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Thyroid dysfunction In Type 1 Diabetic Pediatric Patients And It's Relation To Diabetes Severity

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ABSTRACT

Background; *Type 1 diabetes (T1DM) is an autoimmune disease often associated with thyroid abnormalities.* ***Aim and objectives:*** *To assess the thyroid function in pediatric patients with T1DM and it's relation to diabetes severity.* ***Subjects and methods:*** *This is a cross section study was performed at Zagazig Univeristy hospital in diabetes clinic and Pediatric Diabetes Insurance Clinic in Sharkia Governorate,on two hundred and twelve patients, during a period from November 2019 to April 2020.* ***Results****: children who had both T1DM and hypothyroidism most of them experienced Diabetic Ketoacidosis (DKA) as the first presentation of their disease (68%) and had higher HbA1C levels (11.37 ±2.10) in comparison to (36.3%) and (10.02 ± 1.89) respectively in diabetic patients with normal thyroid function.* ***Conclusion****: Hypothyroidism is prevalent among pediatric patients with T1DM and is associated with a more aggressive form of the disease. Patients with T1DM and hypothyroidism have higher rates of DKA and develop the disease at younger ages*.

Keywords: *Autoimmune, DKA, insulin, ketoacidosis, thyroid.*

I. Introduction

Type 1 Diabetes Mellitus (T1DM) is one of the most prevalent endocrine disorders among children worldwide; annually an estimated of 65,000 children develop the disease and its incidence is increasing 3% each year. Between 10 to 70% of these children present in Diabetic Ketoacidosis (DKA) as their first presentation of the disease **[1].**

Hypothyroidism and subclinical Hypothyroidism is prevalent among pediatric patients with T1DM; while the reported prevalence of hypothyroidism among general pediatric population is 0.1 to 2% **[2].** The incidence of autoimmune thyroid disease is well recognized with prevalence rates ranging from 3.9% to 50% , leading to subclinical Hypothyroidism in 11% and overt hypothyroidism in 3% of patients**.** This could be

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due to the shared autoimmune disposition for both T1DM and hypothyroidism; recent studies have identified some shared genes involved in the susceptibility for both conditions **[3].**

Additionally hypothyroidism and metabolic derangement in patients with T1DM might form a vicious cycle aggravating disease severity; hypothyroidism has been shown to increase insulin resistance and impair glucose metabolism. While metabolic derangement has been shown to depress pituitary–thyroid axis impairing thyroid function **[4]**

children with T1DM who have simultaneous hypothyroidism might have a more aggressive form of the disease requiring tighter control and also might have higher chance of developing DKA at initial diagnosis**.** There are no enough studies searching for the relationship between hypothyroidism and the severity of T1DM, the Hemoglobin A1C (HbA1C) levels, and the required Insulin doses to control the disease. Whether pediatric patients with both T1DM and hypothyroidism have more aggressive onset of the disease (DKA) is not clearly identified **[5].**

AIM OF THE WORK- Early diagnosis of thyroid dysfunction among pediatric patients with T1DM.

II. PATIENTS AND METHODS

This cross section study was performed on 212 children with documented T1DM diagnosis at Zagazig Univeristy hospital in diabetes clinic and Pediatric Diabetes Insurance Clinic in Sharkia Governorate during a period from November 2019 to April 2020.

Two hundred and twelve patients is our sample size, was assumed by using Open Epi program with confidence level 95% and power of test 80%.

➢ **Inclusion criteria:**

1. Children with documented T1DM diagnosis.

2. Age up to 18y.

3. Both sexes will be included.

➢ **Exclusion criteria:**

1. Missing medical records.

2. Other metabolic diseases.

3. Chronic systemic illnesses (ex. Malabsorption, Chronic liver disease, Syndromes,… etc)**.**

- **Steps of performance:**

All patients have been subjected to the following:

A- Full history taking as regarding :

1) Age, sex and age at diagnosis of DM.

2) Family history of DM and Thyroid disease.
3) History of consanguinity.
4) Medications including required insulin dose.
5) Occurrence of DKA at first presentation and complications.

B-Complete clinical examination (general and systemic examination)

C- Investigations: - HbA1c, Thyroid function tests (TSH, Ft4) Antithyroid antibodies (Tg Ab).

- **Collection of samples:**

5 ml of whole blood sample was taken from every participant under complete aseptic conditions and collected in sterile serum separating tubes (SST), after centrifugation, 2 ml of serum prepared for immunology and biochemistry work in laboratories of Zagazig University Hospital.

