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Relation between Latent Tuberculosis and Type 1 Diabetic Children

Saad Ahmed Mansour[1], EhabAbdElhamidAbdElsalam[2],Rehab Ahmed Rabie[3],NaglaaFathyAbdElrazik Ibrahim[4]

[1]Professor of Pediatrics, Faculty of Medicine – Zagazig University.[2] Professor of Pediatrics, Faculty of Medicine – Zagazig University,[3]Lecturer of Medical Microbiology and Immunology, Faculty of Medicine – Zagazig University, [4] M.B.B.CH, Menoufia University.
Corresponding Author Name: NaglaaFathyAbdElrazik Ibrahim
Email:doc.naglaafathy33@gmail.com

Abstract

Background: Diabetes mellitus (DM) is the most common endocrine disease and one of the chronic condition affecting children . Type 1 DM (T1DM) is a chronic condition characterized by persistent hyperglycemia due to relative or absolute insulin deficiency. T1DM classified to two types:- Immune mediated. Idiopathic. Latent TB infection (LTBI) is a subclinical infection caused by Myobactaeria tuberculosis complex without clinical, bacteriological or radiological evidence of manifest TB disease.Aim of the work: Early detection of latent T.B in type 1 diabetic children at Zagazig university pediatric hospital. To estimate association between type 1 DM and LTBI.**Methods:**This comparative cross sectional study was conducted over in the period fromoctober 2019 to October 2020. It Included 81 cases had type 1 DM and 81 *healthy children as control group*. This study was conducted at Zagazig University Pediatric Hospital.

All patients were subjected to the following: *Tuberculin test*, *HbA1C*, *CBC* and BCG scar.**Results:**In the current study, mean of age among cases group was 10.90 ± 4.47 This study showed that, the percentage of Tuberculin test was higher among cases group than controls group (32.1%, 7.4%) p value= 0.000 .OR estimate for DM on risk of TB was 5.9 (95% CI 2.27 to 15.33). This study showed that, there was no statistically significant difference between positive and negative regarding duration of DM. This study showed that, there was statistically significant increase in HBA1C among Positive than Negative Tuberculin test. This study showed that, there were statistically significant positive correlation between Tuberculin test and HBA1C.

Conclusion: The percentage of tuberculin test was higher among diabetic group than control group. There was no significant difference between diabetic group and control group regarding BCG scar. There was no statistically significant difference between positive and negative tuberculin regarding age and duration of DM. There was statistically significant increase in HBA1C among positive than negative tuberculin test.

Key words: Latent Tuberculosis- type I diabetes mellitus- Association.

Introduction:

Diabetes mellitus (DM) is the most common endocrine disease and one of the chronic condition affecting children .DM is a non communicable disease which can impair host immunity and increase susceptibility to various infectious diseases including tuberculosis**. (1).**

Type 1 DM (T1DM) is a chronic condition characterized by persistent hyperglycemia due to relative or absolute insulin deficiency. T1DM classified to two types:- Immune mediated. Idiopathic. Latent TB infection (LTBI) is a subclinical infection caused by Myobactaeriatuberculosis complex without clinical, bacteriological or radiological evidence of manifest TB disease.**(2).**

LTBI result from contact with active case of TB which can be tested by tuberculin test or interferon gama release assays (IGRAS).[3].

Children with LTBI have an increased risk of developing active TB. Children under age of four are at higher risk progression to active TB. It has been reported that up to 40% of infected children who are at particul-ar risk for developing TB including malnourished, immunocompromised or living in high TB burden area.[4; 5].

The number of diabetic patient increase with increase in low to middle income countries and at the same time these countries are dealing with high burden of TB.[6; 7].

In the first half of 20th century, when there is impairment in antidiabetic treatment, it was considered a risk factor for TB.[8].

Studies proved that DM and high blood glucose lead to impaired innate immunity. So diabetic patient has 25 %-75% increase risk of pneumonia.[9; 10;11].

A population based cohort study from Hong Kong and other studies found that DM increase risk of TB infection. [12; 13].

As prevalence of diabetes increase globally so it is important to detect any association with TB infection so that strategy for controlling TB can be appropriately targeted [7; 14].

