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THE GLOBAL PREVALENCE AND INCIDENCE OF DIABETES MELLITUS AND PULMONARY TUBERCULOSIS

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Abstract

Diabetes Mellitus (DM) and Tuberculosis (TB) are two chronic diseases which have a major impact on the population health in developing countries. DM is a chronic, non-communicable disease, characterized by hyperglycemia, caused by insulin-resistance, inadequate insulin secretion or both. TB is a disease caused by Mycobacterium tuberculosis, an airborne bacteria. DM implies a three times greater risk of developing TB and their association can be considered one of the most important challenges regarding TB control. TB can cause a temporary impaired glucose tolerance, which is a risk factor for DM development. The possibility of relapse or death of a patient with TB is significantly higher when the patient also has DM. The DM-TB association represents an important threat to the population health and requires the implementation of adequate programs in order to reduce the prevalence and incidence of the two diseases.

key words: *diabetes mellitus, pulmonary tuberculosis, prevalence, incidence.*

Introduction

Tuberculosis (TB) and Diabetes Mellitus (DM) contribute to the increase of morbidity and mortality worldwide. DM-TB association has been known for 1000 years, being documented for the first time in the 11th century by Avicenna, persian philosopher, who observed the fact that tuberculosis determines complications in the case of patients with diabetes, but also that diabetes increases the risk of developing tuberculosis, then known as phthisis [1]. The indian Yugimahamuni described the symptoms caused by TB and diabetes as a syndrome which he named "meganoikal", symptoms which include obesity, thirst, incontinence, glycosuria, respiratory symptoms and unconsciousness [2]. More recent data, from the last decade, prove the importance of DM-TB association [3-10]. Two systematic analyses, conducted in 2007 by the Medical Research Council, World Health Organization Britain's Newcastle University [11], and in 2008 by researchers from Harvard University [12], as well as other systematic analyses published in 2009, 2010 and 2014 [4,13,14], clearly proved that diabetes increases the risk of developing TB by two to three times and that the association of the two diseases constitutes a threat to the health of the entire population. As a result of these data, in 2011, the

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World Health Organization and International Union Against Tuberculosis and Lung Disease launched The Collaborative Framework for Care and Control of Tuberculosis and Diabetes, to encourage research and implement routine bidirectional screening [15].

Diabetes Mellitus – epidemiological data

Diabetes is one of the most important diseases of the 21st century; the World Health Organization estimates that worldwide hyperglycemia is the third cause of premature death, after arterial hypertension and smoking [16].

There are now 415 million people with DM globally, and an increase to 642 million (with a prevalence of 10.4%) is estimated by the year 2040. Currently, 1 in 11 adults has diabetes (a prevalence of 8.8%) [17].

Every 6 seconds a person dies because of diabetes. In 2015, 5 million deaths were recorded from this cause. Diabetes represents 14.5% of all-cause mortality, almost half (46.6%) of these in subjects under the age of 60 [17].

Regarding the distribution by gender, the number of subjects with diabetes is slightly higher in men than in women (215.2 million men vs 199.5 million women). 320.5 million subjects with diabetes are of working age (20-64 years old), while only 94.2 million are between 65-79 years old. The majority of subjects with diabetes (269.7 million) live in the urban environment and only 145.1 million in the rural environment [17].

The top 10 countries with the highest number of adults with DM are: China – 109.6 million, India – 69.2 million, United States of America – 29.3 million, Brazil – 14.3 million, Russia – 12.1 million, Mexico – 11.5 million, Indonesia – 10 million, Egypt – 7.8 million, Japan – 7.2 million and Bangladesh – 7.1 million [17].

Type 1 DM is less frequent than type 2 DM. However, it is estimated that each year around 86,000 children under the age of 15 develop type 1 DM, in 2015 the total number of them exceeding for the first time half a million (542,000). The highest incidence of type 1 DM is in Finland, Sweden and Kuwait [17].

