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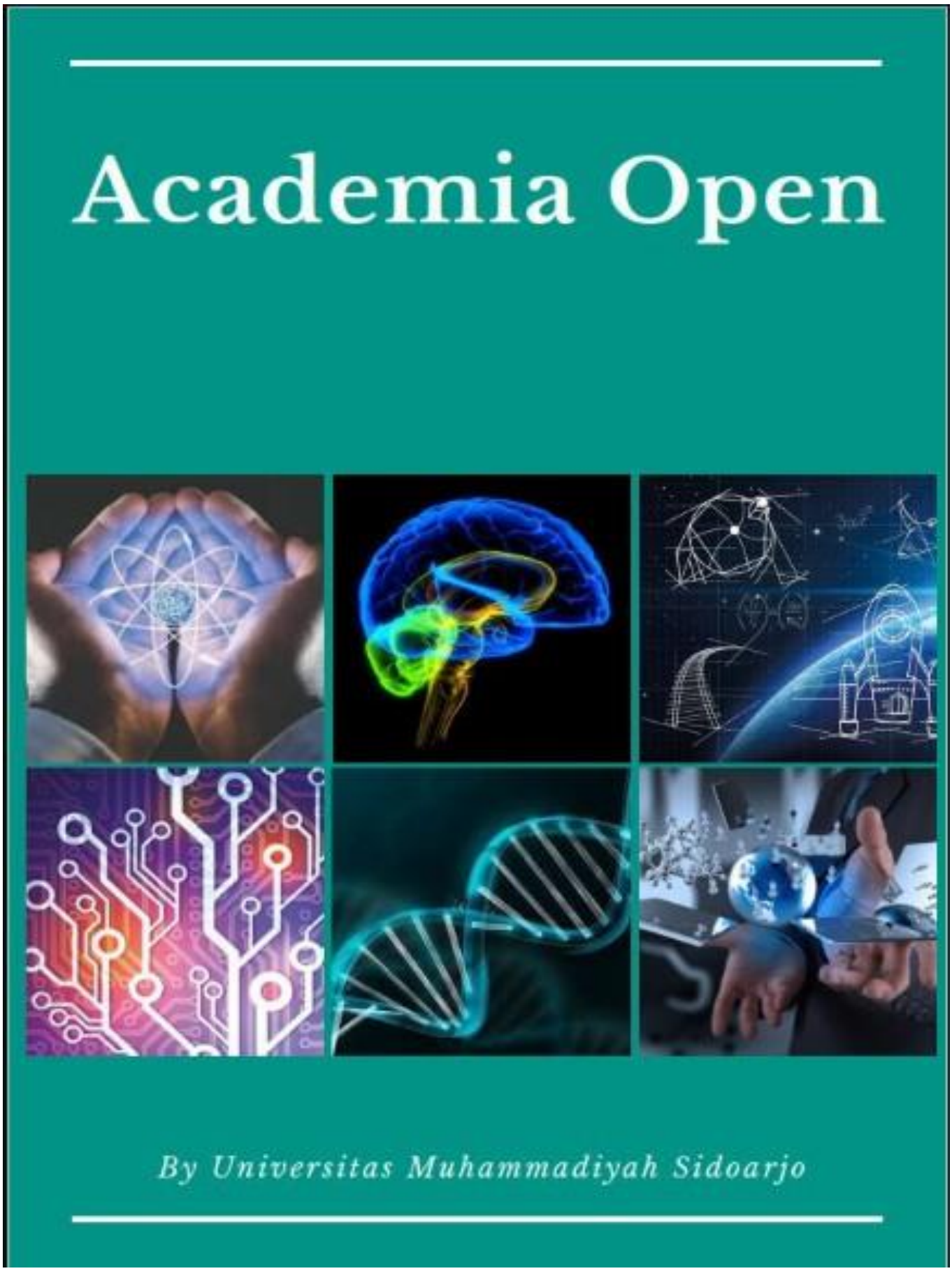

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Prevalence of Latent Tuberculosis among Diabetic Patients: A Cross-Sectional Study

