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المجلس العراقي للاختصاصات الطبية

DISTRIBUTION OF HYPOTHYRODISM IN A SAMPLE OF CHILDREN WITH TYPE 1 DIABETES MELLITUS .

A Dissertation

Submitted to the Iraqi board for medical specialization in partial fulfillment of the requirements for the degree of fellowship in pediatric medicine

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيم

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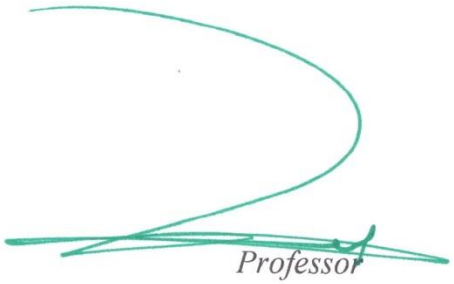

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Dedication

To the sake of Allah , the merciful lord who give us the strength and health to continue the learning of this way of humanity and medical sciences ….

To the prophet of the world Mohammed (may Allah bless and grant him) ,the first teacher and leader to us in the ethics and the science …

To my parents who still giving the meaningful support and their hearts beats with love to me and all their prayers to Allah that the God bless my way …

To all teachers throughout my life who give us the support and flame the candle to us to see clearly the way of this blessing science , and their merit will be persistent in our hearts and souls ….

To all faithful people in this world who work hardly looking for blessing of their God …

To all pediatric patients in my country who still strong and smiling in spite of their suffering from illness .

I dedicate this thesis

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Abbreviation	Full name
ADA	American diabetic association
Anti TG	Anti-thyroglobulin
Anti TPO Ab	Anti thyro peroxidase antibody
AT	Autoimmune thyroiditis
DKA	Diabetic ketoacidosis
T1DM	Type 1 Diabetes mellitus
DR3/DR4	Death receptors ¾
GAD	Glutamic acid decarboxylase
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
HT	Hypothyroidism
ICA	Anti-islet cell antibody
IDDM1	Insulin dependent diabetes mellitus type 1
No.	Number
NPH insulin	Neutral protamine hagedorn insulin
OGTT	Oral glucose tolerance test
PAS	Polyglandular autoimmune syndrome
Pts.	Patients
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
T3 FT3	Triiodothyronine Free Triiodothyronine
TSH	Thyroid stimulating hormone
Yr.	Year

Abstract

Background *Type 1 diabetes mellitus is due to cellular-mediated autoimmune destruction of the pancreatic beta-cells. It is defined by one or more autoimmune markers, including islet cell autoantibodies and autoantibodies to insulin, the disease has strong HLA associations, patients are also prone to other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, Graves' disease and others.*

Aims of study *To identify the distribution of hypothyroidism in type 1 diabetic patients , the association between type 1 diabetes mellitus control and duration with the development of hypothyroidism , the significance of family history of both diabetes mellitus type 1 and hypothyroidism in both diseases , and to identify the main frequent symptoms of hypothyroidism in type 1 diabetic patients and the treatment*

Patients *a cross sectional retrospective study conducted in endocrinology departments of pediatrics in Al- Imamain AL-Kadumain Medical City & Child Central Teaching Hospital from the 1st of February 2022 till the 30th of July 2022 from the archive files of patients in the previous years from 2015-2021 . The study included patients diagnosed with type 1 diabetes mellitus who divided in to two groups: first group include patients diagnosed without hypothyroidism , the second group include patients with hypothyroidism . the two groups studied regarding their ages, duration of the diabetes, HbA1c, recurrent hypoglycemia & diabetic ketoacidosis at presentation ,symptoms of hypothyroidism and it's treatment ,the family history of both diseases, and the development of other autoimmune diseases.*

