance rate.
Badawi et al, The World, 2014[31]	VI	Estimates of incidence and prevalence of TB and DM in 196 countries.	To examine the global relationship between the prevalence of DM and the incidence of TB to assess their coexistence worldwide.	Countries with a high prevalence of DM showed a significant association with the incidence of TB.

FIGURE 3: Distribution of the international articles included in the review. São Luís, MA, Brazil, 2020

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DISCUSSION

The studies selected in this review indicated that there is a positive association between the prevalence of DM and high rates of TB[18,20-23,26,27,29,31]. Corroborating these findings, patients with DM are at a higher risk of contracting TB, with consistent evidence of a two to four times increase in the risk of developing TB[32].

It was shown that DM has an impact on the TB rates in some countries, especially in those with a high prevalence of DM, greater than 7.6%[31], such as Mexico (33%)[23], India (24.3%)[25] and Brazil (14.6%)[18]. This finding was verified in other studies, in which it is shown that developing or underdeveloped countries had a high prevalence of comorbidity, as in the studies carried out in Nigeria (9.4%)[8] and Peru (11.1%)[33].

In this review, most of the studies pointed out that advanced age was associated with the TB/DM comorbidity[16-22,24-27,29], possibly due to the fact that there is a decline in the immune status and physiological changes with advancing age, which favors both the aggravations caused by chronic non-communicable diseases, as well as infectious diseases[34]. Changes in the pulmonary function and mucociliary clearance in older adults may favor a reactivation of Koch's bacillus that, associated with immunosuppression caused by DM, contributes to the development of tuberculous lesions[35].

In addition, the incidence of TB in the age group above 40 years old coincides with DM, which makes age a risk factor for patients with both diseases, since the association between TB/DM provides the occurrence of more severe clinical signs in a TB patient[18,35]. And this risk mainly affects females, since women over 60 are 41% more likely to have DM than women in other age groups[16].

Related to this, there was an association between the occurrence of comorbidity and the female gender[16,24], which presented 1.7 times more chances to have the comorbidity when compared to the male gender[26]. It was pointed out that the prevalence of 19.1% among women with diabetes was higher than in the general population[29].

Females have a higher prevalence of DM, possibly related to gender issues, as men have a greater lack of knowledge about the diagnosis of the disease and commonly attend the health services less frequently, unlike women, who manage family health care and periodically access the health services[36].

Furthermore, it is pointed out that the chance of diabetes being a risk factor among women with tuberculosis is greater than for men[29]. This can be related to the misuse of the health services, the care of women with the patients and the influence of estrogen on the inhibition of cytokines that causes an immunosuppressive effect potentiated by DM; such factors increase the vulnerability of women to DM and, consequently, to TB[26].

The eligible studies revealed a strong relationship between TB and unfavorable socioeconomic conditions, since the concentration of cases in certain regions is related to poor housing conditions, such as poorly ventilated houses and urban areas, factors that determine the influence of poverty on the transmission of *Mycobacterium tuberculosis*[9,18].

Collaborating with such data, it was shown that patients with DM in low or middle income countries in Asia, in a scenario of high incidence rate for TB, had a higher risk of TB than patients with DM in high-income countries, such as in the Europe region and in the United States and Canada[32].

Regarding the clinical aspects, patients with comorbidity showed more severe signs and symptoms, considering that DM is one of the risk factors for the development of infections, due to the decline in the immune response, as it affects the body's defense cells: the phagocytic cells (macrophages and lymphocytes). In addition, low insulin levels and hyperglycemia negatively contribute to the control of TB bacilli, as they alter the chemotactic function, phagocytosis and antigen presentation[3,37]

It should be noted that the frequency of fever was three times higher among patients with TB and DM, this fact is due to the high bacterial load and slower time in the smear-negativation after the start of the treatment[19].

Regarding the occurrence of lung cavities and smear-positivity, a number of studies suggest that a higher rate of positivity to the smear is associated with greater formation of cavities and greater lung damage due to DM[19,29]. Furthermore, the recovery of lung injuries occurs more slowly in the group of diabetic patients when compared to non-diabetics[18].

In this perspective, it is pointed out that the radiological examination may present alterations considered atypical and that the pulmonary cavities are more frequent in a patient with the comorbidity[38], as they present a greater bacillary load and longer time in the conversion of the culture, which increases the risk of recurrence and death in these patients[19].

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Regarding treatment failure, the findings of this review are consistent with a study that investigated resistance to the TB treatment and verified that diabetic patients developed drug resistance more frequently in the treatment of TB[39].

It is worth mentioning that ecological studies contribute to the analysis of socio-environmental risks and the identification of areas most vulnerable to the occurrence of comorbidity[8]. Some studies have shown the spatial distribution of TB[9,10] and DM[40] in isolation but, when considering TB infection in association with DM, the literature is scarce on the theme.

A study carried out in a region of Mexico with a higher incidence of TB and a high prevalence of DM, using the global Moran analysis, showed a non-random distribution among patients with TB and DM who were geospatially aggregated around the health center where they received health care[23].

It is noteworthy that the georeferencing technologies allow for the spatial and spatial-temporal analysis of TB/DM cases and provide a relevant contribution to public health, since the maps obtained reveal socioeconomic conditions relating them to the health-disease process in the territory[9]. Thus, it is suggested that scientific investigations be carried out with this approach so that there is a better understanding of the distribution of this comorbidity in the territory, considering the existing socio-spatial inequalities, with a view to directing strategic actions for health interventions.

It is worth mentioning that the studies on the distribution and sociodemographic characteristics of diseases are relevant, as they serve as tools that can guide health surveillance actions, assisting in the formulation of public policies[10]. In this sense, the synthesis of information contained in the literature about the clinical and epidemiological characteristics of the TB/DM comorbidity carried out through this integrative review, contributes to evidence-based practice by favoring the link between theory and practice[11], highlighting important points to be rethought and directed to the clinical management, control and surveillance of the comorbidity.

It should also be noted that most of the selected studies were classified with moderate and weak levels of evidence. It is important to emphasize that the changes and the basis of the care practice are based on the production of scientific knowledge; therefore, studies with the best levels of evidence are indispensable and essential for the health services[11-15]. Thus, it is suggested that studies with strong evidence, such as randomized clinical trials, be developed, especially in TB endemic regions with high prevalence rates of DM.

Study limitations

The limitations of this integrative review include the possibility of underreporting cases of comorbidity, as most of the studies used secondary data and, in the case of studies conducted in Brazil, the field of disease associated with TB in the notification forms is not mandatory to be filled in, which makes it impossible to have a reliable knowledge of the epidemiological situation of the comorbidity. It is also noteworthy the difficulty of accessing some restricted publications, only open access texts and available in full being included in the study. In addition, there was scarcity of articles addressing the spatial and spatio-temporal distribution of cases of TB/DM comorbidity and absence of studies with strong evidence levels.

CONCLUSION

The findings showed that DM negatively affects TB control, as it contributes to an increase in infection rates by *Mycobacterium tuberculosis* in some regions of the world, especially in developing countries, causing more severe symptoms of TB and hindering its treatment. In addition, this comorbidity is heterogeneously distributed in space, reaching groups of greater social vulnerability.

It is noteworthy that the implementation of measures aimed at controlling the growing epidemic of DM, focusing on the main risk factors, can have a beneficial influence on TB rates, especially in regions where there is a strong association between such conditions. Such pointed evidence has the potential to guide health interventions and enable the implementation of more effective health actions.

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