- **Administrative consideration:**

❖ Approval obtained for performing the study from pediatrics department, Faculty of Medicine, Zagazig University.

❖ Approval obtained for performing the study from Pediatric Diabetes Insurance Clinic.

❖ Ethical committee in the faculty of medicine and consent from patient's parents will be included in the study.

❖ Institutional Review Board (IRB) approval.

Statistical analysis

Data entry, processing and statisticsl analysis was carried out using Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). The following statistical tests and parameters were used: 1- Paired t-test: For normally distributed quantitative variables, to compare between two periods. 2- Wilcoxon signed ranks test: For abnormally distributed quantitative variables, to compare between two periods Significance of the obtained results was judged at the 5% level (0.05). $P > 0.05$: Non significant., $P < 0.05$: Significant and $P < 0.005$: Highly significant.

III. RESULTS

Table (1): Distribution of the studied cases according to demographic data (n=212)

	No.	%
Sex		
Male	103	48.6

Female	109	51.4
Age		
≤10	128	60.4
>10 - <18	84	39.6
Min. – Max.	1.50 –15.0	
Mean ± SD.	9.01 ±3.91	
Median(IQR)	9.0(5.50 –13.0)	

The current study showed the socio demographic data of the studied patients, their age was ranged from 1.50 – 15.0 years with mean of 9.01 ± 3.91 years old and (60.4%) less than 10 years, there were 51.4% females and 48.6% male.

Table (2): Distribution of the studied cases according to family history (n=212)

Family history	No.	%
DM	135	63.7
Consanguinity	42	19.8
Thyroid disease	17	8.0

The current study showed that 63.7% of cases had +ve family history for DM, 19.8% of cases had +ve Consanguinity and 8.0% of cases had +ve family history for Thyroid disease.

Table (3): Distribution of the studied cases according to duration of DM (n=212)

Duration of DM	No (years)
Min. – Max.	0.10 –5.0
Mean ± SD.	3.7 ±0.83

The current study showed that the distribution of the studied cases according to duration of DM; their Duration of DM was ranged from 0.10 – 5.0 years with mean of 3.7 ±0.83 years.

Table (4): Descriptive analysis of the studied cases according to total insulin dose and HbA1C % (n = 212)

	Min. – Max.	Mean ± SD.	Median(IQR)
Total insulin dose (unit/day)	10.0 –73.0	31.44 ±15.15	30.0(20.0 –40.0)
Total insulin dose (unit/kg/day)	0.62 –1.33	0.95 ±0.18	0.94(0.93 – 0.98)
HbA_1C %	8.70 –16.20	11.37 ±2.10	10.80(9.60 –13.0)

The current study showed that the range of Total insulin dose (unit/day) was 10.0 – 73.0 (mean =31.44 ± 15.15) and the range of Total insulin dose (unit/kg/day) was 0.62–1.33 (mean =0.95 ±0.18) and range of HbA1C % was 8.70 –16.20 and its mean was 11.37 ± 2.10.

Table (5): Distribution of the studied cases according to TFT (n=212)

	Results	
TSH (µiu/ml)		
Min. – Max.	0.01 –41.50	
Mean ± SD.	6.25 ±10.56	
Median(IQR)	2.49(1.79 –3.22)	
FT4		
Min. – Max.	0.49 –2.65	
Mean ± SD.	1.27 ±0.39	
Median(IQR)	1.26(1.0 –1.45)	
Anti TG AB	**No.**	**%**
Negative	187	88.2
Positive	25	11.8

The current study showed that the range of TSH was 0.01 – 41.50 and its mean was 6.25 ± 10.56 and the range of FT4 was 0.49 – 2.65 and its mean was 1.27 ± 0.39, 187 (88.2%) of cases was Negative Anti TG AB.

Table (6): Distribution of the studied cases according to complication (n=212)

Complication	No.	%
DKA	**% From total**	
Once	119	56.1
First presentation	85	40.1
More than once	16	7.5
Infection	**% From total**	
UTI	8	3.8
Chest infection	8	3.8
Admission	**(n=142)**	
Min. – Max.	1.0 –4.0	
Mean ± SD.	1.58 ±0.92	
Median(IQR)	1.0(1.0 –2.0)	

The current study showed that 56.1% of cases had DKA once and 40.1% had DKA on first presentation & 7.5% more than once, 3.8% had UTI, 3.8% had chest infection, and mean± SD of hospital admission was 1.58 ±0.92 days.

