Tuberculosis and diabetes mellitus – an underappreciated association

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Abstract

The current review presents up-to-date knowledge on tuberculosis (TB) in diabetic patients. On the basis of available literature, there is little doubt about the close relationship between these two conditions. Diabetes mellitus in this association may still contribute substantially to the burden of TB and negatively affect control of the latter. Chronic hyperglycemia at least to some extent may alter the clinical manifestation, radiological appearance, treatment outcome and prognosis of TB. Although the pathogenesis is not clear, diabetes may impair both innate and adaptive immune responses to *Mycobacterium tuberculosis*. Eventually, effective screening and dual management of the diseases have to be addressed both in low- and high-income countries in order to limit the negative effects of the forthcoming global diabetes epidemic.

Key words: *Mycobacterium tuberculosis*, hyperglycemia, epidemic, screening.

Introduction

There is robust evidence to support an association between diabetes mellitus (DM) and tuberculosis (TB). A recent meta-analysis showed that DM increases the risk of TB development three-fold compared to non-diabetics [1]. This association was confirmed as early as in 1934, when Root found that adolescents with diabetes contracted tuberculosis ten times more frequently [2].

The absolute number of TB cases has been falling since 2006 and dropped at a rate of 2.2% between 2010 and 2011 [3]. The prevalence of diabetes is projected to double from 171 million in 2000 to 552 million patients in 2030 [4]. At the moment, the estimated number of diabetes cases is more than 371 million worldwide and over 3 million in Poland [4]. Half of people with diabetes are undiagnosed and the vast majority of the diabetic population lives in the 'developing world' countries which are well known to be endemic for TB. In view of the steady rise in diabetes worldwide, especially in these low-income countries, the importance of the TB-DM association cannot be overemphasized. In the year 2000 developing countries were expected to share around 67% of the global DM burden [4]. This proportion is predicted to rise to 78% in 2030. According to the newest data, the prevalence of DM in TB patients varies

from 5.7% in Nigeria to 16.3% in Thailand [5, 6]. Among these, 30–50% of patients had developed diabetes at TB diagnosis. These facts highlight the need to raise awareness on screening for DM in TB patients. The adverse effect of diabetes on TB outcomes has been recently proved [7]. With regard to the fact that the looming DM epidemic is a threat to TB control, adequate knowledge on the interaction of these two old disorders is critical. Consequently, we firmly believe that this topic is worth presenting and such a current update is highly desired. Without any doubt, it is an appropriate moment for such a review.

Our aim was to evaluate the literature and present a concise review on the following topics: the epidemiology of diabetes and tuberculosis from the global perspective, the effect of diabetes on clinical presentation of TB including its radiological presentation, various issues of treatment, its outcomes and prognosis. We also discuss the potential mechanisms by which diabetes may increase TB incidence. Data for this review were collected by a thorough search of PubMed combining 'tuberculosis' and 'diabetes mellitus' as free texts and MeSH terms. We added to these terms others such as 'clinical presentation', 'prognosis', 'risk factors', 'radiological', and 'treatment'. We also systematically checked full text papers referenced in retrieved articles. Of note, the first case-report was published back in 1917 [8].

In this review we discuss a few new issues relevant to the TB-DM association. Firstly, the risk of TB in DM patients in both high- and low-burden countries is addressed in a wide perspective. Next, we draw attention to the fact that this association should not be neglected and underappreciated any longer in low TB burden countries such as Poland. In fact, work published on TB-DM in Poland so far has been scarce. Another new issue is clearly an adverse DM impact on TB treatment as well as slightly different clinical features in diabetic patients. Finally, we also emphasize the need for close cooperation between diabetologists and respiratory specialists caring for TB patients. That is fundamental both for effective screening for both disorders and their successful therapy. Moreover, metabolic control seems to be the cornerstone to achieve satisfactory outcomes in TB treatment.