Results *the total patients were 105, hypothyroidism accounts for 16.1 %, females higher than male in both groups with a P-value of 0.05, the mean age of diabetic children is 8.6 years and the hypothyroid children is 13 years, hypothyroidism mostly distributed in 5-10 years duration of diabetes 8.6 % , Hypothyroidism with diabetes type1 associated with higher hemoglobin A1c than patients with only diabetes with a p value of 0.01. hypothyroidism significantly associated with recurrent hypoglycemia but non-significant association with diabetic ketoacidosis*

at presentation .hypothyroidism significantly associated with family history of type1 diabetes in 29.4 % and hypothyroidism in 11.8 % .according to the age the highest distribution of hypothyroid patients is > 10 years old (82 percent) while the type 1 diabetes only (3-7 years 58 %) Most of the hypothyroid patients are asymptomatic 65 % and having normal body weight 70.5 % and only 35 % taking treatment.

Conclusion *hypothyroidism has significant association with poor control diabetes and longer duration of the disease , there is significant association between the development of hypothyroidism and the family history of both diabetes mellitus type 1 and hypothyroidism ,most of the hypothyroidism in type 1 diabetes are asymptomatic..*

Introduction

Diabetes mellitus

Definition

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both. The diagnostic criteria for diabetes are based on thresholds of glycaemia . [(1)]

Classification of Diabetes

The majority of cases of diabetes can be classified into two categories: type 1 diabetes and type 2 diabetes. The classification of diabetes is summarized in the Table I, including less common forms associated with genetic mutations, diseases of the exocrine pancreas (such as cystic fibrosis), other diseases or drug exposure, [(2)]

Table I etiological classification of DM. [(3)]
Type 1 (B cell destruction usually leads to absolute insulin deficiency) - ***Autoimmune*** - ***idiopathic***
Type 2 (may range from predominantly insulin resistance with relative insulin deficiency)
Gestational diabetes
Other specific types ***- genetic defect of Beta –cell function*** ***- genetic defect of insulin action*** ***- disease of the exocrine pancreas*** ***- endocrinopathy*** ***- drug or chemical induced*** ***- infection*** ***- Uncommon form of immune mediated diabetes***

Differentiating between type 1 & type 2 is important but can be difficult at the time of diagnosis in certain situations. Table II highlights the main features of type 1 diabetes, type 2 and neonatal diabetes..

neonatal diabetes, which typically presents by 6 months of age and is indistinguishable from type 1 diabetes in its clinical features, but may be amenable to therapy with oral sulfonylurea in place of insulin therapy. For this reason, all infants diagnosed before 6 months of age should have genetic testing. [(4)]

The presence of autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell (ICA) autoantibodies, may be helpful in identifying type 1 diabetes [(5)]

In cases where it is difficult to distinguish between type 1, type 2, presence of 1 or more autoantibodies (GAD and ICA) indicates type 1 diabetes with a need for insulin replacement therapy;. [(6)]

very low C-peptide levels measured after months of clinical stabilization may favor type 1 diabetes [(7)]

Table II Clinical features distinguishing type 1,2 and neonatal diabetes [4]			
Clinical feature	*T1DM*	*T2DM*	*neonatal DM*
Age of onset (years)	*Most <25 but can occur any age (not before 6 months)*	*Usually >25 but incidence increasing in adolescent with increasing rate of obesity in children and adolescent*	*Usually <6 months*
Weight	*thin*	*>90% at least overweight*	*Similar to general population*
Islet autoantibodies	*present*	*absent*	*absent*
C- peptide	*Undetectable/low*	*Normal/high*	*normal*
Insulin production	*absent*	*present*	*Usually present*
First line treatment	*Insulin*	*noninsulin anti hyperglycemic agents ,gradual dependence on insulin may occur*	*Depends on subtypes*
DKA	*Common*	*rare*	*Rare(except in neonatal diabetes)*
Family history of diabetes	*Infrequent (5-10%)*	*Frequent (75-90%)*	*,autosomal pattern of inheritance*

Epidemiology

T1DM accounts for approximately 10% of all cases of diabetes, affecting more than 15 million people in the world, a recent study indicates that approximately 15,000 youths are diagnosed with type 1 diabetes each year. [8]