The International Diabetes Federation (IDF) estimates that around 193 million people, almost half (46.5%) of the people with diabetes, are undiagnosed, the majority of them having type 2 DM. Worldwide, 81.1% of undiagnosed patients live in low and middle income countries. In sub-Saharan Africa the percentage of undiagnosed patients with diabetes is 66.7% [17].

Worldwide, 318 million people (6.7% of adults) have prediabetes, a risk factor for developing diabetes, half of them under the age of 50. The majority (69.2%) live in low and middle income countries. North America and the Caribbean have the highest prevalence of prediabetes (15%), while Europe has the lowest (4.8%) [17].

Hyperglycemia during pregnancy can be classified as: gestational diabetes, diabetes diagnosed for the first time during pregnancy and diabetes diagnosed before pregnancy. It is estimated that in 2015, 20.9 million (16.2%) of newborns come from mothers with hyperglycemia during pregnancy. Of these cases, 85.1% can be attributed to gestational diabetes, 7.4% to other types of diabetes diagnosed during pregnancy and 7.5% to diabetes diagnosed before pregnancy. The majority of cases (87.6%) live in low and middle income countries. South-East Asia has the highest prevalence of hyperglycemia during pregnancy (24.2%), and Africa has the lowest prevalence (10.5%) [17].

In Europe, the prevalence of diabetes is 9.1% (59.8 million adults) and will increase to 10.7% (71.1 million) by 2040. 23.5 million cases are undiagnosed. The highest crude prevalence

can be found in Malta (13.9%). Turkey has the highest age-adjusted comparative prevalence (12.8%) and is the third country in Europe by the number of people with diabetes (6.3 million), after Russia (12.1 million) and Germany (6.5 million). Europe has the highest number of children with type 1 DM (140,000), with 21,600 new cases annually. The highest incidence of type 1 DM is in Finland (62.3 cases/100,000 children/year), and the countries with the highest number of children with type 1 DM are Great Britain, Russia and Germany. 31.7 million people (4.8%) have prediabetes and an increase to 36.6 million (5.5%) is estimated by 2040. In 2015, 627,000 people have died because of diabetes, 26.3% of deaths occured in patients under the age of 60 [17].

Between 2013-2014, a large epidemiological survey regarding diabetes prevalence was conducted in Romania - the PREDATORR study (National Study Regarding the Diabetes, Prediabetes, Overweight, Obesity, Dyslipidemia, Hyperuricemia and Chronic Kidney Disease Prevalence in Romania). According to this study, the prevalence of diabetes in Romania was 11.6% in adults aged 20-79 years old, 2.4% being cases previously undiagnosed. The prevalence of diabetes increased with age and was higher in men than in women. The prevalence of prediabetes was 16.5%, the highest percentage being attributed to the 60-79 years age group and to women [18].

Pulmonary tuberculosis – epidemiological data

Tuberculosis is a major cause of morbidity and mortality worldwide, a third of the population being infected with Mycobacterium tuberculosis [19]. Approximately 5-15% of these will develop active TB during their life. HIV/AIDS represents the most important risk factor for the development of active TB. Diabetes is also one of the top 8 risk factors [20].

In 2014, 13 million people with TB were recorded. 9.6 million new cases of TB were estimated worldwide, the equivalent of 133 cases/100,000 people. Of these, the majority are men (5.4 million), 3.2 million women and 1 million children. There are an estimated 1.2 million new cases of TB-HIV positive, of whom three quarters (74%) live in Africa. Only 6 million new cases were reported to the National Authorities, over a third (37%) remaining undiagnosed or unreported. Also, there were 1.5 million reported deaths attributed to TB, of which 1.1 million people HIV-negative and 0.4 million HIV-positive, 890,000 men, 480,000 women and 140,000 children. 95% of the deceased persons lived in low and middle income countries [20].

