INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and airways of people with the active respiratory disease ***(Global tuberculosis report, 2013).***

Approximately 9.4 million new cases and 1.7 million deaths were encountered per year worldwide ***(Rudeeaneksin et al., 2012).***Morbidity and mortality are especially high in specific populations such as those with underlying immunosuppression or very young children ***(Heather & Zarir, 2013).***

Tuberculosis remains a public health problem in Egypt. Although Egypt is in the era of epidemiological transition from communicable to non-communicable diseases like many other countries, TB, still, must be addressed and handled as a health problem affecting large sectors in the society, especially the poor and the vulnerable ***(NTP, 2012).***

More than 350 million people have diabetes; prevalence is similar in both low- and middle- income countries ***(WHO report, 2013).***

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels ***(WHO media center, 2013).***

People with diabetes are at higher risk of developing tuberculosis (TB) than those without diabetes. Tuberculosis, an infectious disease of the lungs, affects 9.4 million people and kills 1.7 million worldwide every year ***(WHO report, 2013).***

Several studies have looked at the association between diabetes and tuberculosis in developed countries and found that people with diabetes are around 2.5 times more likely to develop tuberculosis. These findings were also true of developing regions including Africa where one study found that the prevalence (%) of diabetes was twice as high in people with tuberculosis than in people without tuberculosis ***(Jeon & Murray, 2013).***

Not only does diabetes contribute to a person's risk of developing tuberculosis, but it also makes it more difficult to treat those who have both diseases. A review looking at the impact of diabetes on tuberculosis treatment found that people

with diabetes are more likely to fail treatment and more likely to die during treatment compared to those without diabetes ***(Baker et al., 2011).***

Strikingly little work has been done to assess the relationship of TB and diabetes at the individual level in countries where TB prevalence is highest and diabetes prevalence is rising most rapidly. Given increases in diabetes and the persistence of TB in these areas, the relationship of individual risks, social determinants and population health impacts due to interactions between diabetes and TB should be assessed **(*Eremy et al., 2013).***

AIM OF THE WORK

To assess the clinical determinants of development of pulmonary tuberculosis among diabetic patients in comparison to patients with DM alone.

TUBERCULOSIS

Tuberculosis is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra pulmonary TB). The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing. In general, a relatively small proportion of people infected with M. tuberculosis will develop TB disease; however, the probability of developing TB is much higher among people infected with HIV. TB is also more common among men than women, and affects mostly adults in the economically productive age groups ***(Global Tuberculosis report, 2013).***

Historical aspects of tuberculosis

Tuberculosis, only a few decades ago, was believed to be under control and decreasing in incidence, in both developed and developing countries. A number of scientists and physicians have contributed to the understanding of tuberculosis and have been honored on postage stamps by several countries around the world ***(Shampo & Rosenow,***

2009). Tuberculosis (TB) has a long history. It was present before the beginning of recorded history and has left its mark on human creativity, music, art, and literature; and has influenced the advance of biomedical sciences and healthcare. Its causative agent, Mycobacterium tuberculosis, may have killed more persons than any other microbial pathogen ***(Daniel, 2006).***

TB was documented in Egypt, India, and China as early as 5000, 3300, and 2300 years ago, respectively ***(Daniel, 2006)***. Typical skeletal abnormalities, including Pott's deformities, were found in Egyptian and Andean mummies and were also depicted in early Egyptian and pre-colombian art ***(Sotomayor et al., 2004).***

Tuberculosis, also known as the white plague, received the title of "captain of all these men of death" by John Bunyan in the second half of the 17th century, when the disease reached a high level of death rates in Europe. Although it was probably described for the first time in Indian texts, pulmonary TB is known since the time of Hippocrates as "phthisis", which is derived from the Greek for "wasting away". In 1689, the English Doctor Richard Morton used the term "consumption" to specifically denote TB, & finally, in 1819, the inventor of the stethoscope, the French Doctor René Laennec identified for the first time the TB manifestation unit ***(Ducati et al., 2006)***.

One of the greatest works on TB was performed in 1882 by Robert Koch, an esteemed scientist of his time. Koch isolated and cultured M. tuberculosis from crushed tubercles. His experimental work identified the bacterium as the TB etiological agent ***(Daniel, 2006)***.

The tuberculin skin test became the principal tool for infection diagnosis. In the same period, Koch developed staining methods for the identification of the bacillus; these techniques were subsequently improved by the German Doctor and bacteriologist Paul Ehrlich, whose method for detection of the bacillus provided the basis for the development of the Ziehl-Nielsen staining, which still is an important tool to diagnose TB ***(Ducati et al., 2006)***.

