Introduction
Tuberculosis (TB) continues to be the leading killer among bacterial diseases worldwide. Globally, in 2017, there were an estimated 10.0 million incident cases of TB and 1.3 million TB-related deaths [1]. In the same year, diabetes mellitus (DM) affected 425 million adults and killed 4.0 million people [2]. It is projected that the number of people affected by DM will increase to 629 million by 2045, and approximately 80% of these people live in low- and middle-income countries, where TB is endemic [2]. The association between DM and TB presents a major public health problem either in the current time or near future especially in low- and middle-income countries where TB is endemic disease and the prevalence of DM is high and rising. According to a meta-analysis study, DM patients have a three-fold greater risk of contracting TB than do non-diabetics (95% confidence interval [CI]: 2.3-4.3) [3]. Another systematic review and meta-analysis done by Al-Rifai et al revealed a resilient positive association between DM and TB with a substantial variation in the effect size between different studies [4]. Other systematic reviews of bidirectional screening for TB and DM reported that the prevalence of TB among diabetics ranged between 0.38% and 14%, with median global value of 4.1% [5, 6]. DM increases the risk of developing TB as well as its complications e.g., treatment failure, relapse and death rate [7]. Accordingly, this association has a negative impact on TB control program. Screening of high risk group as diabetic patients has been part of the Stop TB strategy for many years. In 2011, the estimated incidence rate of TB in Egypt was 18 per 100,000 populations. In 2017, this figure showed improvement, as the estimated incidence rate declined to 13 per 100,000 populations [1]. The prevalence of DM among those aged 15 to 64 years increased from 15.8% in 2005 to 17.2% in 2011-12 then slightly declined to 15.5% in 2017. Accordingly, a large proportion of Egyptians will be exposed to the risk of DM, and DM patients themselves will be exposed to a high risk of acquiring TB. Moreover, patients with both TB and DM will be more likely to develop complications than TB patients without DM [8, 9]. TB screening in selected risk groups as persons with DM is considered affordable and of low cost and at the same time will improve the low case detection of TB and reduce the delay of TB diagnosis [10].

The objectives of this study are to describe the feasibility of implementing a screening program to screen DM patients for TB within the governmental health settings affiliated to the Ministry of Health and Population of Egypt and identifying factors associated with high detection rate of new TB cases.
Methods

Study design
This study was a national multicenter cross-sectional study.

Study population and sampling selection
The study population was adult DM patients aged ≥ 18 years old. All study DM patients were diagnosed by fasting blood sugar (FBS) test (≥ 126 mg/dl) and postprandial blood glucose (PPBG) test (≥ 200 mg/dl). According to the last population surveys done in Egypt, the prevalence of TB and DM differed in urban and rural areas, therefore, in this study a multistage sampling was applied to represent different geographical areas of Egypt. The country was divided geographically into 5 sectors: Greater Cairo, the Coastal zone, Upper Egypt, the Suez Canal zone, and Lower Egypt. One governorate was selected by a simple random sample from each sector except for Lower Egypt due to its high population density; in this case, two governorates were selected randomly. The selected governorates were Cairo, Alexandria, Gharbia, Daqahlia, Ismailia and Suhag. In each selected governorate, DM patients who attended outpatient clinics were recruited from all governmental hospitals from June 2012 to December 2012. A total of 4283 patients were recruited. A simple questionnaire was designed to collect data from the DM patients. These data included age, gender, residence area (urban/rural), type of treatment of DM, duration of DM (years), history of chronic diseases, history of previous TB, details of symptoms of suspected TB that used for symptom screening test.

Diagnosis of TB
All DM patients were asked about having a history of TB i.e. history of previous TB diagnosis (known TB). If the answer was yes, then those patients were excluded from the screening test but included in the study. If the answer was no, then those DM patients were screened first by a predefined questionnaire (screening by symptoms) for detecting suspected TB. This symptom screening tool is used in Egypt and almost in all developing countries as it is cheap and affordable method for detecting suspected TB cases especially among high risk groups as diabetic patients. According to the Egyptian National TB Program, suspected TB was based on having a cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (e.g., shortness of breath, chest pains, and hemoptysis) and/or constitutional symptoms (e.g., loss of appetite, weight loss, fever, night sweats, and fatigue). DM patients who showed positive symptoms suggesting suspected TB were further subjected to chest X-ray and sputum analyses (smear and culture) for pulmonary TB and histopathology and/or culture for extra-pulmonary TB. The validity of this algorithm for screening of TB was assessed by World Health Organization-Guideline Development Group [10] and reported the followings: the pooled sensitivity of using symptom screening alone was 57% and pooled specificity was 80%. While using chest radiography these percentages increased to 87% for pooled sensitivity and 89% for pooled specificity.