In 1994, the World Health Organization (WHO) developed a strategy to control TB, named DOTS (*Directly Observed Treatment Short* course) [21]. In order to extend DOTS, in 2006 the Stop TB 2006-2015 Strategy was launched, together with the Global Plan to Stop TB [22,23]. Starting with 2016, the aim is to eradicate the global TB epidemic by launching The End TB Strategy. Thus, the aim is that by 2035 TB caused mortality to decrease by 95% compared to 2015, the incidence of TB to decrease by 90% (under 10 cases/100,000 people) and that no family is affected by the catastrophic costs associated with TB [24]. As a result of these strategies, the prevalence of TB decreased by 42%, and the mortality decreased by 47% from 1990 to the present. An estimated 43 million lives were saved between 2000-2014 through efficient diagnosis and treatment [20].

Worldwide, it is estimated that 3.3% of newly diagnosed cases and 20% of relapses present multidrug-resistant tuberculosis (MDR-TB). Of the 480,000 MDR-TB cases estimated for 2014, only 41% were reported (123,000 cases). 54% of MDR-TB cases are found in

India, China and Russia. Worldwide, only 50% of MDR-TB cases were treated efficiently. 9.7% of MDR-TB people have extensively drug-resistant tuberculosis (XDR-TB), most of the cases being reported in Belarus (29%). In 2014, 190,000 people died as a result of MDR-TB [20].

58% of newly diagnosed cases in 2014 were found in South-East Asia and the Western Pacific region. The highest incidence of TB was found in Africa (281 cases/100,000 people), more than double compared to the global incidence (133 cases/100,000 people). The highest number of people with TB out of the total worldwide cases was reported in India (23%), Indonesia (10%) and China (10%) [20].

In Europe, 440,000 TB cases were estimated, 340,000 being newly diagnosed cases (incidence: 37 cases/100,000 people). 321,421 people with TB were reported, 273,381 being newly diagnosed cases. 3.8% are children under the age of 15. The ratio men/women is 2. 20,000 of the subjects affected by TB are HIV-positive. 15% of the new cases and 48% of the relapses are MDR-TB. 76% of the total cases and 49% of the MDR-TB cases were successfully treated. In 2014, 37,000 people with TB died, 3,200 being HIV-positive. [20].

In Romania, the global incidence of TB is the highest in the European Union and one of the highest in Europe. 16,000 cases of TB were estimated, the equivalent of an incidence of 81 cases/100,000 people [20]. 14,938 subjects with TB were reported (70.2/100,000 people), 12,562 (59.1/100,000 people) being new cases of TB. The highest incidence is in Dolj county (113.4/100,000 people), Giurgiu county (113.1/100,000 people), Mehedinţi county (106.7/100,000 people), Olt county (105.7/100,000 people) and Teleorman county (104.7/100,000 people), and the lowest in Covasna county (21.3/100,000 people) and Harghita county (22/100,000 people). Although Romania is the first in the European Union regarding the global incidence, it decreased by 48.7% in the last 12 years [25]. 312 subjects are TB-HIV positive. 2.8% of the new cases and 11% of the relapses are MDR-TB. 85% of the total cases were successfully treated, but only 34% of the MDR-TB cases [20]. In 2014, 1,125 subjects with TB died (6.4/100,000 people), 54 of them being HIV-positive. Romania is ranked 6th in Europe regarding the rate of mortality caused by TB [20,25].

Diabetes Mellitus – Pulmonary tuberculosis association

Diabetes can increase the risk of developing TB through mechanisms directly linked to hyperglycemia and cellular insulinopenia, but also through indirect mechanisms on the function of macrophages and lymphocytes [4].

People with diabetes present a risk approximately three times higher of developing active TB compared to people without diabetes [4,11-14].

In the situation in which 95% of the subjects with TB and 70% of the subjects with DM live in low and middle income countries, the prevalence of DM increases in countries in which TB is endemic, researchers expressing concern regarding this association [3,4,26-29].