Epidemiology

Both diabetes and tuberculosis are well recognized for their huge global burdens. Nearly one-third of the world's population is infected with *M. tuberculosis* and about 10% is at risk of developing an active disease in their lifetime. At the same time, we are experiencing an increasing prevalence of diabetes alongside other noncommunicable diseases. There are numerous studies from different regions of the world supporting this association.

A country with one of the largest number of TB cases is India. In this highly endemic country, over 25% of TB patients were found to have diabetes and 24% pre-diabetes [9]. Altogether almost 50% of TB patients had some form of hyperglycemia. The odds ratio (OR) for diabetes was estimated as 3.06 (95% CI: 1.69–5.52, $p < 0.001$) and was especially high for positive smear patients. The risk factors for diabetes were similar to those in the general population such as increasing age, body mass index (BMI) category (18.5–22.9 kg/m^2), positive family history and sedentary occupation. Of interest, among TB patients with diabetes, almost 60% had been diagnosed with diabetes before. It is most likely that long-term diabetes has a negative effect on the immune response and may enhance TB morbidity. In another study from India, the number of TB patients needed to screen (NNS) to find one newly diagnosed diabetic case was 4 [10]. It was confirmed that nearly half of TB patients had diabetes, which was independently associated with male sex and age above 50 years. Around half of these patients were newly diagnosed during this study with HbA_{1c} (glycated hemoglobin) as a screening tool.

In another retrospective study from India, diabetes was found as the most frequent risk factor for pulmonary tuberculosis, far more common (30.9%) than classic risk factors for TB such as smoking (16.9%), alcoholism (12.6%), human immunodeficiency virus (HIV) (10.6%), malignancy (5.8%) as well as history of contact with TB (3.4%) and chronic corticosteroid therapy (2.9%) [11]. The strength of DM as a risk factor for TB appears to be equivalent to that of HIV infection. In a case-control study conducted in California, Pablos-Méndez *et al.* found that among Hispanics aged 25–54 the estimated risk due to DM was 25.2% whereas that due to HIV infection was 25.5% [12]. Higher risk for TB among diabetic patients was also confirmed in a Mexican study (prevalence of DM among TB patients: 39% in Texas and 36% in Mexico) [13]. Namely, diabetes contributed to TB five times more often than HIV infection (25% vs. 5%). It could be stated that the risk of TB due to DM seems to be smaller at the individual level compared with that of HIV infection (113–170-fold) [14]. However, it can also be said that at the population level the sheer numbers of diabetic patients are likely to have an equal or even greater effect. What is more, established risk factors for TB such as alcohol and drug abuse as well as HIV infection were found less frequently in the diabetic group [13, 15].

Although in Indonesia the prevalence of diabetes among TB patients is moderately low compared to India (13.2% vs. 30.9%), it is still strong-

ly associated with TB [16]. Tuberculosis patients were significantly leaner compared to the controls, but the adjustment for BMI increased even that risk. This suggests that the association might not be explained by differences in body weight. Patients with diabetes in Asia are generally leaner and younger than in Europe. However, in high-burden countries such as India the fall in BMI has the strongest adverse effect on TB incidence, especially among men living in rural areas [17]. Moreover, the increasing number of diabetes raised the annual TB prevalence in India by 46% from 1998 to 2008. It seems that the nutritional and demographic trends affect TB incidence more significantly in high- than in low-burden countries (India vs. Korea).

In Zambia, another country with a very high TB burden (462/100 000 population) [3], it was found that TB comorbidity was significantly associated with diabetes (OR = 6.5, 95% CI: 1.7–25.3) [18]. In Tanzania, the association was much stronger in HIV uninfected (OR = 4.2, 95% CI: 1.5–11.6) compared to HIV infected patients (OR = 0.1) after adjustment for age, sex, demographic factors and elevated serum acute phase reactants [19]. Actually, in such highly endemic regions for TB as Sub-Saharan Africa, there are very few studies exploring this issue. So far, the only available data were from a hospital-based study from Tanzania reporting an increased prevalence of DM among TB patients admitted to hospital (6.5% vs. 0.9% in the general population) [20]. According to a recent systematic review, diabetes is a serious burden in that region, with high proportions of undiagnosed diabetes reaching more than 40% in screening studies [21].