Sample size calculation
Sample size was calculated based on the estimated prevalence of TB among DM patients. From reviewing the literatures of similar studies in developing countries, the prevalence of TB among DM patients was approximately 2 to 7 times higher than the figure in the population or among non-diabetics. In Egypt, the estimated prevalence of TB (at the time of the study) among adult population was 28 per 100,000 adults. Accordingly, we assumed the following assumptions for calculating the sample size of the study: An estimated prevalence of 112 per 100,000 diabetic patients (4 times higher than the figure among adult population), 95% confidence level and 0.10% confidence limits. From the above assumptions, a sample of 4295 DM patients was required. The sample size was calculated using Epi Info version 7. The actual sample size in this study with complete records was 4283 DM patients.

Ethical approval
The protocol of the study was approved by the Institutional Review Board (IRB) of the faculty of medicine, Ain Shams University. All patient data were kept confidential. Informed consent was obtained from each patient included in the study after having been given a clear description of the study objectives. Patients detected by the bidirectional screening were referred to specialized clinics for further management.

Statistical analysis
All data were analyzed using SPSS version 21. Descriptive analyses with 95% confidence intervals (95% CI) were done for all study variables. The only quantitative variables in the study were age (years) and duration of diabetes (years) and both converted to categorical variables. Age was classified as two categories (< 50 years and ≥ 50 years) while the duration of diabetes was classified as less than 10 years and ≥ 10 years. The tests of significance used for qualitative variables were Chi-square test or Fisher’s exact test when appropriate. Binary (simple and multiple) logistic regression models were used for identifying the predictor variables associated with the detection of new cases of TB among DM patients and to adjust for other confounding variables as age and sex. A P value of ≤ 0.05 was considered significant and all tests of significance were two tailed.

Results
In this study, 4283 DM patients were recruited from different primary healthcare centers (PHCs) and hospitals from the selected study sites. Approximately three-quarters of the DM patients aged ≥ 50 years, two-thirds
were females, 52% were from rural areas, 54.7% had DM duration of less than 10 years, approximately half of the patients were under insulin therapy, and 4.9% also suffered from liver disease. Moreover, three quarters of the diabetic patients included in the study were screened at hospitals. Hypertension was reported among 36.8% of DM patients. In this study, the prevalence of known TB was 210.1 per 100,000 population (95% CI: 110.6-398.6) among DM patients, which was further examined by age, sex, residence, screening place (PHCs and hospitals), DM treatment type, DM duration and chronic disease comorbidities. The results revealed that the known prevalence of TB among DM patients was higher among those less than 50 years old, males, urban residents, those under treatment with oral hypoglycemic drugs, those with DM duration of less than 10 years, and those with liver disease. The prevalence of TB was more or less similar among those screened at PHC or hospitals (Tab. I). Screening DM patients who gave no history of TB (n = 4274) revealed that 261 diabetic patients were positive for symptom screening and referred for further assessment by chest radiography and sputum analyses. The final investigations showed five new TB cases, with a detection rate of 117.0 per 100,000 population (95% CI: 50.0-273.6). This screening detection rate was further analyzed according to patient characteristics. A higher screening detection rate of TB was reported among males, those aged ≥ 50 years, rural residents, those under oral treatment with hypoglycemic drugs, those with a DM duration ≥ 10 years, and those with liver disease (Tab. II).

The lowest figure of CDR was among female diabetics (34.6 per 100,000; 95% CI = 6.1–195.8) while the highest value of CDR was reported among diabetic patients with no history of TB.