Table (7): Comparison of the patients' demographics between diabetic patients with and without hypothyroidism

	Hypothyroidism		P alue	OR (95% CI)
	Yes (n = 25	**No (n = 187)**		
Parental consanguinity	17 (68%)	44(23.5%)	0.01*	**2.31 (1.19–5.21)**
Family history of diabetes	8(32%)	35(18.7%)	0.03*	**2.81 (1.17–5.98)**
Family history of hypothyroidism	8 (32%)	23 (12.3%)	0.621	**1.91 (0.91–4.92)**

Patients age at enrolment (Mean ± SD) (yr)	9.01 ± 3.91	9.2 ± 4.1	0.082	–
Duration of T1DM since initial diagnosis (Means ± SD) (yr)	**2.1 ± 1.1**	**2.3 ± 1.3**	**0.521**	–

OR: Odds Ratio, 95%CI: 95% Confidence Interval, SD: Standard Deviation, T1DM: Type 1 Diabetes Mellitus.

The current study showed that children with T1DM and hypothyroidism tended to have a higher rate of consanguinity in their parents (68 vs. 23.5%, P = 0.01) with statistically significant, and a higher rate of diabetes mellitus in their first degree relatives (32 vs. 18.7%, P = 0.03) compared to children with T1DM who had normal thyroid function, while the family history of hypothyroidism was not significantly different between the two groups (32 vs. 12.3%, P = 0.621).

Table (8): Comparison of the disease severity between diabetic patients with and without hypothyroidism

	Hypothyroidism		**P value**	**OR (95% CI)**
	Yes (n = 25	**No (n = 187)**		
DKA at initial diagnosis	17 (68%)	68 (36.3%)	0.003*	**3.54 (1.63–6.71)**
HbA1C levels at enrolment (Means ± SD) (yr)	**11.37 ±2.10**	**10.02 ± 1.89**	**0.01***	–

The current study showed that children who had both T1DM and hypothyroidism most of them experienced DKA as the first presentation of their disease (68%) in comparison to (36.3%) in diabetic patients with normal thyroid function. Additionally children with T1DM and hypothyroidism were experienced a more aggressive disease; in comparison to children with T1DM who had normal thyroid function, children who had both T1DM and hypothyroidism had significantly higher HbA1C levels at enrolment (11.37 ±2.10) therby a higher insulin dose for control.

Table (9): Logistic regression analysis of the factors associated with the occurrence of DKA at the initial diagnosis of T1DM

Factor	B value	P value	OR	95% Confidence Interval
Hypothyroidism	1.10	0.002*	3.52	**1.52–6.81**
Female sex	0.81	0.003*	2.1	**1.8–4.02**
Positive anti-TG antibodies	1.51	< 0.001*	4.62	**2.1–8.72**
Parents consanguinity	0.28	0.361	1.5	**0.98–3.1**
Positive F.H for diabetes	**1.52**	**0.321**	**3.51**	**1.4–9.71**

The current study showed the Logistic Regression model to adjust the results for patients' sex, age at diagnosis, positive anti-TG antibodies, parents consanguinity and family history of diabetes mellitus; after these adjustments hypothyroidism remained significantly associated with the occurrence of DKA as the initial manifestation of the disease in patients with T1DM (B = 1.1, P = 0.002, OR = 3.52 , 95%CI = 1.52–6.81).

IV. DISCUSSION

Type 1 diabetes is a chronic illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Most pediatric patients with diabetes have type 1 and a lifetime dependence on exogenous insulin. [6].

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported, on one hand, thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents [7].

A relationship between the degree of NTIS and severity of metabolic derangement has been previously described in adult and pediatric patients. Moreover, thyroid autoimmunity may be impaired in diabetic patients and could further affect the hypothalamus–pituitary–thyroid axis. Among children and adolescent with newly diagnosed T1DM, in fact, the presence of positive antibody titers varies from 6 to 16 % in the various case series [4]**.**

The aim of our study was early diagnosis of thyroid dysfunction among pediatric patients with T1DM, through achieving the following objectives which were; assessment of the thyroid function in patients

with T1DM , estimate the prevalence of thyroid dysfunction among T1DM, and evaluate the relation between presence of hypothyroidism and disease severity which require tighter control.