Aim of the work: Early detection of latent T.B in type 1 diabetic children at Zagazig university pediatric hospital. To estimate association between type 1 DM and LTBI.

Patients and Methods

This comparative cross sectional study was conducted over in the period fromoctober 2019 to October 2020. It Included 81 cases had type 1 DM and 81 *healthy children as control group*. This study was conducted at Zagazig University Pediatric Hospital.

Sample size: Two sided significance level 95(1-alpha) power (1-beta) % chance 80 of detecting ratio of sample size, unexposed/ exposed 1. Percent of unexposed with outcome 12% percent of exposed with outcome 30% odds ratio 3.1

- Risk / Prevalence ratio 2.5
- Risk / Prevalence difference 18
- Sample size of diabetic children 81
- Sample size of healthy children 81
- Total sample size 162

Inclusion criteria:

1. Written informed consent will obtain from all parents.
2. Patient included in the analysis if they received chest X-ray and attented follow up for TST reading.
3. All children in this study aged from 1 to 18 years old .

Exclusion criteria:

1. If diagnosed with type 1 diabetes for < 1 year.
2. Non type 1 diabetes.
3. No informed consent obtained.
4. Participation in another study at the time of recruitment .
5. Congenital or acquired immune deficiency disease .
6. Steroids intake in the last 4weeks.

Methodology:

All patients were subjected to the following:

1. **Full history taking**

Included age at diabetes diagnosis, current insulin dose, symptoms suggestive of TB, previous history of TB, contact with TB source case.

2. Full general examination

Included height, weight, BMI, chest, cardiac and abdominal examination.

3. Investigation

Cases

- ***Tuberculin test***

TB screening was done for both groups using TST, TST was administered by injecting 0.1 ml of two tuberculin units of purified protein derivative (RT 23; Statens Serum Institute, Copenhagen, Denmark) into the volar surface of the forearm (intradermal) with a disposable syringe and a 27 G needle. The maximal transverse size of induration, not the erythema, was read (in millimeters) 48–72 h later with a ball-point pen and a ruler [(15)].

We used TST more than 10mm as the cut-off-value to determine TST positivity regardless of Bacillus Calmette–Guérinvaccination status [(16)].

This procedure was carried out by a well-trained laboratory technician using the Mantoux technique.

- It was done to all cases
- It was repeated after 2 weeks in negative test in 1st time.

Chest x-ray

- It was done for all cases .

HbA1C

Type 1 DM was diagnosed according to [(17)].

CBC

(Complete Blood Count) with differential cell count, using automated cell counter "Sysmex KX21" supplied by Sysmex corporation (Japan), together with examination of Leishman–stained peripheral blood smears for differential leucocytic count.

Control group

Tuberculin test

- It was done to all Control group
- It was repeated after 2 weeks in negative test in 1st time .

- **Chest x-ray**

It was done for +ve tuberculin test group

- **BCG scar**

Evaluation of BCG scar in all children.

Administrative Design:-

Approval was taken from the institutional review board (IRB)of faculty medicine Zagazig University.

Statistical Analysis:

The collected data were tabulated and analyzed using SPSS version 24 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (X2) was used to analyze categorical variables. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant),.

- **r→Pearson's Product correlation coefficient:** it evaluates the linear association between 2 quantitative variables (one is the independent var.X, and the other is the dependent var., Y). value of "r" ranges from -1 to 1

0= no linear correlation

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1= perfect positive correlation
-1 = perfect negative correlation
Positive= increase in the independent variable leads to increase in the dependent variable
Negative = increase in the independent variable leads to decrease in the dependent variable.