### Tab. I. Prevalence of known TB per 100,000 among DM patients.

|                      | Total sample | Known TB | Prevalence of TB (95% CI) |
|----------------------|--------------|----------|--------------------------|
| Total                | 4283         | 9        | 210.1 (110.6-398.6)      |
| Age                  |              |          |                          |
| < 50                 | 1134         | 3        | 264.6 (90.0-774.9)       |
| ≥ 50                 | 3149         | 6        | 190.5 (87.4-436.7)       |
| Sex                  |              |          |                          |
| Male                 | 1393         | 8        | 574.3 (291.3-1129)       |
| Female               | 2890         | 1        | 34.6 (6.1–195.7)         |
| Residence            |              |          |                          |
| Urban                | 2043         | 6        | 293.7 (134.7-639.3)      |
| Rural                | 2240         | 3        | 133.9 (45.6-393.0)       |
| Screening place      |              |          |                          |
| PHC                  | 954          | 2        | 209.6 (60.0-760.0)       |
| Hospital             | 3329         | 7        | 210.3 (60.0-430.0)       |
| Treatment            |              |          |                          |
| Oral                 | 2127         | 6        | 282.1 (129.4-614.1)      |
| Insulin              | 2156         | 3        | 159.1 (47.4-408.9)       |
| Duration of DM       |              |          |                          |
| < 10 years           | 2343         | 7        | 298.8 (144.8-615.4)      |
| ≥ 10 years           | 1940         | 2        | 103.1 (28.3-375.1)       |
| Chronic disease      |              |          |                          |
| None                 | 2110         | 2        | 94.8 (26.0-344.9)        |
| Liver                | 211          | 2        | 947.9 (260.3-3389.0)     |
| Hypertension         | 1578         | 3        | 190.1 (64.7–557.4)       |
| Others               | 384          | 2        | 520.8 (143.0–1879.0)     |

*a p < 0.001 compared with females  
*b P = 0.044 compared with none chronic diseases

### Tab. II. Screened case detection rate (newly diagnosed) of TB per 100,000 among DM patients with no history of TB.

|                      | Total no. screened for TB A | New cases of TB B | Screen detection rate (95% CI) A/B * 100,000 | Number needed to screen A/B |
|----------------------|-----------------------------|-------------------|---------------------------------------------|----------------------------|
| Total                | 4274                        | 5                 | 117.0 (50.0-273.6)                          | 855                        |
| Age                  |                             |                   |                                             |                            |
| < 50                 | 1131                        | 1                 | 88.4 (15.6-499.1)                           | 1131                       |
| ≥ 50                 | 3143                        | 4                 | 127.3 (49.5-326.8)                          | 786                        |
| Sex                  |                             |                   |                                             |                            |
| Male                 | 1385                        | 4                 | 288.8 (112.4-740.2)                         | 346                        |
| Female               | 2889                        | 1                 | 34.6 (6.1-195.8)                            | 2889                       |
| Residence            |                             |                   |                                             |                            |
| Urban                | 2037                        | 2                 | 98.2 (26.9-557.3)                           | 1019                       |
| Rural                | 2237                        | 3                 | 134.1 (45.6-395.5)                          | 746                        |
| Screening place      |                             |                   |                                             |                            |
| PHC                  | 952                         | 0                 | NA                                          | NA                         |
| Hospital             | 3322                        | 5                 | 150.5 (60.0-350.0)                          | 664                        |
| Treatment            |                             |                   |                                             |                            |
| Oral                 | 2121                        | 3                 | 141.4 (48.1-415.0)                          | 707                        |
| Insulin              | 2155                        | 2                 | 92.9 (25.5-338.1)                           | 1077                       |
| Duration of DM       |                             |                   |                                             |                            |
| < 10 years           | 2336                        | 2                 | 85.6 (23.5-311.6)                           | 1168                       |
| ≥ 10 years           | 1938                        | 3                 | 154.8 (52.7-454.1)                          | 646                        |
| Chronic disease      |                             |                   |                                             |                            |
| None                 | 2108                        | 3                 | 142.3 (48.4-417.6)                          | 705                        |
| Liver                | 209                         | 1                 | 478.5 (84.5-2660.0)                         | 209                        |
| Hypertension         | 1575                        | 1                 | 63.5 (46.2-1468.0)                          | 1575                       |
| Others               | 382                         | 0                 | NA                                          | NA                         |

NA = Not Applicable due to zero detected cases
with liver diseases (478.5 per 100,000). The number needed to screen (NNS) to detect one new case of TB among diabetics was 855. Furtherly, NNS values were calculated according to the patient characteristics. The results showed that the lowest value (NNS = 209) was found among DM patients with liver disease, followed by male patients (NNS = 346). The NNS values ranged from 209 to 2889 (Tab. II).