It is greatest among the youngest children. Girls and boys are almost equally affected, but there is a modest female preponderance;. Peaks of presentation occur in 2 age groups: at 5-7 yrs. of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion, which antagonizes insulin. [8]

Pathogenesis and genetics

Type 1 diabetes (T1DM) is a chronic autoimmune disorder that occurs in genetically susceptible individuals and that may be precipitated by environmental factors. In a susceptible individual, the immune system is triggered to develop an autoimmune response against pancreatic beta cell antigens. Approximately 85% of T1DM patients have circulating islet cell antibodies that mostly directed against glutamic acid decarboxylase (GAD) within pancreatic beta cells [9]

The risk for diabetes increases with increasing the number of antibodies detected in the serum. In individuals with only one detectable antibody, the risk is only 10-15% while in individuals with three or more antibodies the risk is 55-90%. When 80-90% of the βeta cell mass has been destroyed, the remaining βeta cell mass is insufficient to maintain euglycemia and clinical manifestations of diabetes result [10]

Type 1 diabetes mellitus is characterized by loss of the islets of Langerhans in the pancreas, leading to insulin deficiency. [10]

Sensitivity and responsiveness to insulin are usually normal. Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells in the pancreas, leading to insulin deficiency. [10]

The presence of diabetes susceptibility genes, an unknown environmental insult presumably triggers the autoimmune process.. These include, viral infectious agents (coxsackie virus, cytomegalovirus, mumps, rubella), , and perinatal factors. T1DM is thought to be primarily a T cell mediated disease. [10]

The cause of the initial clinical findings of diabetes in childhood is the sharply diminished secretion of insulin. Although basal insulin concentrations in plasma may be normal in newly diagnosed patients, , but decreased and usually disappears over a period of months to years. [11]

The clinical appearance of symptomatic diabetes that usually manifests when insulin-secreting reserve is 20% or less than normal for that individual [12]

T1DM has long been known to have an increased prevalence among persons with such disorders as Addison disease and Hashimoto thyroiditis , in whom autoimmune mechanisms are known to be pathogenic. [11]

Increased susceptibility to a number of diseases has been related to one or more of the identified HLA antigens. The inheritance of HLA DR3 or DR4 confers a twofold to threefold increased risk for developing T1DM. [12]

When both DR3 and DR4 are inherited, the relative risk for developing diabetes is increased 7- to 10-fold.with the benefit from this clinical data is to screen other family member about T1DM [12]

In T1DM, the homozygous absence of aspartic acid at the HLA DQ b chain (non-Asp/non-Asp) confers an approximately 100-fold relative risk for developing T1DM. [13]

Histological examination of pancreas from patients with type 1 diabetic patient revealed lymphocytic infiltration around the islets of Langerhans. Later, the islets become progressively hyalinized and scarred, a process suggesting an ongoing inflammatory response that is possibly autoimmune. However, these changes are often patchy in distribution, so that areas that appear to contain normal beta cells are interspersed with areas of beta-cell destruction,. [14]

Studies in identical twins and in family pedigrees demonstrate that the existence of ICA may precede by months to years the appearance of symptomatic T1DM. [15]

Clinical manifestation

Stages of Type 1 diabetes

Type 1 diabetes is characterized by four stages

- *Stage 1 Multiple islet antibodies, normal blood glucose, pre-symptomatic*
- *Stage 2 Multiple islet antibodies, raised blood glucose, pre-symptomatic*
- *Stage 3 Islet autoimmunity, raised blood glucose, symptomatic*
- *Stage 4 Long standing type 1 diabetes* [16]

Classical presentation

The classic presentation of diabetes in children is a history of polyuria, polydipsia, polyphagia, and weight loss, recurrence of bedwetting in a previously toilet trained child. Unexplained weight loss should raise suspicion of the existence of diabetes that need measurement of blood glucose, first in the postprandial and later in the fasting state. The urine should also be checked for the presence of glycosuria. The duration of these symptoms varies; it often is less than 1 month, but careful history may reveal weeks of symptoms [(17)]