Conversely, in countries with a low TB burden such as Australia (5.8/100 000), TB risk in diabetic patients was increased only moderately (adjusted relative risk RR = 1.48; 95% CI: 1.04–2.10) [22]. Nevertheless, this association was much higher among patients on insulin (RR = 2.27; 95% CI: 1.41–3.66). The latter may be regarded as a marker of longer duration or poorly controlled type 2 diabetes. In a cohort study from Hong Kong, patients with well-managed diabetes (HbA_{1c} < 7%) had lower risk for TB (adjusted hazard ratio aHR = 0.68, 95% CI: 0.33–1.36) [23]. That finding suggests that hyperglycemia itself rather than DM diagnosis per se may play a role in the development of active TB. In contrast, patients with poor metabolic control (HbA_{1c} > 7%) were found to have a significantly raised TB risk (HR = 2.56, 95% CI: 1.95–3.35) adjusted for various confounding clinical and sociodemographic variables. In the Indian study, though not designed to address this issue, there was no difference in new and relapsed TB cases between various HbA_{1c} categories [9].

In the next country with low TB prevalence, the United Kingdom, TB rates due to DM varied greatly among ethnic minorities [24]. The highest frequency of TB due to DM (population attributable fraction) was found among Asian men and women, who have high risk of DM and comparatively high risk of TB (respectively: 19.6% and 14%). In general, according to this study around 11% of TB cases may be attributable to DM, with over a half in the Asian population and 8% in both the black and the white one. However, the age structure for TB among the black minority was significantly younger than in white patients. It reflects age-related differences in diabetes prevalence in the black population. In another UK study, the overall adjusted OR for TB in people with DM was found to be 3.8 (95% CI: 2.3–6.1) [25]. In contrast, in Denmark, a country with a low TB burden, OR for TB in diabetic patients after controlling for comorbidities such as cardiopulmonary disease was substantially lower (OR = 1.18, 95% CI: 0.96–1.45) [26]. There was no evidence for any connection between TB and hyperglycemia (OR = 1.18, 95% CI: 0.96–1.45).

The majority of studies have reported increased prevalence of TB among type 2, not type 1 diabetes. The former accounts for well over 90% of diabetes in Sub-Saharan Africa, with the population prevalence ranging from 1% in Uganda to 12% in Kenya [21]. Nonetheless, in highly endemic regions for TB such as South Africa it was reported that almost 30% of children and adolescents with type 1 diabetes had active TB [27]. In multivariate analysis, poor glycemic control and contact with an active TB case were associated significantly with TB diagnosis.

There is little doubt that it is diabetes predisposing to TB rather than TB infection leading to DM. Reports on increased incidence of diabetes among patients diagnosed first with TB are scarce [20]. Though in a study on community-acquired pneumonia and TB 10% of the latter patients were glucose intolerant and 9% had diabetes, these findings were reversible, secondary to infection and not specific to TB [28]. On the face of it, all patients had a normal glucose tolerance test 3 months and 2 years after the onset of treatment. In contrast to rather acute TB symptoms, diabetes is insidious and can persist unrecognized for years. Consequently, it is difficult to assess the accurate duration of DM due to often delayed diagnosis [18]. Diabetes is still more frequently diagnosed earlier than TB [9, 29]. That risk of developing TB is directly associated with HbA_{1c} [23]. To conclude, there is rather firm evidence that it is diabetes that precedes TB. Nonetheless, screening for any glucose impairment in TB patients has to be underscored [10].

Clinical course of tuberculosis in diabetes mellitus

There is some evidence to suggest that TB in diabetic patients may have a slightly different clinical manifestation. In fact, diabetes may modify TB symptoms, radiological findings, treatment, final outcomes and prognosis. There is still a lot of controversy about a genuine effect of DM on clinical presentation of TB.