To study factors associated with the total prevalence (diagnosed and newly detected cases) of TB among diabetics; both bivariate and multivariate logistic regression models were applied (Tab. III). The results from the bivariate analysis showed that male DM patients and those with liver disease had a significantly higher prevalence of TB. After adjusting for age and other variables using a logistic regression model, both the male gender and the presence of liver disease remained as independent risk factors, with adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of 12.57 (2.73-57.82) and 6.44 (1.45-28.72) respectively.

**Discussion**

This present study is considered the first national base survey in Egypt to study the feasibility of screening the comorbidity of TB and DM. Recently, there is growing evidence supporting DM as a risk factor for developing TB. There are many published reports suggesting the mechanisms of developing TB among DM patients, such as uncontrolled hyperglycemia, alveolar macrophage dysfunction, decrease in monocyte chemotaxis and neutrophil count and immune system depression that favors infection [11, 12]. However, the mechanism linking DM and TB susceptibility requires further study [13]. In this study, high prevalence of known TB (previously diagnosed elsewhere) among DM patients was found (210.1 per 100,000), which is 7.5-fold higher than the national prevalence of TB (28 per 100,000). Similar to our results, higher prevalence of TB than national figure was reported among diabetic patients in China, Ethiopia, India and Mexico [14-18]. Diabetes mellitus is considered a strong risk factor for developing TB as well as worsening the outcome of treatment and increasing the mortality rates among comorbid patients (TB with DM). Although TB is more associated with other immune suppressive diseases as HIV, yet the prevalence of HIV in Egypt is very low and the prevalence of diabetes is high and with rising prevalence. Therefore, diabetes is considered powerful significant risk factor for TB infection among Egyptian population which in turn adversely affects the global TB control [1]. Our results revealed that male patients experienced 16.6 fold higher in prevalence of TB than females. Also, diabetic patients with liver diseases showed higher significant prevalence of TB than those without chronic diseases. Other patients’ characteristics were insignificantly associated with the prevalence of TB such as age, residence, type of treatment and duration of diabetes. Our results were in agreement to the report of Lin et al. [19] in China who reported higher significant increase in the prevalence of TB among male diabetics and those with liver cirrhosis.

**Tab. III.** Factors associated with the total prevalence of TB among DM patients.

| Characteristic | Total prevalence of TB (previously diagnosed and newly detected) | Simple logistic regression | Multivariate logistic regression |
|---------------|---------------------------------------------------------------|---------------------------|---------------------------------|
|               |                                                              | P value | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) |
| Age           |                                                              |         |                         |         |                         |
| < 50          |                                                              | 0.900   | 1.11 (0.35-3.55)        | 0.545   | 1.63 (0.16-12.90)      |
| ≥ 50          |                                                              |         |                         |         |                         |
| Sex           |                                                              | 0.001   | 12.55 (2.80-56.14)      | 0.001   | 12.57 (2.73-57.82)     |
| Residence     |                                                              | 0.479   | 1.46 (0.51-5.25)        | 0.701   | 0.80 (0.26-2.44)       |
| Urban         |                                                              |         |                         |         |                         |
| Rural         |                                                              |         |                         |         |                         |
| Screening place|                                                              | 0.477   | 1.72 (0.39-7.71)        | 0.264   | 2.43 (0.51-11.53)      |
| PHC           |                                                              |         |                         |         |                         |
| Hospital      |                                                              |         |                         |         |                         |
| Treatment     |                                                              | 0.273   | 1.83 (0.61-5.46)        | 0.505   | 1.49 (0.46-4.87)       |
| Oral          |                                                              |         |                         |         |                         |
| Insulin       |                                                              |         |                         |         |                         |
| Duration of DM|                                                              | 0.471   | 1.49 (0.50-4.46)        | 0.533   | 1.46 (0.45-4.74)       |
| < 10 years    |                                                              |         |                         |         |                         |
| ≥ 10 years    |                                                              |         |                         |         |                         |
| Chronic Illness|                                                              |         |                         |         |                         |
| None          |                                                              |         |                         |         |                         |
| Liver         |                                                              | 0.005   | 6.07 (1.44-25.59)       | 0.015   | 6.44 (1.45-28.72)      |
| Hypertension  |                                                              | 0.813   | 1.07 (0.29-3.99)        | 0.529   | 1.55 (0.40-6.01)       |
| Others        |                                                              | 0.658   | 2.20 (0.43-11.40)       | 0.184   | 3.14 (0.58-16.97)      |