An insidious onset lethargy, weakness, and weight loss is also quite common... Pyogenic skin infections and candidal vaginitis in girls or candidal balanitis in uncircumcised boys are occasionally present at the time of diagnosis of diabetes. [(17)]

Diabetic ketoacidosis

Diabetic Ketoacidosis is responsible for the initial presentation of about 25% -40% of diabetic children. Ketoacidosis may be relatively mild and consist of vomiting, polyuria, and dehydration. In severe cases, Kussmaul respiration is present—and there is an odor of acetone on the breath. Laboratory findings include glycosuria, ketonuria, hyperglycemia, ketonemia, and metabolic acidosis. [(18)]

Diagnosis

The majority (>95%) of newly diagnosed patients seek medical care owing to the presence of symptoms while a minority are diagnosed by routine glucose screening.[19]

The 2016 American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus are based on signs of abnormal glucose metabolism, regardless of the diabetes type and the age of onset (table below). [20]

Table III American diabetic association diagnostic criteria for DM [20]
Diabetes including T1DM is diagnosed when one or more of the following criteria are present
• ***fasting plasma glucose level >126 mg/dl (7mmol/l)***
• ***Plasma glucose level ≥ 200 mg/dl (11.1 mmol/l) measured 2 hours after glucose load of 1.75 gm/kg (max. 75gm) via an oral glucose tolerance test (OGTT). most children and adolescent with T1DM are symptomatic and have plasma glucose concentration above this threshold , thus an OGTT is seldom nessessary to diagnose T1DM***
• ***a glycated hemoglobin (HbA1c)level ≥ 6.5% .***
• ***a random venous plasma glucose level ≥ 200 mg/dl(11.1 mmol/l) in a patient with classical symptoms of hyperglycemia or hyperglycemic crises .***

The cornerstones of the diagnosis of T1DM are insulinpenia,. If β-cell-targeting autoantibodies are present, a diagnosis of autoimmune T1DM. If patients have a clinical picture that is consistent with T1DM but no

autoantibodies are categorized as idiopathic T1DM [21]

Long-Term Glycemic Control Measurements of hemoglobin A1c (HgbA1c) reflect the average blood glucose concentration over the preceding 3 months and provide a means for assessing long-term glycemic control. HgbA1c should be measured four times a year, The ADA has set HgbA1c targets for children at <7.5%. [22]

Hemoglobin A1c

HbA1c is a form of hemoglobin that is chemically linked to a sugar, analysis of glycated hemoglobin (HbA1c) in blood provides individual's average blood glucose during the previous two to three months, which is the predicted half-life of red blood cells, a target range for all age groups of < 7.5 % is recommended, [23]

Good glycemic control was defined by ADA guidelines. as following :-

HbA1c <8.5 % for patients lower than 6 yrs. Of age.

HbA1c <8 % for patients with 6-12 yrs. Of age.

HbA1c <7.5% for patients with 13-18 yrs. Of age [24]

Insulin therapy in T1DM

Insulin therapy, with the goal of maintaining blood glucose as close to normal as possible, can delay the onset and slow the progression of complications of diabetes., a goal of HgbA1c <7.5% is set for children of all ages. Pre-prandial blood glucose target concentrations are 90-130 mg/dL and concentrations before bedtime and overnight of 90-150 mg/dL. Goals of therapy need to take into account other individual characteristics,

such as a past history of severe hypoglycemia and the abilities of the patient and family [25]

Insulin Regimens

1- Basal bolus regime (multi dose injections regime)

Multiple injections of rapid-acting insulin given with meals in combination with long-acting basal insulin given at bedtime. This regimen provides flexibility but requires administration of many injections per day. After the total daily dose of insulin is determined, 30-50% is given as long-acting insulin, and the remainder is given as fast-acting insulin.