This was a cross sectional study; that was carried out on 212 children with documented T1DM diagnosis at Zagazig University hospital in

, the study was conducted on 212 diabetic children,

In our study, we assessed the socio demographic data of the studied patients and revealed that their age was ranged from 1.50 – 15.0 years with mean of 9.01 ± 3.91 years old and (60.4%) less than 10 years, there were 51.4% females and 48.6% male. In comparison with a study of **Fatourechi et al., [5]** which evaluated 330 children with T1DM who were referred to Diabetes Clinic between 2013 and 2015 The mean ± standard deviation (SD) for the patients' age was 11.6 ± 2.4 yr.

In a cohort of **Al-Agha et al., 2011 [8]** icluded 63 patients (15.83%) had hypothyroidism, [female; 40 (63.49%), male; 23 (36.51%), pre-pubertal; 26 (41.3%), post-pubertal; 37 (58.7%)]. Mean and SD for age were 11.6 ± 4.01 years in patients with hypothyroidism and 12.14 ± 4.02 years in children with normal thyroid function.

As regard family history among participant children, in our study, we demonstrated that 63.7% of cases had family history of DM in their first degree relatives, 19.8% of cases were positive consanguinity but 8.0% of cases had family history of thyroid disease. Which come in line with our findings, the study of **Fatourechi et al., [5]** reported that parents' consanguinity was observed in 86 patients (26%); 55 children (16.6%) had a family history of DM in their first degree relatives; 39 children (11.8%) had a family history of hypothyroidism in their first degree relatives.

In another study of **Alkot et al., [9]** family history of thyroid dysfunction was positive in 66.2% of diabetic patients having thyroid dysfunction versus 31.8% of diabetics without thyroid dysfunction, this difference was statistically significant.

In our study, we assessed the distribution of the studied cases according to duration of DM; their Duration of DM was ranged from 0.10 – 5.0 years with mean of 3.7 ±0.83 years. Which in contrast to the study of **Fatourechi et al., [5]** which reported that age at initial diagnosis of T1DM (Mean ± SD) was 7.3 ± 3.2 years.

In our study we found that the range of total insulin dose among the patients was 10.0 – 73.0 units (0.95±0.18 IU/kg/day) and its mean was 31.44 ± 15.15 and the range of HbA1C % was 8.70 –16.20 and its mean was 11.37 ± 2.10. which in agreement with our findings, the study of **Fatourechi et al., [5]** the required Insulin dose was 0.83 ± 0.23 international unit (IU) / kg/d; the HbA1C level was 8.8 ± 1.9.

Another study of **Salemyr et al., [10]** reported that HbA1c (mean ± SD) was lower at 3-5 months (5.5 ± 0.89 vs. 6.2 ± 0.89%, $p < 0.05$) and 6-9 months (5.6 ± 1.14 vs. 6.6 ± 0.99%; $p < 0.001$) in insulin treated. After 12 months, HbA1c was significantly lower in insulin treated (6.3 ± 1.56 vs. 7.1 ± 1.28; $p < 0.01$). Reported total insulin doses were similar at nadir (0.5 U/kg BW × 24 h), but significantly lower at 12 months in insulin treated (0.64 ± 0.23 vs. 0.86 ± 0.3 U/kg BW × 24 h; $p < 0.001$).

In a harmony with our findings, the study of **Ridha and Al Zubaidi, [11]** reported that from the sera of 150 patients withType-1 diabetic patients; The positivity of thyroid Anti TPO was 17.3% of patients

while Anti TG was positive in 28% of patients and both tests was positive in (11.6%) of patients. Based on autoantibody positivity and TSH concentration; TSH concentration was high in ten patients (6.6%) and autoimmune thyroid disease (AITD) were newly diagnosed only in three patients (2%).

In the study of **Fatourechi et al., [5]** revealed that hypothyroidism was a prevalent problem among children with T1DM, complicating 9.6% of these children.

This was in accordance with other studies; based on a 2010 review 3–8% of pediatric patients with T1DM have been reported to develop autoimmune hypothyroidism [12].

While a recently published review and a meta-analysis reported a much higher rate of 7–30% for the prevalence of hypothyroidism in patients with T1DM [**3; 13**].

On the other hand, as regard complications among the participant cases, we revealed that 56.1% of cases had DKA once and 40.1% had DKA on first presentation, 3.8% had UTI, 3.8% had chest infection, and mean± SD of hospital admission was 1.58 ±0.92 days.

In comparison with our results, another study of **Al-Fifi, [14]**reported that a total of 181 children with Type1 diabetes were admitted to the hospital during this period. Of these, Diabetic ketoacidosis was present in 46.7 % of children; the mean±SD of hospital admission was 4.6±3.5days. There were a significantly higher percentage of the children presented with accompanying upper respiratory tract infections (URTI) and dehydration (30% and 72% respectively).