Radiographic findings in tuberculosis diabetes mellitus patients

It is well known that atypical radiological localization of TB is more frequently seen in diabetics compared with non-diabetics. A typical site is defined as middle- and lower-zone involvement on a PA (posterior-anterior) chest radiogram. Tatar *et al.* found in a retrospective analysis of 1 063 TB cases in Turkey including a total of 78 (7.35%) DM patients that the latter presented with atypical images much more often [30]. Cavities and a wider range of pulmonary infiltration were found in diabetic patients more often as well. This observation was confirmed by Pérez-Guzmán *et al.* in a large sample of 192 diabetic tuberculous patients. He found an increased frequency of lower lesions in DM TB patients compared with the controls (19% vs. 7%, $p < 0.01$) [31]. Moreover, up to one-fifth of TB DM patients developed lesions only in the lower lung fields without affecting the upper ones. Such a radiological image may mask the diagnosis of TB with a consequent delay in appropriate treatment. Of note, multiple logistic regression showed that diabetes was the most important factor for lower lung lesions and cavities [31].

One possible explanation for this atypical presentation may be that in the elderly and diabetics increased alveolar oxygen pressure in the lower lobes promotes disease development in these areas. It is based on the concept that multiplication of *M. tuberculosis* is favored by high oxygen tension. The proportion of patients with lower lung lesions progressively increases with age ($r_s = 0.89$, $p < 0.01$) [32]. However, the frequency of cavities steadily decreases with age ($r_s = –0.79$, $p < 0.05$). A higher proportion of both cavities and lower lung lesions was still observed in the diabetic group in all age categories (almost always more than 70%). This observation was not due to a more prolonged course of diabetes as there was no relationship between the duration of symptoms of both TB and DM and the frequency of atypical lesions. Hence, diabetes and aging predispose to similar changes in patients with TB. In a study from Saudi Arabia lower lung field lesions as well as cavitary lesions were also significantly more common in DM TB than in the control group (respectively, 23% vs. 2% and 50% vs. 39%) [33].

By contrast, Hadlock *et al.* reported a much lower distribution of unusual radiographic findings in a diabetic population with TB (8.3%) [34]. The difference in that incidence compared with the non-diabetic TB population was slight and of marginal clinical significance. Of note, this review questioning the increased incidence of atypical radiological manifestation of TB in diabetic patients is relatively old. These conflicting observations may be partly due to varied patient selection. In a much more recent Indonesian study, diabetic patients were found to have fewer cavities, but after adjustment for other factors there was no association between DM TB and cavitary presentation [35]. Similarly, in a retrospective American study focused on treatment outcomes, no difference was found in cavitary disease in the TB DM vs. TB group (39% vs. 37%, $p = 0.88$) [36]. To conclude, it is much more likely that TB DM patients will present with lower lung lesions compared with nondiabetic patients. It is much less clear whether cavities are genuinely more common in this group of patients.

Influence of diabetes on manifestations and treatment of tuberculosis

There is a debate whether diabetes has a significant effect on the clinical presentation of TB. Patients with DM TB were found to be more symptomatic, with a symptom score > 4 out of 6 (cough, hemoptysis, dyspnea, fever, night sweats and weight loss), as well as to have lower performance status [35]. Such a presentation was not associated with more severe TB disease evaluating the sputum mycobacterial load, radiological findings, anemia and inflammatory markers. In a study from Turkey the only symptom more commonly found in diabetic patients was cough. That suggests that the distribution of symptoms is not seriously affected by diabetes [29]. Likewise, in a retrospective analysis of 692 TB patients no difference was found in presenting symptoms between the TB DM and control TB group [33]. The most common symptoms observed equally in both groups were low-grade fever and productive cough. Of interest, DM antedated TB infection by a mean period of 4 years [29]. In general, in almost half of the DM TB patients the duration of diabetes is less than 10 years [30]. Apart from that, it appears that the initial period of infection (from first presentation to commencement of therapy) in DM TB is shorter compared to the control group (2.6 vs. 4.5 months) [36]. That could be explained by the more extensive pulmonary involvement and more severe symptoms which are easily detectable.