Results:
There was no statistically significant difference between cases group and controls group regarding sex and age**Table (1)**.
The percentage of Tuberculin test was higher among cases group than controls group (32.1%, 7.4%) p value= 0.000**Table (2)**.
There was no statistically significant difference between cases group and controls group regarding BCG scar**Table (3)**.
This table shows that the mean of platelet was (283.04± 18.03) and ranged between 230 and 348, the mean of WBC was (8.08± .292) and ranged between 7.4 and 8.7, the mean of HB was (10.97± .269) and ranged between 10.3 and 11.6, the mean of HBA1C was (7.57 ± 0.60) and ranged between 6.8 and 8.9 and the mean of ESR at 1st hour was (12.3±4.7) and ranged between 3 and 23. The mean of ESR at 2nd hour was (24.6±3.5) and ranged between 10 and 35**Table (4)**.
There was no statistically significant difference between positive and negative regarding Age, Duration of DM and sex. There was statistically significant increase in HBA1C among Positive than Negative Tuberculin test**Table (5).**
Table (6) and figure (1,2,3) show that there were no statistically significant correlation between Tuberculin test and age and Duration of DM, and there were statistically significant positive correlation between Tuberculin test and HBA1C.

Table (1): Comparison between cases group and controls group regarding age and sex.

			Cases Group (No.=81)	Controls group (No.=81)	t.test	P. value	OR	95% Confidence Interval
Age (years)	**Range**		1.5-17	1.5-17	2.940	0.09		
	Mean ± SDs		10.90 ± 4.47	9.90 ±4.20				
Sex	**Female**	**No.**	47	38	X^2 2.005	0.157	0.6	0.34 - 1.19
		%	58.0%	46.9%				
	Male	**No.**	34	43				
		%	42.0%	53.1%				

Table (2): Comparison between cases group and controls group regarding Tuberculin test.

			Cases group (No.=81)	Controls group (No.=81)	X^2	P. value	OR	95% Confidence Interval
Tuberculin test	**negative**	**No.**	55	75	15.577	0.000	5.9	2.27 - 15.33
		%	67.9%	92.6%				
	positive	**No.**	26	6				
		%	32.1%	7.4%				

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Table (3): Comparison between cases group and controls group regarding BCG scar.

			Cases group (No.=81)	Controls group (No.=81)	X^2	P. value	OR	95% Confidence Interval
BCG scar	Absent	No.	2	1	0.340	0.560	0.5	0.044- 5.55
		%	2.5%	1.2%				
	Present	No.	79	80				
		%	97.5%	98.8%				

Table (4): Laboratory Data among cases group including CBC, HBA1C and ESR.

	Rang	Mean ± SDs
Platelet*10^3	230 - 348	283.04± 18.03
WBC *10^3	7.4 – 8.7	8.08± 0.292
HB mg/dl	10.3 – 11.6	10.97± 0.269
HBA1C	6.8 – 8.9	7.57 ± 0.60
ESR at 1st hour	3 – 23	12.3±4.7
ESR at 2nd hour	10 – 35	24.6±3.5

Table (5): Comparison Positive tuberculin test and Negative tuberculin test regarding (Age, Duration of DM, HBA1C and sex).

		Positivetuberculin test (No.=26)	Negativetuberculin test (No.=55)	t.test	P. value
Age	**Mean ± SDs**	9.52 ± 5.40	11.56 ± 3.84	-1.954-	0.054
Duration of DM	**Mean ± SDs**	2.77 ± 2.27	3.56 ± 3.31	-1.106-	0.272
HBA1C	**Mean ± SDs**	7.88 ± 0.65	7.42 ± 0.52	3.397	0.001
Sex	**female**	12 (46.2%)	35 (63.6%)	X^2 2.215	0.137
	male	14 (53.8%)	20 (36.4%)		

Table 6): Correlation between Tuberculin test and (Age, Duration of DM, HBA1C).

Correlation	Pearson's correlation	
	r	p
Age * Tuberculin test	-.218	.051
Duration of DM * Tuberculin test	-.098	.383
HBA1C * Tuberculin test	.539	.000