2- three injection regime

Some families may be unable to administer 4 daily injections. In these cases, a compromise may be needed. A 3 injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid- acting analog bolus at supper, and glargine or NPH at bedtime may provide fair glucose control.

3- conventional regime (2 injection regime)

Further compromise to a 2 injection regimen may occasionally be needed and frequently involves use of premix insulin (e.g., 70/30) which is not preferred in pediatric .

4- Insulin pumps that provide a continuous SC infusion of short-acting insulin also are available . [25]

It was found that the rate of good glycemic control in patients is significantly higher in the basal bolus regime [26]

Insulin dosing

Table IV Insulin dosing [25]		
Insulin dose (u/kg/d)	***Non DKA***	***DKA***
Pre pubertal	*0.25-0.50*	*0.75- 1*
pubertal	*0.50-0.75*	*1.0-1.2*
post pubertal	*0.25-0.50*	*0.8-1.0*

Table V	Types of insulin [25]		
insulin	**onset**	**Peak action**	**duration**
Very short acting			
Lisipro, aspart	5-15 minute	30-90 minute	3-5 hour
Short acting			
regular	30-60 minute	2-3 hour	5-8 hour
Intermediate acting			
NPH	2-4 hour	4-10 hour	10-16 hour
Long acting			
glargine	2-4 hour	none	20-24 hour
detemir	2-4 hour	6-14 hour	16-20 hour

Blood Glucose Testing

Blood glucose should be routinely monitored before each meal and at bedtime. Additional testing at 2 or 3 A.M. to ensure that there is no consistent hypoglycemia or hyperglycemia. **(25)**

Complications

The complications of the DM can be acute or chronic

The acute complications include the following:-

1- *DKA*
2- *Hypoglycemia*
3- *Hyperglycemia* **(27)**

While the chronic complications of DM can be divided into 3 major categories:

1. *micro vascular complications, (, retinopathy and nephropathy)*
2. *macrovascular complications, (accelerated coronary artery disease, cerebrovascular disease, and peripheral vascular disease)*
3. *diabetic neuropathies, both peripheral and autonomic,* **(27)**

A-diabetic Retinopathy

The risk of diabetic retinopathy after 15 yr. duration of diabetes is 98% for individuals with T1DM . prevalence rates are substantially higher with increased duration of diabetes, and higher HbA1c, blood pressure, and cholesterol.

B- diabetic nephropathy

Diabetic nephropathy affects 20-30% of patients with T1DM .The risk of nephropathy increases with duration of diabetes (up until 25-30 yr. duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Tight glycemic control will delay the progression of nephropathy.

.C- diabetic neuropathy

Peripheral neuropathy may present in some adolescents with a long-standing history of diabetes. Poor metabolic control and long- standing disease during puberty appears to induce this complication **(27)**

Table VI long term complication & associations of T1DM: first screen and follow up [27]		
condition	***When to commence screen***	***frequency***
retinopathy	*After 5 yrs. duration in pre pubertal children, after 2 Yrs. in pubertal children*	*1-2 yrs.*
nephropathy	*After 5 yr. duration in pre pubertal children, after 2 Yr. in pubertal children*	*annually*
neuropathy	*Unclear in children; adults at diagnosis in T2DM and 5 yr. after diagnosis in T1DM*	*unclear*
Micro vascular disease	*After age 2*	*Every 5 yrs.*
Thyroid disease	*At diagnosis*	*Every 2-3 yr. or more frequently based on symptoms or the presence of ant thyroid antibodies*
Celiac disease	*At diagnosis*	*Every 2-3 yrs.*

Type 1 diabetes mellitus & autoimmune diseases

T1DM is due to cellular-mediated autoimmune destruction of the pancreatic B-cells. It is defined by one or more autoimmune markers, including islet cell autoantibodies and autoantibodies to insulin & GAD . The disease has strong HLA associations, ***(28)***

These patients are also prone to other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, Graves' disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia ***(28)***