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in addition to other factors as smoking and subjective body loss. Also, Castellanos-Joya et al in Mexico [18] reported highly significant increase in the prevalence of TB among males and those with history of TB or in contact with TB patients. Our screening of DM patients with an unknown history of TB detected 5 new cases of TB with a case detection rate of 117 per 100,000 population. DM patients face frequent infections, which can mainly be attributed to hyperglycemia adversely affecting the immune system. The highest detection rates of new active cases of TB among diabetics were found among those with liver diseases (478.5 per 100,000 population, 95% CI = 84.5-2660.0) and males (288.8 per 100,000 population, 95% CI =112.4-740.2). The NNS of DM patients for detecting one new TB patient was 858 with a range between 209 for those with liver diseases and 2899 for female patients. A similar result (NNS = 812) was reported by Prakash et al. in South India [17] while lower values were reported as 71 and 490 in Mexico and Ghana [18, 21]. The NNS of diabetic patients to find a new case of active TB depends mainly on the prevalence of TB and DM in the community. Egypt is considered to have one of the highest prevalence rates of DM in the Middle East; and there is at least 3 million cases with DM visiting the healthcare facilities thus, the screening of DM patients in Egypt, as well as in similar countries with high DM prevalence rates, will yield a significant number of new TB cases. When the screened detected cases are added to the total number of annual notifiable TB cases it will intensify the case detection rate of TB. Therefore, screening of DM patients for TB in countries with high prevalence of DM and low rate of case detection is of great importance not only for the proper management of patients with the double burden of DM and TB but also for improving the case detection rate of TB. In this study, male diabetics and those with liver disease exhibited a significantly higher prevalence of TB and a higher detection rate of new active cases. These results were confirmed even after adjusting for age and illness duration. Most DM patients with liver disease were classified as such mainly due to hepatitis C virus infection. Egypt is considered to have the highest prevalence of hepatitis C virus infection [22]. Therefore, it is of the utmost importance when starting to treat DM patients with liver disease and TB to closely monitor their liver functions, as the first-line drugs for treating TB increase the risk of hepatitis (hepatotoxic drugs) and can lead to an increase in mortality rate.

In conclusion, the results of this study showed that screening for TB among diabetic patients is feasible and could be implemented in a governmental setting. We found a high yield of TB among DM patients, and early TB detection will improve not only the treatment outcome of this comorbidity but also the case detection rate of TB. Furthermore, the early detection of TB among DM patients will reduce the transmission of TB among DM patients. The prevalence of TB among diabetics was more prominent among males and those with liver disease. These findings support the advantages of implementing TB screening as a routine investigation during the management of diabetes, particularly in developing countries with high prevalence of DM and considered one of the strategies for addressing TB control and increasing case detection rate. There are some limitations of this study. The study sample used for screening diabetic patients for detection of TB was restricted only to patients seen in governmental hospitals affiliated to the Ministry of Health and Population while there are other Universities and private hospitals not included in this study. This is a cross-sectional study with the inability to demonstrate a temporal relationship between exposure and outcome. However, the results of this study may throw the light on the potential risk factors associated with high detection of new TB cases among diabetic patients.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors’ contributions

All authors had participated in the design, implementing the study, analysis of the results and writing all sections of the manuscript. In addition, AW, FM, AM have provided substantial contribution in data collection and field supervision. GM and MA have substantial contribution in data interpretation and data cleaning. All authors have reviewed and approved the final version.

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