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Abstract

General Background Diabetes mellitus significantly elevates susceptibility to active tuberculosis infection worldwide. **Specific Background** Identifying latent tuberculosis infection in diabetic populations allows early preventive therapy to interrupt disease transmission. **Knowledge Gap** However, localized clinical data evaluating latent tuberculosis prevalence across specific diabetic risk profiles remain limited. **Aims** This study investigates latent tuberculosis infection prevalence and its correlation with glycemic status and clinical factors in diabetic patients. **Results** Screening 100 diabetic patients revealed a 15% tuberculin skin test positivity rate, which was significantly higher in patients with uncontrolled HbA1c levels ($p = 0.034$) as well as those with diabetic retinopathy and nephropathy. **Novelty** This study demonstrates that poor glycemic control and microvascular complications directly correlate with increased latent tuberculosis positivity. **Implications** Integrating targeted latent tuberculosis screening into routine diabetic management can substantially enhance early case detection and preventive control strategies.

Key Findings Highlights

Tuberculin skin test positivity reached 15% among the evaluated diabetic cohort.

Uncontrolled HbA1c levels significantly correlated with higher latent tuberculosis prevalence.

Diabetic nephropathy and retinopathy exhibited strong associations with skin test positivity.

Keywords: Latent Tuberculosis, Diabetes Mellitus, Tuberculin Skin Test, Glycemic Control, Microvascular Complications

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Introduction:

One of the leading causes of disease and mortality worldwide is still tuberculosis (TB). According to estimates from the World Health Organization (WHO), there were 9.27 million new cases of tuberculosis (TB) in 2007, which resulted in almost 1.3 million fatalities . Reactivated latent infection accounts for almost 80% of tuberculosis cases in the United States (US) , and a course of antibiotic treatment could avert almost 80% of these occurrences . In order to eradicate tuberculosis in the United States, the U.S. Public Health Service advises screening and treating those who are more susceptible to latent tuberculosis .

The WHO estimates that over two billion people worldwide have latent Mycobacterium TB infections. Immunological indicators of the immune response are essential for identifying such situations . In LTBI, chest radiographs are typically normal; nevertheless, they may show pleural thickening (i.e., scarring), calcified, non-enlarged regional lymph nodes, or dense nodules with calcifications (i.e., a Ghon complex) . Since these isolated findings are not linked to a higher risk of development to active TB when compared to radiographs with no abnormalities, patients with these lesions can receive treatment for LTBI .

Until 2001, the TST was the only method for diagnosing LTBI . The test was named for Charles Mantoux and Clemens von Pirquet, who implemented it in 1907 after Robert Koch first described it in 1890 .

Due to the effects of Bacille Calmette-Guerin (BCG) vaccines and non-tuberculous mycobacteria (NTM), previous TSTs used to detect LTBI had issues with specificity. On the other hand, Interferon-gamma Release Assays (IGRAs), which quantify interferon-γ produced from lymphocytes as a result of activation of TB-specific antigens, have exceptional specificity. April 2005 saw the start of QuantiFERON®-TB-2nd generation use; as of 2010, QuantiFERON®-TB-3rd generation (QuantiFERON®-TB-Gold In-Tube) was in use. Since November 2012, T-SPOT® .

Many factors lead to a high risk for developing active TB, including the following: diabetes; hemodialysis; use of drugs with an immunosuppressive effect, such as corticosteroids; smoking; alcoholism. People with diabetes are thought to have a 1.5–3.6 times higher chance of developing tuberculosis than the general population .

The higher incidence of tuberculosis in those with diabetes mellitus, especially in those with complications from the disease . More than a millennium ago, Avicenna (980–1027 AD) recorded the first account of the connection between DM and TB. Since then, a number of epidemiological research have generally supported the association between DM and TB as well as the nature of their interaction regarding comorbidity. The impact of diabetes mellitus on tuberculosis was a significant concern for researchers in the early 20th century, but with the development of effective treatments for both illnesses in the second half of the century, this issue was largely ignored .

In the UK, collaborative treatment clinics for DM and TB were conducted in the 1950s , and the notion that DM and TB are related is not new. "Phthisis" (TB) was described as a "complication" of diabetes in the fifth century , repeating Root's 1934 assertion that DM comes before TB . Men are more likely than women to contract tuberculosis (TB), which starts in early adulthood and lasts a lifetime. It has long been believed that men are more likely than women to be exposed to tuberculosis in the community [17-19]. Therefore, this study aimed to identify the Prevalence of LTBI among diabetic patients and the relationship with age and gender.