Pulmonary tuberculosis is the ninth most frequent complication of diabetes mellitus [30]. Worldwide, there is a number of people with TB and diabetes equivalent with the number of people with TB-HIV coinfection [13]. In 2013, approximately 1 million cases of TB were associated with diabetes, and 15% of TB cases in adults were attributed to DM. Regarding the prevalence of DM-TB at WHO regions, in South-East Asia there were 423,000 cases (14%), in the Western Pacific 238,000 cases (16%), in Africa 194,000 cases (9%), in the Eastern Mediterranean region 94,000 cases

(17%), in Europe 51,000 cases (15%) and in America 41,000 cases (17%). The countries with the highest number of patients with DM-TB association are India (302,000), China (156,000), South Africa (70,000), Indonesia (48,000), Pakistan (43,000), Bangladesh (36,000), Philippines (29,000), Russia (23,000), Burma (21,000) and Democratic Republic of the Congo (19,000) [13,31].

Recent studies have shown an increased prevalence of diabetes in people with TB. Unpublished data from the South Pacific shows the fact that between 40% and 45% of the subjects with TB have DM [3]. The prevalence of DM in patients with TB is also high in other regions: Kerala, India (44%) [32], Karnataka, India (32%) [33], Puducherry, India (29%) [26], Tamil Nadu, India (25.3%) [34], Texas (39%) [35], Mexico (36%) [35], Tanzania (16.7%) [36], Pakistan (16%) [37] and Indonesia (14.8%) [38].

A systematic review [39], which included 12 studies about TB screening in subjects with DM and 18 studies about DM screening in subjects with TB show a prevalence of TB in subjects with DM between 1.7% Sweden [40] and 36% in South Korea [41]. The prevalence of DM in subjects with TB is between 1.9% in Nigeria [42] and 35.2% in Mexico [5].

DM specifically increases the risk of developing pulmonary TB, but not the risk of extrapulmonary TB [33,34]. DM-TB association is more frequent in men [43]. Patients with TB and DM are older, with a higher body mass index, more prone to hemoptysis and pulmonary cavities, sputum positive at diagnosis, which positively persist at the end of the first or the second month of treatment [14].

Risk of death, treatment failure and relapse is significantly higher in people with TB and DM, compared to those without diabetes [34,44,45].

Although type 2 DM is more frequently associated with TB [43], fact explained by the much higher number of patients with type 2 DM compared to type 1, it seems that people with type 1 DM are more prone to developing TB [13]. Moreover, the risk of developing TB is higher in patients with insulin treatment, especially those who need high doses of insulin [38,46].

Patients with HbA1c≥7% have a risk of developing TB 2.5 times higher compared to patients with HbA1c <7%, which do not have a risk of developing TB higher than people without diabetes [8]. Thus, a good glycemic control can reduce the risk of developing pulmonary tuberculosis in people with diabetes mellitus [47,48].

DM is also associated with latent tuberculosis infection (LTBI), this being significantly more frequent in people with DM (43.4%) and prediabetes (39.1%), compared to people without DM (25.9%). Similarly, mean HbA1c is higher in patients with LTBI (5.7%), compared to those without LTBI (5.5%) [49].

It is estimated that the increasing prevalence of diabetes will offset the downward trend of the worldwide incidence of TB with 3% by 2035, or even with 8% in the case of a pessimistic scenario (a 25% increase of the number of people with DM) [50].

Conclusions

The increasing prevalence of DM will determine an increase of the prevalence of TB in developing countries in the next decades, the association of the two diseases being one of the biggest challenges of the tuberculosis eradication programs. Patients with TB and DM have an increased risk of death, failure of anti TB therapy, relapse after ending treatment and remain contagious longer compared with those without DM.

The DM-TB association has to receive the required attention, the implementation of bidirectional screening and monitoring programs being necessary, with the aim of prevention, early diagnosis and efficient treatment. These need technical and financial support from the national and international authorities. It is necessary that researchers discover more data regarding the DM-TB association in order to improve the management of the two diseases.

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