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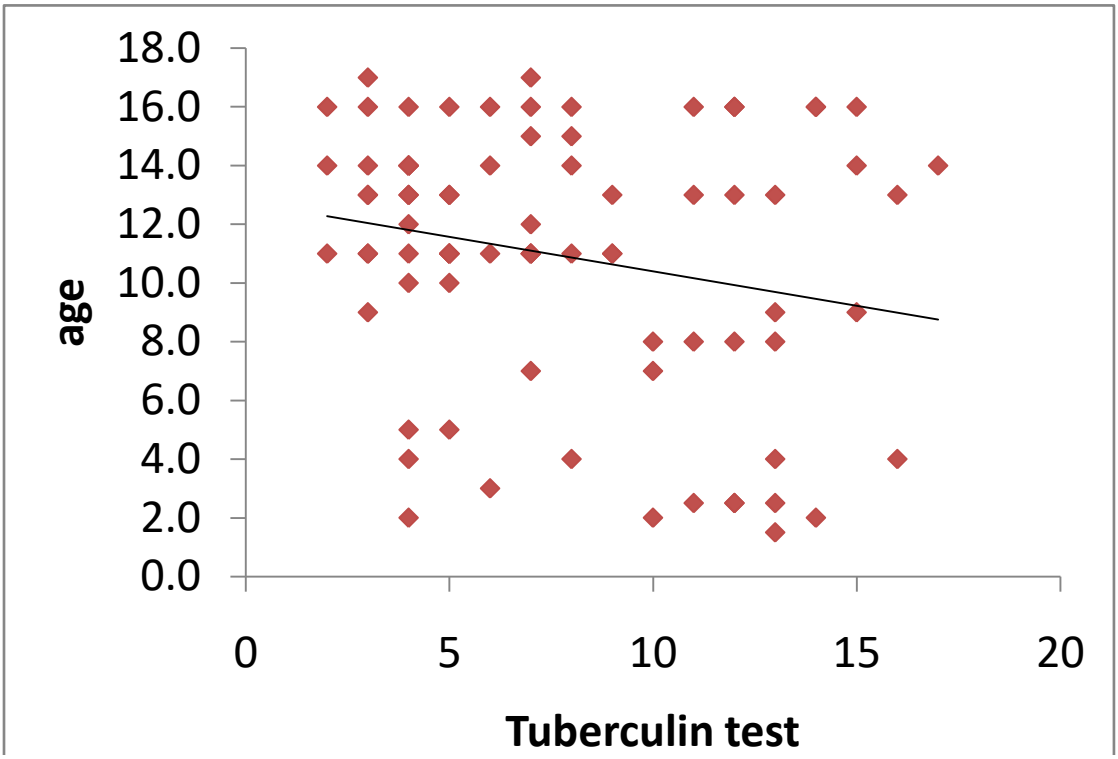

Figure (1): Correlation between Tuberculin test and age.