However, what diabetes does seem to modify in the clinical course of TB is the sex distribution.

It is widely acknowledged that there is higher frequency of pulmonary TB in males. That is usually explained by the greater level of social activity predisposing them to higher transmission rate. Pérez-Guzmán *et al.* found that in TB DM there was a male predominance up to age 40 but from this point a steady decline in the percentage of males was found, resulting in a female predominance from age 50 onwards [37]. Intriguingly, diabetes does not affect the sex ratio in the age groups 15–29 and 30–39 years. This is supported by Restrepo *et al.*, who also found that DM TB patients were more likely to be older women [15]. This suggests that there are factors other than socio-culturally important ones for male domination in pulmonary non-diabetic TB. Moreover, diabetic patients with TB appear to be older than nondiabetics [30, 35].

The clinical manifestation of TB may be affected by diabetes with regard to higher BMI of these patients compared to nondiabetic TB subjects [35, 36]. In the vast majority of studies on TB DM diabetes was classified as type 2 (type 2 vs. type 1, respectively 96% vs. 3%) [38], which by definition is closely linked with obesity. On the other hand, Şahin *et al.* found in nondiabetic TB patients that a decrease in BMI was associated with elevated inflammatory markers as well as a more advanced radiological manifestation [39]. It is a well-recognized fact that weight loss in TB is evidently related to the acute phase response.

With respect to the bacteriological aspect of TB, there are conflicting reports. It is evident that these patients have a higher pretreatment bacillary load. Diabetes mellitus is an independent risk factor associated with more numerous acid-fast bacilli (AFB) on sputum smear examination [33, 36]. The immune suppression induced by DM could be responsible for a higher smear-positivity rate. Furthermore, that could be associated with wider lung damage due to TB in DM patients. On the other hand, after adjustment for such factors as BMI, age, sex, and duration of disease, DM was no longer significantly linked with mycobacterial load [35]. Similarly, Tatar *et al.* did not find a significant difference in smear positivity between these two groups, either [30].

Another effect of diabetes on TB course which has not been clarified is the response to treatment, in short- and long-term outcomes. Both positive sputum smear after 2 month-long treatment and positive culture at this point after adjustment for various factors such as age, sex and BMI were not associated with diabetes [35]. However, a significant relationship between diabetes and positive sputum culture was found after 6 months. In fact, more than twice as many diabetic patients had a culture result positive for *M. tuberculosis* at that time. The negative influence of diabetes on treatment response was confirmed by Restrepo *et al.*, who found that within 60 days the mycobacterial clearance was delayed by 5 days [15]. It was also found that diabetic patients are more than 4 times more likely to relapse after 2 years [38]. Finally, in a recent prospective study from Mexico, it was found that patients with TB and DM had a more severe clinical course [8]. They had more advanced clinical manifestations such as cavities on the chest X-ray, delayed sputum conversion and higher likelihood of failed treatment and recurrence (aHR = 1.83, 95% CI: 1.04–3.23). The majority of recurrent TB infections were caused by the same strain as the previous episode. These results show that indeed DM can exacerbate the clinical course of TB.

However, according to other authors the presence of diabetes did not affect treatment outcomes negatively [33]. Precisely, there was even a shorter mean time for smear conversion in DM TB (4.6 vs. 5.4 weeks, $p = 0.002$) as well as a higher rate of sputum conversion at the end of 3 months. Favorable outcomes such as cured/treatment completed as well as failure, death and default were comparable in both groups. Dooley *et al.* found that 2-month culture conversion proportions and odds of treatment failure were similar [36]. There was no difference in 2-month smear conversion between TB, DM TB and TB HIV groups [40]. These findings confirm that the current drug regime is effective in all these various groups of patients.