In 1900, Calmette and Guerin discover the vaccine (BCG) that was obtained from attenuation of a strain of Mycobacterium bovis ***(WHO, 2012).***

Streptomycin (1943), P-aminosalicylic acid (1949), Izonaizid (1952), Pyrazinamide (1954), cycloserine (1955), Ethambutol (1962) and Rifampicin (1963) were introduced as anti-TB agents, leading to progressive decline in TB incidence in the industrialized countries ***(WHO, 2012).***

EPIDEMIOLOGY OF TB

Tuberculosis (TB) remains a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV).

Tuberculosis (TB) is a top infectious disease killer worldwide. In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44. In 2014, an estimated 1 million children became ill with TB and 140,000 children died of TB. TB is a leading killer of HIV-positive people: in 2015, 1 in 3 HIV deaths was due to TB. Globally in 2014, an estimated 480,000 people developed multidrug-resistant TB (MDR-TB). The Millennium Development Goal target of halting and reversing the TB epidemic by 2015 has been met globally. TB incidence has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000 .The TB death rate dropped 47% between 1990 and 2015. An estimated 43 million lives were saved through TB diagnosis and treatment between 2000 and 2014.

(WHO, 2015)

Epidemiological situation in Egypt

Tuberculosis remains a public health problem in Egypt. Although Egypt is in the era of epidemiological transition from communicable to non-communicable diseases like many other countries, TB, still, must be addressed and handled as a health problem affecting large sectors in the society, especially the poor and the vulnerable ***(NTP, 2012).***

Table (1): TB situation in Egypt (cases notification and burden) ***(WHO, 2015)***

Estimates of TB burden * 2014	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	0.22 (0.2–0.25)	0.25 (0.22–0.27)
Mortality (HIV+TB only)	0.043 (0.035–0.051)	0.05 (0.04–0.06)
Prevalence (includes HIV+TB)	23 (12–37)	26 (13–42)
Incidence (includes HIV+TB)	13 (12–15)	15 (13–16)
Incidence (HIV+TB only)	0.035 (0.028–0.044)	0.04 (0.03–0.05)
Case detection, all forms (%)	54 (49–60)	

Estimates of MDR-TB burden * 2014	New	Retreatment
% of TB cases with MDR-TB	3.4 (1.9–4.9)	15 (12–18)
MDR-TB cases among notified pulmonary TB cases	160 (87–220)	89 (72–110)

TB case notifications 2014	New **	Relapse
Pulmonary, bacteriologically confirmed	3 697	309
Pulmonary, clinically diagnosed	886	0
Extrapulmonary	2 285	0
Total new and relapse	**7 177**	
Previously treated, excluding relapses	290	
Total cases notified	**7 467**	

Among 6 868 new cases:
429 (6%) cases aged under 15 years; male:female ratio: 1.4

Table (2): TB situation in Egypt (MDR-TB, TB/HIV, success rate) ***(WHO, 2015)***

Reported cases of RR-/MDR-TB 2014	New	Retreatment	Total **
Cases tested for RR-/MDR-TB	45 (1%)	358 (60%)	403
Laboratory-confirmed RR-/MDR-TB cases			86
Patients started on MDR-TB treatment ***			72

TB/HIV 2014	Number	(%)
TB patients with known HIV status	1 690	(23)
HIV-positive TB patients	12	(<1)
HIV-positive TB patients on co-trimoxazole preventive therapy (CPT)	12	(100)
HIV-positive TB patients on antiretroviral therapy (ART)	12	(100)
HIV-positive people screened for TB		
HIV-positive people provided with IPT		

Treatment success rate and cohort size	(%)	Cohort
New and relapse cases registered in 2013	(86)	7 876
Previously treated cases, excluding relapse, registered in 2013	(72)	307
HIV-positive TB cases, all types, registered in 2013	(29)	7
RR-/MDR-TB cases started on second-line treatment in 2012	(63)	52
XDR-TB cases started on second-line treatment in 2012		0

According to WHO Tuberculosis profile of Egypt published in 2015, 13 thousands incident cases, 23 thousands prevalent cases, 0.22 thousands deaths among HIV-negative people. Of the incident tuberculosis cases; 0.035 thousands were HIV-positive. 54 thousand cases of all forms of tuberculosis were detected. The total new and relapsed cases detected were 7177, including 3697 smear-positive TB, and 2285 extra-pulmonary tuberculosis. Retreated cases were 703. HIV-positive TB patients were < 1% ***(WHO, 2015).***

HIV situation in Egypt

According to the UNAIDS annual global gap report based on national data, the number of people over fifteen years of age living with HIV in 2014 was 7,200 with a range of 4,400 to 12,000. If Egypt has a population of 84 million and 68% of this population is over the age of fifteen years then 0.013% of the population over fifteen years old is living with HIV. There were 4,631 people known to be living with HIV at the end of 2014. 1,715 or 37% of them were currently taking antiretroviral and this percentage is 24% when the denominator is 7,200.

