Diabetes & Metabolic Syndrome: Clinical Research & Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Detrimental association between diabetes and tuberculosis: An unresolved double trouble

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Clinical outcome
Diabetes
India
Prevalence
Tuberculosis

ABSTRACT

Despite significant efforts made to control tuberculosis (TB) through DOTS program, the increasing burden of diabetes mellitus (DM) threatens the progress in reducing TB-related mortality, particularly in developing countries. In recent years, TB-DM comorbidity continues to remain high in countries where DM is on rampant. DM increases the risk of TB, reactivates the dormant TB and worsens the TB treatment outcome. The present review highlights the current findings regarding the prevalence and association of TB-DM comorbidity along with their public health implications. This review will increase the awareness among researchers, policymakers and clinicians, regarding the current scenario of TB-DM association.

Contents

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https://doi.org/10.1016/j.dsx.2018.05.009
1871-4021/

1. Background: diabetes set to undermine success in global TB control

Since early 20th century, tuberculosis (TB) remained a serious and deadly threat in patients with diabetes mellitus (DM), however, the prognosis improved dramatically after the emergence of effective management strategies for both diseases [1]. In the last decade, there has been a huge upsurge in DM patients at low-and-middle-income countries (LMICs) with a gradual decline in global TB incidence [2]. The current data revealed that around 95% of TB patients and 70% of DM patients live in LMIC [3]. Notably, eight of ten countries with the highest incidence of DM are classified as high TB burden countries by WHO [4]. India alone accounting for 23% of the world's incident cases and 21% of world's deaths due to TB [5]. Among DM complications, pulmonary tuberculosis (PTB) is the ninth most frequent complication. The relative contribution of DM to TB epidemic is increasing due to rising prevalence of DM in many countries, thereby needs a better understanding of this co-morbidity [6]. The countries with high DM prevalence (>7.6%) revealed a significant positive association with TB incidence ($r = 0.17$, $P = 0.01$) [7]. This dual burden necessitates identifying the nature of this coexistence to assist in developing public health approaches that control their mounting burden.

2. Prevalence and risk factors for TB-DM comorbidity

Multiple studies were conducted in different regions of the world to determine the prevalence of DM and explained associated factors of TB-DM comorbidity. The worldwide prevalence of DM was ranging from 1.9% to 44.0% among TB patients [1,8,9]. Around 35% to 61% of DM patients diagnosed with diabetes just after detection of TB [1]. Data from the World health organization (WHO), World bank sources, and International Diabetes Federation (IDF) estimated the worldwide DM prevalence to be 6.6 ± 3.8% and TB incidence of 135.0 ± 190.5 per 100,000 populations from 2000 to 2012 [10]. The peak prevalence of TB-DM comorbidity was observed in countries of Asia, North America and Oceania. In Asian countries, the prevalence of DM among TB patients was ranging from 5% to more than 50%, whereas the prevalence of TB among DM patients was 1.8 to 9.5 times higher than that of the general population [11]. A multicenter prospective study in South Korea reported 23.8% of TB patients diagnosed with DM, of which, 68.8% had uncontrolled DM (HbA1c≥7.0% [53 mmol/mol]) [12]. In an epidemiological study, Viswanathan and co-workers reported a prevalence of DM and pre-diabetes in 25.3% and 24.5% patients, respectively, in a cohort of TB patients from Southern region of India [9]. DM also accounts for a larger proportion of TB cases in Indian and Mexican settings with the burden of 14.8% and 25%, respectively [13]. In a recent systematic review, the median global prevalence of TB-DM comorbidity was 16% (IQR 9.0%-25.3%) [14]. Multiple studies from both developing and developed countries like Africa, United States, Australia, Barcelona, Brazil and Mexico have demonstrated a considerably higher DM prevalence among TB patients [14]. Table 1 listed recent studies showing DM prevalence among TB patients in different countries.

3. Pathophysiology of the TB-DM interaction

Alveolar macrophages, in collaboration with lymphocytes, play a critical role in eradicating mycobacterial infection and is found less active in TB patients complicated with DM. Around 90% of DM patient remains asymptomatic and have a latent infection, without developing the overt disease [14]. It has been estimated that approximately two billion people (one-third of the world population) have a latent TB infection with the risk of possible reactivation [31]. The reactivation is largely influenced by immune insufficiency. The risk of undergoing an obvious disease is

Table 1
Prevalence studies of DM among TB patients in different countries.

Study	Design	Country	People with TB	Assessment criteria of T2DM	Diabetes prevalence		
					Total % [Number]	New % cases [Number]	Known % cases [Number]
Kumar et al. (2013) (Indian Tuberculosis-Diabetes Study Group) [15]	Prospective observational	India	8269	FBG ≥126 mg/dl	13.0% [1084]	5.0% [402]	8.0% [682]
Chachra and Arora (2014) [16]	Cross-sectional	India	700	FBG ≥126 mg/dl	12.6% [88]	9.1% [64]	3.5% [24]
Shidam et al. 2015 [17]	Cross-sectional	India	570	WHO criteria	21.2% [121]	12.1% [69]	9.1% [52]
Kornfeld et al. 2016 [18]	Cohort Study	India	209	FBG, OGTT and HbA1c	54.1% [113]	17.7% [37]	36.4% [76]
Manjareeka et al. 2016 [19]	Cross-sectional	India	110	WHO criteria	13.9% [16]	NR	NR
Siddiqui et al. 2016 [20]	Cross-sectional	India	316	FPG and OGTT	15.8% [50]	6.33% [20]	9.49% [30]
Rajapakshe et al. 2015 [21]	Cross-sectional	Sri Lanka	112	FPG	9.0% [10]	1.8% [2]	7.1% [8]
Aftab et al. 2017 [22]	Cross-sectional	Pakistan	3027	HbA1c	39.6% [1199]	13.5% [408]	26.1% [790]
Irfan et al. 2016 [23]	Cross-sectional	Pakistan	211	HbA1c>6.5% (48 mmol/mol) and random blood sugar>180 mg/dL	11.4% [24]	8.0% [17]	3.4% [7]
Zhao et al. 2016 [24]	Cross-sectional	China	1252	FBG and HbA1c	7.7% [97]	45.4% [44]	54.6% [53]
Chen et al. 2014 [25]	Cross-sectional	China	1126	FBG	16.2% [182]	1.6% [18]	14.6% [164]
Wu et al. 2015 [26]	Retrospective cohort	China	201	Medical records	19.9% [40]	NR	NR
Lee et al. 2017 [27]	Case-control	South-Korea	1044	ADA 2012	24.2% [252]	NR	NR
Park et al.2012 [28]	Retrospective cohort	South-Korea	492	HbA1c ≥6.5% (48 mmol/mol)	25.2% [124]	NR	NR
Sulaiman et al. 2013 [29]	Retrospective cohort	Malaysia	1267	WHO criteria	26.7% [338]	NR	NR
Duangrithi et al. 2013 [30]	Prospective	Thailand	227	ADA 2010	16.3% [37]	4.8% [11]	11.5% [26]

ADA: American diabetes association; FBG: Fasting blood glucose; FPG: Fasting plasma concentration; NR: Not reported; OGTT: Oral glucose tolerance test; TB: Tuberculosis, T2DM: Type 2 diabetes mellitus; WHO: World health criteria.

Please cite this article in press as: A.N. Siddiqui, et al., Detrimental association between diabetes and tuberculosis: An unresolved double trouble, Diab Met Syndr: Clin Res Rev (2018), https://doi.org/10.1016/j.dsx.2018.05.009