There are conflicting reports on the prevalence of drug resistance in diabetic patients. Zhang *et al.* found in a retrospective analysis of over 2000 patients that the frequency of multidrug-resistant TB was more than twice as high in diabetic patients (17% vs. 8%, $p < 0.01$) [38]. Likewise, Tatar *et al.* found drug resistance in 26% and in 5% in culture positive DM and non-DM cases, respectively [30]. Although both the duration of bacteriological conversion intervals and cure rates were the same, diabetic patients still required significantly longer (> 6 months) therapy to achieve a cure [30]. Conversely, Singla *et al.* found that there was actually lower frequency of drug resistance compared with the control group without diabetes (respectively, 6% vs. 16%, $p = 0.007$) [33].

Prognosis of diabetes mellitus tuberculosis patients

With respect to the long-term prognosis for these patients, diabetes is a risk factor for death. Diabetic TB patients had a higher mortality (7.5%) in comparison with TB only (1%) and DM only (2%) [29]. After adjustment for HIV status, age, weight and foreign birth, the odds for death were

6.5 times higher in DM patients (OR = 6.5; 95% CI: 1.1–38.0, p = 0.039) [37]. Diabetes is a poor prognostic factor for patients who developed TB earlier or concomitantly with lung cancer [41]. In addition, DM is an independent predictor of acute respiratory distress syndrome (ARDS) in miliary tuberculosis [42]. Such a negative influence of diabetes was not confirmed in one report [33].

These discrepancies in studies on DM effects on TB treatment as well as clinical course may be explained by either different levels of glycemic control or by ethnic origin of the study subjects. The former is rarely available, which makes comparison even more difficult. Patients with diabetes are included in such an analysis irrespectively of the classification of diabetes and antidiabetic therapy, making the diabetic population quite heterogeneous. Furthermore, it is not clear whether the reported increased mortality is due to TB severity or to DM-related comorbidities.

Anti-tuberculosis therapy in diabetic population

The treatment of tuberculosis in diabetic patients may be quite challenging due to the negative effect of poor metabolic control. The slow response to treatment can be explained by the altered pharmacokinetics of anti-TB drugs in diabetic patients. In one study the exposure to rifampicin during the continuation phase was strongly reduced in DM TB patients with poor metabolic control (HbA_{1c} 9.3%). Body weight, diabetes and hyperglycemia were strongly and inversely associated with rifampicin concentration [43]. In the following study there were no differences in the oral bioavailability and metabolism of anti-TB drugs in the intensive period of TB treatment despite unsatisfactory glycemic control (HbA_{1c} 11%) [44]. It may be explained that in the earlier study patients were not matched for BMI or gender, and it was conducted in the continuation phase with medications taken 3 times a week. Therefore, diabetes itself may not affect the pharmacokinetics of anti-TB drugs at least in the intensive phase. On the other hand, higher BMI in diabetic patients may have a negative effect on the pharmacokinetics of drugs and on TB treatment, especially in the continuation period. With reference to antidiabetic medications, there is no evidence that they affect the pharmacokinetics of TB drugs [45]. Intriguingly, diabetes itself is not among risk factors for side effects of TB therapy such as old age, anemia, multi-drug-resistant TB medications, overweight/obesity status and smoking history [46].

Antihyperglycemic therapy in diabetic patients with tuberculosis

Diabetes in patients with TB should be treated in order to achieve good metabolic control. Although oral antihyperglycemic agents (OAHA) may be used in the treatment, insulin therapy is often started to achieve strict control of glycemia [47]. Thus, in the course of TB treatment in people with type 2 diabetes previously treated with OAHA, provisional insulin therapy is recommended with the basal-bolus as a preferred regimen [48].

Pathogenesis of the association

The pathogenesis of the association of diabetes and TB is quite complex. It is not clear if diabetes increases susceptibility to initial TB infection or it makes the development of active TB disease from latent infection more likely. There is well founded evidence that diabetes modestly raises the respiratory infection risk [26].

There is evidence that the *M. tuberculosis* association (attachment and ingestion) with monocytes is significantly lower in diabetic patients [49].