(UNAIDS, 2015)

Epidemiological Factors

Socioeconomic development and access to quality of health services appear to be at least as important as any specific TB control measure. The likelihood of success of TB control efforts is likely related to socioeconomic indicators, including gross domestic product per capita, mortality of children <5, access to clean water, and adequate sanitation and health expenditure per capita.

The importance of addressing these socioeconomic factors to achieve TB control is reinforced by the fact that many countries have experienced a rapid decline in TB burden without good access to high-quality TB treatment. In Europe, for example, TB morbidity and mortality declined long before effective chemotherapy was available, largely because of socioeconomic development, improved living conditions, better nutrition, and isolation of infectious cases in sanatoria ***(Lienhardt, 2001).***

Risk factors for TB:

Risk factors for TB may be divided as follows:

I. Impaired immunity (host factors).
II. Increased exposure to infection (environmental factors).

I- Host factors:

Categories of host factors are outlined in the following sections. The relative risk for selected risk factors is outlined below. The relative importance of different risk factors varies with prevalence of exposure across regions.

Substance abuse:

Substance abuse is the most commonly reported behavioral risk factor among patients with TB in the United States ***(Oeltmann et al., 2009).***

- ***Drug use***: The epidemiologic factors associated with injection and non-injection drug use (e.g., homelessness, incarceration) contribute to the high prevalence of TB among drug users (***Fremond et al., 2004).***
- ***Tobacco***: Cigarette smoking confers a relative risk of about 1.5 to 2.0 for the development of tuberculosis ***(Lin et al., 2009).*** Smoking has been found to be associated with both risk of relapse of TB and TB mortality. Passive smoking also increases the risk for TB ***(Leung et al., 2010).***

- ***Alcohol***: the risk of active tuberculosis is substantially elevated in individuals who consume more than 40 g alcohol per day. This may be due to the effect of alcohol and alcohol-related conditions on the immune system ***(Lönnroth et al., 2008).***

Nutritional status:

Malnutrition is generally understood to be an important risk factor for tuberculosis, although the relation between impaired immunity due to malnutrition and risk of acquiring TB has not been well characterized ***(Cegielski & McMurray, 2004).***

- ***Underweight:*** Persons who are underweight (body mass index of <18.5) have increased risk for TB by a factor of 2.6 (1.2 to 4.8) ***(Edwards et al., 1971).***

- ***Vitamin D***: Vitamin D plays an important role in macrophage activation and restriction of mycobacterial growth, and diminished serum vitamin D levels appear to increase risk for tuberculosis infection. Among African immigrants in Australia, for example, individuals with latent or active tuberculosis were observed to have substantially lower serum vitamin D levels than those without tuberculosis ***(Gibney et al., 2008).***

Systemic diseases:

The diseases discussed in this section have been noted to confer some degree of increased risk for TB reactivation. However, in some cases it can be difficult to discern the relative risk of systemic diseases for development of active tuberculosis, since many studies were performed in areas where the prevalence of TB is relatively low.

- ***Silicosis***: the risk of tuberculosis is increased among miners with silicosis. The mechanism is not fully understood but may be related to impairment of pulmonary macrophage function by silica crystals. The relative risk depends on the severity of the silicosis and has been estimated at 1.4 to 2.9 ***(Cowie, 1994).***
- ***Malignancy:*** the risk of tuberculosis is increased in patients with hematologic malignancies and head and neck cancer ***(Kamboj & Sepkowitz, 2006).***

- ***Diabetes***: poorly controlled diabetes confers a 2.9-fold increase in the risk of developing pulmonary tuberculosis; the risk associated with well-controlled diabetes was minimal ***(Pablos-Méndez et al., 1997).***

- ***Renal disease***: the risk of tuberculosis is increased among patients with chronic renal disease. Uremia causes reduced cellular immunity. Other factors that may diminish immunity in the setting of renal failure include malnutrition, vitamin D deficiency, and hyperparathyroidism ***(Hussein et al., 2003).***

- ***Celiac disease***: celiac disease (autoimmune inflammation of the small intestine) is a risk factor for tuberculosis; the mechanism is not fully understood but may be related to malabsorption ***(Ludvigsson et al., 2007).***

- ***Gastric surgery***: gastric resection for peptic ulcer disease has been described as a risk factor for tuberculosis (relative risk 1.7 to 2.0). Although this procedure is no longer performed routinely, gastric bypass is a similar procedure that may confer similar risk. It may be related to loss of gastric acidity; however, the risk of TB among persons with gastric achlorhydria has not been studied ***(Bruce & Wise, 1977).***