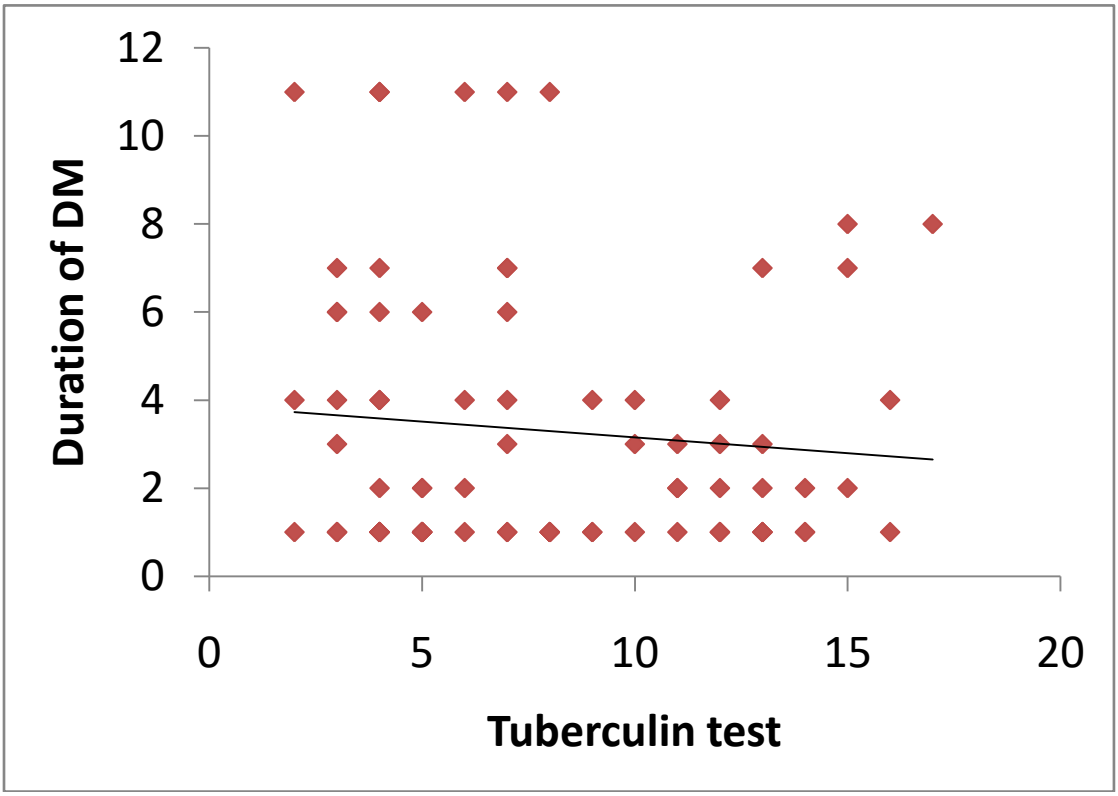

Figure (2): Correlation between Tuberculin test and Duration of DM.

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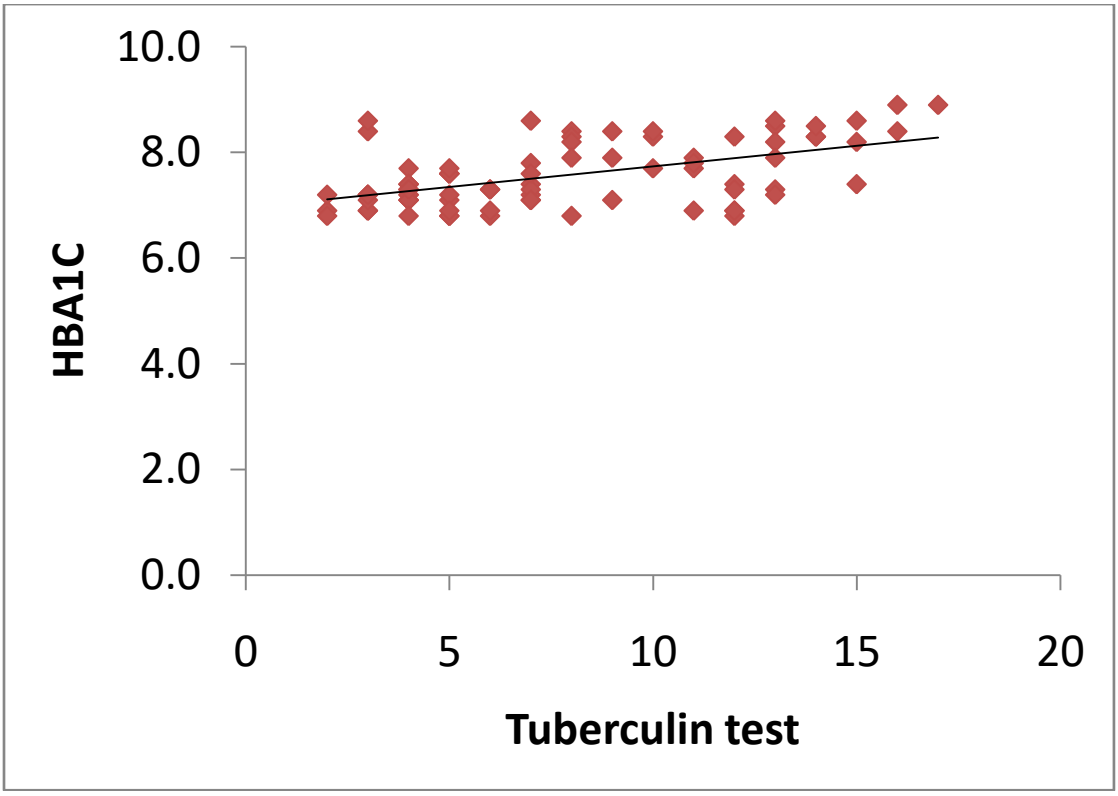

Figure (3): Correlation between Tuberculin test and HBA1C.