Table I. Clinical recommendations on patients with tuberculosis and diabetes

Diabetic patients should be routinely screened for TB symptoms such as persistent cough (> 2 weeks), night sweats, weight loss and fever as part of regular clinical check-ups. Patients with a positive symptom screen should be referred to TB service for further evaluation in accordance with the local guidelines. Diabetes mellitus may modify the clinical course of TB. Also, diabetic patients may have slightly different TB radiological presentation.
Patients with newly diagnosed TB should be screened for DM. It is advisable to screen with fasting blood glucose and/or HbA_{1c} at the time of TB diagnosis, and repeat it after 3 months of TB treatment. The best screening test is still not known.
Diabetes treatment has to be optimized during TB therapy in order to achieve good metabolic control. Insulin therapy is the most suitable regimen for TB patients with poor control on oral agents.
All diabetic patients with TB should be treated with the current standard four-drug treatment regimen of first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). It requires a minimum of 6 months in two phases: 2 months of all four drugs in the intensive phase and 4 months of isoniazid and rifampicin in the continuation stage.
It is recommended to pay special attention to outcomes of TB therapy in diabetic patients. Diabetes adversely affects the treatment in terms of negative smears, cultures and radiological improvement. Patients may need longer treatment in order to achieve success.
Diabetic patients after completion of TB treatment should attend a TB outpatient clinic in order to ensure follow-up and rapid detection of a possible relapse.

Male gender and poor metabolic control were associated with lower such interaction. The host cell recognition is altered in diabetic patients with the incorrect response. As a result, it may cause higher replication of ingested bacteria. Additionally, it was also shown experimentally that increased susceptibility to TB in DM was caused by a delayed innate immune response to the presence of infected alveolar macrophages [50]. Tuberculosis specific IFN-γ-producing T cells migrate later both to lymph nodes and to lung. Moreover, the cytokines associated with the innate (IL-1β, IL-6, TNF-α, IL-8) and adaptive type 1 (IL-10, IL-2, IFN-γ) response were reported to be up-regulated in diabetic TB patients, especially in those with elevated HbA_{1c} [51]. This suggests that diabetes affects the immune response to *M. tuberculosis*. Finally, with regard to the adaptive response there is a shift towards T helper 2 (Th2) bias in diabetic patients which, at least in part, may contribute to TB development in diabetic patients [52]. Contrary to the Th1 response, Th2 cells and their cytokines correlate with susceptibility to TB. Of interest, in spite of this immune dysregulation in patients with DM and TB, the sensitivity of the IFN-γ release assays (IGRAs) is not compromised [53].

Among various mechanisms underlying this association, vitamin D deficiency is also considered [54]. It is associated with TB (OR = 2.9, 95% CI: 1.3–6.5) and with the elevated risk of type 1 and 2 diabetes. *In vitro* phagocytosis of *M. tuberculosis* by monocytes and macrophages is heavily dependent on the concentration of this vitamin.

Conclusions

In our opinion, the association of TB and DM is underappreciated. There is no doubt that the rising diabetes epidemic poses a threat to TB control. Unfortunately, in Poland there are very few reports on the prevalence of the association [55]. There is now firm evidence of an adverse influence of diabetes on TB manifestation and treatment [8].

However, there is a large number of unclarified issues regarding this problem. Though diabetes is associated with obesity and is more prevalent among middle-aged patients, at least in some low-income countries it is more frequent among lean and young patients [56]. It is still unresolved how much diabetes affects the clinical presentation of TB. Secondly, we do not know if there are any diabetic subgroups more at risk of TB infection. Next, we need to know if optimal metabolic control reduces the TB risk and improves the outcome for these patients.

Nevertheless, what we do know is that in close collaboration between diabetes and respiratory specialists we should screen for both diseases, manage them and design further clinical studies addressing this challenging though slightly neglected association. The suggested clinical recommendations identified in this review are listed in Table I. In contrast to TB, diabetes is rather insidious and may persist unrecognized for years with an increased risk of chronic complications. Therefore, the infrastructure for TB control could serve for better detection of diabetes.

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