Patients and Methods:

A case-control study was carried out on (100) diabetic patients registered in Al-Faiha Diabetes Endocrine and Metabolism Center at Basrah, from October 2013 to August 2014. The data were collected from each patient, including: age, gender, job, associated chronic illnesses, social history (smoking and alcohol consumption), drug history (steroids, chemotherapy, and diabetic therapy), types and complications of DM. Legally, all patients were informed about the study, and permission was obtained.

Patients excluded from the study include: pregnancy, elderly patients (>70 years old), patients younger than 14 years old, critically ill patients, those with psychiatric problems, and those with symptomatic chest infections.

A group of 100 patients (39 males and 61 females, aged 15-70 years with a mean age of 53.23 years), types of DM (12 with type1, 85 with type 2 and 3 with gestational DM), regarding their level of HbA1C (38 with controlled HbA1C i.e. ≤7, 62 with uncontrolled HbA1C i.e.> 7), diabetic complications; (62 with neuropathy which diagnosis by their symptoms and bedside clinical examination not by electrophysiological study, 22 with nephropathy which screened by dip stick urinalysis, 19 with retinopathy which diagnosis by ophthalmologist, 3 with diabetic foot evaluated by orthopedical). Those with drug history (18 on chronic use of steroids,1 on chemotherapy for breast cancer, and 14 patients on insulin only, 45 on oral therapy, and 41 on combination therapy at the time of data collection), and social history (41 patients with a history of smoking,1 patient with alcohol drinking).

All patients were examined for LTBI by chest X-ray and TST. Findings on chest x-ray do not exclude LTBI; fine lesions are sometimes detected by computed tomography . Taking into account the cost and the amount of radiation exposure from CT, it was not done in this study. TST administration using the Mantoux Method. The Mantoux procedure, which involves injecting 0.1 mL of 5 Tuberculin Units (TU) of PPD tuberculin intradermally to create a wheal (6 to 10 mm) in diameter, is the preferred TST . Other concentrations (1 or 250 TU per dose) are not well standardized, less sensitive and specific, and

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not recommended .

Conversion: One of the following is referred to as skin test conversion:

- In the event of recent exposure, a positive TST up to eight weeks following an initial negative TST.
- In the context of a baseline negative TST, a positive TST found during serial testing with a persistent risk of exposure (such as healthcare professionals).

Statistical analysis:

The statistical package for the social sciences (SPSS) software version 20 was used to analyze the collected data. The mean ± standard deviation, frequency, and percentage of each value were used in the descriptive analysis. Significance was defined as a p-value of less than 0.05.

Results

Table 1: Demographic distribution of the study shows that the 100 diabetic patients who participated in the study included 39 (39%) males and 61 (61%) females, aged 15–70-year-old with a mean age of 53.23 years; duration of diabetes ranged from 0 to 15 years, with a mean duration of 7.43 years. While those with positive TST were 15 (15%), 85 (85%) had negative TST. Most of the diabetic patients had an uncontrolled HbA1c (62%), compared to 38%) had a controlled HbA1c. Most of the patients had type 2 diabetes mellitus (85%), whereas (12%) had type 1 diabetes mellitus, and only a small percentage (3%) had gestational diabetes.

Most of the patients with diabetes were taking oral medications (45%), whereas 41% were taking a combination of oral medications and insulin, and a small percentage were taking insulin only (14%). Most of the patients have diabetes mellitus for more than 5 years (35%), whereas approximately one-third of the patients have diabetes mellitus for more than 10 years (34%), and approximately one-third of the patients have diabetes mellitus for 5 to 10 years (31%), with a mean score and standard deviation of 7.430 ± 4.519, respectively. Most of the patients have neuropathy as a complication of diabetes mellitus (62%), whereas approximately one-fifth of the patients have retinopathy as a complication of diabetes mellitus (19%), and only a small percentage of the patients have diabetic foot (3%).