Discussion

In the current study, mean of age among cases group was 10.90 ± 4.47

This was in accordance with **Hassan et al.,** [18] who found the age-specific incidence increased with age, as they have 12 cases aged 6–10 years and 18 cases aged 10–15 years in a total of 30 positive cases in their study. The mean age of all diabetic children was 11.3 ± 2.8 years.

In agreement also with **El-Ziny et al.,** [19] who aimed to define the incidence, prevalence and demographic characteristics of T1DM in children (0-18 years) living in the Nile Delta region, one of the most densely populated areas in Egypt. They found more patients presented at 12 and 10 years of age.

In harmony with, **Demirbilek et al.,** [20] who showed that the incidence of T1DM peaked in the age group 10-14 years.

In the study of **Karvonen *et al.*** [21]**,** age-specific incidence of T1DM was calculated in 5-year age groups (0–4, 5–9, and 10–14 years). In most populations, the incidence rates increased with age and were the highest among children aged 10–14 years.

In children under age 15, the DiaMond Project Group reported a higher risk of developing T1DM in the 10-14 year age group, while the age group 5-9 years had a medium risk and the age group 0-4 years had a lower risk. The age group 10-14 years had about twice the risk of developing T1DM compared to children younger than 5 years and this trend did not vary by gender. [22].

This study showed that, the percentage of Tuberculin test was higher among cases group than controls group (32.1%, 7.4%) p value= 0.000 .OR estimate for DM on risk of TB was 5.9 (95% CI 2.27 to 15.33).

In agreement with a recent systematic review concluded the pooled OR estimate for DM on risk of LTBI was 1.18 (95% CI 1.06 to 1.30). [23]**.**

This study showed that, there was no statistically significant difference between positive and negative regarding duration of DM.

In agreement with**Lin et al., [24]** who investigated the combined effect of longer duration of DM and TB. They found they did not affect the risk of LTBI.
This finding was comparable with that of **Pealing *et al*. [25]** in their study reported that duration of DM did not affect the association between TB and DM.
There have been several studies on cases of pre-diabetes or untreated early diabetes supported the hypothesis. **[14; 26].**
Patients with diabetes with longer disease duration tend to have a smaller social network and less contact with their family members or friends. **[27; 28]** This may reduce the opportunity of social contact with TB cases and trumped the risk for recent TB infection.
This study showed that, there was statistically significant increase in HBA1C among Positive than Negative Tuberculin test.This study showed that, there were statistically significant positive correlation between Tuberculin test and HBA1C.
This was in accordance with **Cabrera et al., [29]** who reported strength of association between HbA1c and tuberculosis.
Martínez-Aguilar *et al*. [30] reported that increased HBA1C was significant risk factors.
This is an expected observation especially when knowing that TST induration depends on cellular immune reaction **[31]** which is impaired in poorly controlled diabetic cases **[32]**.
Webbet al., [33]demonstrated Raised HbA1c was associated with prevalent TB. Poor glycaemic control was significantly associated with prevalent TB disease. Poor glycaemic control may predispose to TB disease by reducing cytokine production.
In disagreement with **Bakr et al., [34]** who found there was a statistically significant negative correlation between TST induration diameter and HBA1C.
A study from Japan showed that interferon-gamma (IFN-γ) production was significantly lower in diabetics with poor glycaemic control than in patients with good control, and showed a significant negative correlation to HbA1c. **[35]**.
The level of hyperglycaemia has been found to have a distinct influence on the microbicidal role of macrophages, with even short-lived blood glucose concentrations of 200 mg/dl (11.1 mmol/l) significantly reducing the macrophage respiratory burst. **[36]**.

Conclusion:

The percentage of tuberculin test was higher among diabetic group than control group. There was no significant difference between diabetic group and control group regarding BCG scar. There was no statistically significant difference between positive and negative tuberculin regarding age and duration of DM. There was statistically significant increase in HBA1C among positive than negative tuberculin test.

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