Additionally, the study on the hand illustrated that children with T1DM and hypothyroidism tended to have a higher rate of consanguinity in their parents (68 vs. 23.5%, P = 0.01) with statistically significant, and a higher rate of diabetes mellitus in their first degree relatives (32 vs. 18.7%, P = 0.03) compared to children with T1DM who had normal thyroid function, while the family history of hypothyroidism was not significantly different between the two groups (32 vs. 12.3%, P = 0.621).

Come in line with our findings, the study of **Fatourechi et al., [5]** reported that Children with T1DM and hypothyroidism tended to have a higher rate of consanguinity in their parents (43.7 vs. 24.1%, P = 0.01), and a higher rate of diabetes mellitus in their first degree relatives (31.2 vs. 15.1%, P = 0.02) compared to children with T1DM who had normal thyroid function, while the family history of hypothyroidism was not significantly different between the two groups (18.7 vs. 11%, P = 0.2).

Meanwhile, our study revealed that children who had both T1DM and hypothyroidism, most of them experienced DKA as the first presentation of their disease (68% vs 36.3% ,P =0.003). Additionally children with T1DM and hypothyroidism were associated with a more aggressive disease; in comparison to children with T1DM who had normal thyroid function, children who had both T1DM and hypothyroidism had significantly higher HbA1C levels at enrolment, also, these findings were matched with the study of **Fatourechi et al., [5]** in which patients with T1DM and hypothyroidism had significantly higher rates of DKA at initial diagnosis (62.5 vs. 34.5%, P = 0.002).

Balsamo et al., [4] in their study documented the association of severe metabolic derangement and impaired thyroid function in patients with newly diagnosed T1DM.

The association of thyroid dysfunction with the disease severity in T1DM patients could be explained through several mechanisms; our results supported by the aforementioned studies of **Yeşilkaya et al., [15] and Golden et al., [16]**, document that the occurrence of both T1DM and hypothyroidism might show the presence of polymorphism in some of the immune response regulatory genes, causing a more severe disease with stronger features of autoimmunity.

Finally, Logistic Regression model to adjust the results for patients' sex, age at diagnosis, positive anti-TG antibodies, parents consanguinity and family history of diabetes mellitus in the present study was done; and found that after these adjustments hypothyroidism remained significantly associated with the occurrence of DKA as the initial manifestation of the disease in patients with T1DM (B = 1.1, P = 0.002, OR = 3.52, 95%CI = 1.52–6.81).

Our findings were supported by the study of **Fatourechi et al., [5]** where they used Logistic regression model to adjust the results for patients' sex, age at diagnosis, positive anti-TPO antibodies, parents consanguinity and family history of diabetes mellitus; after these adjustments hypothyroidism remained significantly associated with the occurrence of DKA as the initial manifestation of the disease in patients with T1DM (B = 1.1, P = 0.004, OR = 3.03, 95%CI = 1.41–6.48).

V. Limitations:

In the present study, we had some limitations that should be considered when interpreting the results; we do not have information regarding thyroid function at the onset of T1DM therefore it is not clear whether thyroid dysfunction developed through the course of the disease or it was present at the initial presentation of T1DM. Another limitation was that our patients were not followed to evaluate whether treating hypothyroidism could improve the severity of diabetes and lower the required insulin dose. Additionally in our study thyroid scan and anti TPO antibodies were not evaluated, this might have caused an underestimation of the presence of autoimmune thyroiditis among the patients with T1DM.

VI. Conclusion

Hypothyroidism is prevalent among pediatric patients with T1DM and is associated with a more aggressive form of the disease. Patients with T1DM and hypothyroidism have higher rates of DKA and develop the disease at younger ages. Therefore all patients with T1DM especially those with poorly controlled disease and positive family history for diabetes and consanguinity should be screened for thyroid dysfunction. Interventional studies are required to evaluate the efficacy of treating thyroid dysfunction in these patients and to assess if hormone therapy in these patients could help in a better management of diabetes and reduce its complications.

VII. Recommendations :

Prospective and interventional studies are required to evaluate whether treating hypothyroidism could alleviate the severity of diabetes and lower the required insulin dose in patients with concurrent T1DM and hypothyroidism, and to answer whether controlling diabetes could result in improvement of thyroid function in these patients.

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