Approximately one-fifth of the patients used steroid medications in their history (18%), and only a small percentage of the patients (2%) used chemotherapy medications. Most of the patients were smokers (40%), and only a small percentage were drinking alcohol (1%) as a behavioral history. Most of the patients had hypertension (71%), whereas less than one-fifth of the patients had ischemic heart disease (16%), a small percentage of the patients had cerebrovascular accident (5%), a small percentage of the patients had congestive heart failure (4%), and also a small percentage of the patients (3%) had thyroid gland disorders (hyperthyroidism and hypothyroidism) as an associated chronic illness. Also, a very small percentage of the patients had chronic obstructive pulmonary disease, liver disease, and atrial fibrillation (2%) as associated chronic illnesses. Finally, a very small percentage of the patients had hypoparathyroidism, polyglandular disease, rheumatoid arthritis, malignancy, and peptic ulcer (1%) as associated chronic illnesses.

Table (1): Demographic Distribution of the Study

Variable		Mean ± Sd. Deviation /No. (%)	
Age	15-45 Years	29(29%)	53.23 ± 14.5 Years
	46-65 Years	51(51%)	
	>65 Years	20(20%)	
Gender	Male	39(39%)	
	Female	61(61%)	
TST	+Ve	15(15%)	
	-Ve	85(85%)	
HBA1C	Controlled	38(38%)	
	Uncontrolled	62(62%)	

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Type of Diabetes	Type1	12(12%)	
	Type2	85(85%)	
	Gestational	3(3%)	
Type of Diabetic Therapy	Oral	45(45%)	
	Insulin	14(14%)	
	Combination	41(41%)	
Duration of Diabetes	> 5Years	35(35%)	7.430± 4.519 Years
	5-10 Years	31(31%)	
	<10 Years	34(34%)	
Diabetic Complication No=100	Neuropathy	62(62%)	
	Nephropathy	22(22%)	
	Retinopathy	19(19%)	
	Diabetic Foot	3(3%)	
Drugs History	Steroid	18(18%)	
	Chemotherapy	2(2%)	
Behavioral History	Smoking	40(40%)	
	Alcohol	1(1%)	
Associated Chronic Illness N=100	Hypertension	71(71%)	
	Ischemic Heart Disease	16(16%)	
	Congestive Heart Failure	4(4%)	
	Cerebrovascular Accident	5(5%)	
	Malignancy	1(1%)	
	Chronic Obstructive Pulmonary Disease	2(2%)	
	Liver Disease	2(2%)	
	Hypothyroidism	3(3%)	
	Hyperthyroidism	3(3%)	
	Hypoparathyroidism	1(1%)	

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	Polyglandular Disease	1(1%)
	Rheumatoid Arthritis	1(1%)
	Atrial Fibrillation	2(2%)
	Peptic Ulcer	1(1%)

Table 2: shows the relation between age groups and TST; on comparing TST results among different age groups, those with age group 15-45 years; 6 out 29 were positive, group 46-65 years; 7 out of 51 were positive, and group >65 years; 2 out 20 were positive, there were no statistically significant between those age groups (P = 0.287).

Table (2): The Relation between age group and TST.

		TST		Total
		≥10mm No. (%)	<10mm No. (%)	
Age (Years)	15-45	6(40%)	23(27.05%)	29(29%)
	46-65	7(46.66%)	44(51.76%)	51(51%)
	>65	2(13.33%)	18(21.17%)	20(20%)
Total		15(15%)	85(85%)	100(100%)
Chi-S=1.193		P=0.287		

Table 3 shows the relation between gender and TST; it shows that out of 61 females, 10 were TST positive, while out of 39 males, 5 were positive. However, this difference was not statistically significant (P = 0.62).

Table (3): The Relation between gender and TST

		TST		Total
		≥10mm No. (%)	<10mm No. (%)	
Gender	Male	5(33.33%)	34(40%)	39(39%)
	Female	10(66.66)	51(60%)	61(61%)
Total		15(15%)	85(85%)	100(100%)
Chi-S=0.238		P=0.62	Odds ratio=0.75	

Discussion

DM has been associated with a higher than usual risk of developing tuberculosis [23] [24]. This study revealed those > 65-year-old age group has a low prevalence of positive TST (10%) compared with other age groups. This finding is similar to the result of other studies that had been done by Thompson et al [25] and Tort et al [26], demonstrating that anergy may contribute to the occurrence of decreased relative strength of reaction

or lack of reaction to tuberculin, which rises with age.

Furthermore, the prevalence of the "booster effect" of skin-test responsiveness to antigen rises with age. Therefore, when a negative reaction is measured, all elderly individuals who take a TST must be retested within two weeks, to ensure that a potentially false-negative reaction is recognized.

In the age group 15-45 years old, the study revealed a higher prevalence rate (20.68%) then age group 46- 65 years old prevalence rate (13.7%), similar to a study that was done by Wood et al [27], showed a very high frequency of LTBI in young people due to an exceptionally high rate of TB infection acquisition in childhood and adolescence.

The relation between gender and TST: the study revealed that female slightly greater than male in prevalence of LTBI (16.3%, 12.8%), respectively, due to women more than males attending health care services, as in this study 61 female diabetic patients were screened for LTBI compared with 39 males.

Several studies discussed why diabetic females are more likely to have TB than diabetic males. There are several possibilities. Asch et al [28] discovered that due to lower than recommended chronic health care utilization, male diabetes subjects with TB may be mistakenly labeled as non-diabetics more frequently than female subjects.

Salem et al. [29] discovered that women with diabetes might be more vulnerable to tuberculosis than males with diabetes. Cytokines such alpha tumor necrosis factor and gamma interferon are inhibited by estrogens. Diabetes may increase the likelihood of an immunosuppressive impact. Additionally, a recent study conducted in South India found that women were more likely than men to seek medical attention [30].

Regarding the relation of TST and glycemic state, most of the patients included in this study had poor glycemic control; 49 diabetic patients had HbA1C ≥ 7. The study revealed the prevalence of LTBI was higher in those with HbA1C level ≥ 7 (20.97%) compared with those with HbA1C <7 (5.26%).

An observational study was done by Leung et al [31], discovered that individuals with HbA1c ≥ 7%, which indicates poor recent glycemic control, had a significantly higher risk of tuberculosis (TB) (adjusted HR (aHR) 2.56, 95% CI 1.95 to 3.35), whereas those with HbA1c < 7% did not (aHR 0.81, 95% CI 0.44 to 1.48).

The relationship between TST and diabetic complications: this study screened 100 diabetic patients; 19 patients had retinopathy, 22 had nephropathy, and the study revealed that the highest statistically significant positive TST was observed in DM retinopathy and nephropathy. A prospective cohort study by Baker et al. [32] discovered a higher incidence of tuberculosis in those with diabetes, especially in those with DM-related comorbidities. Diabetic autonomic neuropathy can contribute significantly to the increased risk of respiratory tract infections, including tuberculosis, in diabetic patients by causing abnormal basal airway tone due to changes in vagal pathways. This can result in decreased bronchial reactivity and bronchodilation.

In contrast to our study, which included 62 diabetic patients with neuropathy but showed no significant relation with TST. The explanation for our finding that patients with diabetic neuropathy were diagnosed by their symptoms and bedside clinical examination, not by electrophysiological study.

Regarding the relation of TST to type of DM. This study revealed a high prevalence of positive TST in those with type 2 DM (12.9%) compared to those with type1and gestational DM. Chang et al [33] demonstrate that, after controlling for confounding variables, patients with type 2 diabetes have a greater risk of tuberculosis than control subjects. In areas where tuberculosis is endemic, the present diabetes pandemic may cause the disease to resurface. To further lower the incidence of tuberculosis, preventative interventions should be implemented, including addressing the potential that type 2 diabetes enhances an individual's susceptibility to incident TB.

Conclusion

Prevalence of LTBI estimated by chest X-ray and TST was higher among those with uncontrolled HbA1C (≥7), diabetic nephropathy, retinopathy, those with risk factors like steroid users and smokers, and it was not correlated with types or duration of DM. According to our findings, TB control programs should target people with diabetes for treatments like active case detection and latent TB treatment; on the other hand, efforts to diagnose, detect, and treat DM may have a positive effect on TB control.

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