T1DM manifests separately as a mono glandular autoimmunity, but also appears collectively with a variety of other autoimmune diseases. ***(28)***

Type1 diabetes mellitus & thyroid disorder

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with T1DM. At the time of diagnosis, about 25% of children with type 1 diabetes have thyroid autoantibodies . Their presence is predictive of thyroid dysfunction and most commonly hypothyroidism, thyroid function tests should be performed soon after a period of metabolic stability and good glycemic control. Subclinical hypothyroidism may be associated with Increased risk of symptomatic hypoglycemia and reduced linear growth rate ***(29)***

Hypothyroidism

Definition

Thyroid hormones are necessary for normal growth and development since fetal life. Deficiency in the production or in the activity of thyroid hormones leads to hypothyroidism, one of the most frequent hormone diseases in children.

Hypothyroidism results from deficient production of thyroid hormone, from either a defect in the gland itself (primary hypothyroidism) or a result of reduced thyroid - stimulating hormone (TSH) stimulation (Central hypothyroidism);

the disorder may be manifested from birth (congenital) or acquired. When symptoms appear after a period of apparently normal thyroid function, [30]

Epidemiology of hypothyroidism in T1DM.

some genetic factors might contribute to the co-occurrence of autoimmune thyroid disease and T1DM , [31]

T1DM patients develop thyroid disease at an early age compared with the general population, and therefore autoimmune hypothyroidism is present in 25% of children with T1DM . Its onset is associated with a poorly controlled diabetes in pediatric patients with T1DM, [31]

Clinical Manifestations

Deceleration of growth is usually the first clinical manifestation, but this sign often goes unrecognized. Weight gain is mostly fluid retention (myxedema), not true obesity; constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. [32]

Additional features include bradycardia, muscle weakness or cramps,. Osseous maturation is delayed, , Adolescents typically have delayed puberty; older adolescent girls manifest menometrorrhagia. Younger children might present with galactorrhea or pseudoprecocious puberty. Galactorrhea is a result of increased TRH stimulating prolactin secretion . All these changes return to normal with adequate replacement of T4. [32]

Diagnosis of hypothyroidism

The serum TSH concentration is elevated in primary hypothyroidism and its determination is an appropriate screening test for thyroid dysfunction. In mild hypothyroidism, serum FT3 can remain in the normal range due to the increased conversion of FT4 to FT3. For this reasons, measurement of the serum T3 and FT3 concentration is not a useful testin the diagnosis or monitoring of patients with primary hypothyroidism. Anti-TPO antibodies are the most sensitive screen for autoimmune hypothyroidism , thyroid ultrasound recommended to confirm autoimmune hypothyroidism diagnosis . [33]

The typical patient with hypothyroidism due to autoimmune process will have an elevated TSH ("typically" over 10 IU/mL), a low FT4, and positive anti- TPO antibodies. In early stages of the disease, TSH may be normal and anti-TPO antibodies may be positive with or without goiter. Later, TSH elevation becomes modest (5–10 IU/mL) with a normal FT4 (biochemical or subclinical hypothyroidism). Up to 90% of patients with hypothyroidism secondary to autoimmune process are anti-TPO antibody positive. [(34)]

If anti-TPO antibodies are absent, less common etiologies of primary hypothyroidism should be considered: transient hypothyroidism due to post sub-acute thyroiditis, hypothyroidism related to external irradiation, and Para neoplastic vascular tumors [(35)]

Subclinical hypothyroidism is defined as TSH elevation with normal concentrations of circulating thyroid hormones (FT4 and FT3).. The majority of these patients are asymptomatic, but studies in the adult population suggest that individuals with the combined of TSH level above the normal limit and positive thyroid antibodies (anti- TG or anti-TPO) are at high risk for progression to overt hypothyroidism. For this reason, we recommend thyroid hormone replacement in all patients with TSH values >10 IU/mL or with TSH values >5 IU/mL in combination with goiter or thyroid autoantibodies [(34)]

Effect of T1DM on thyroid function

Diabetes influences thyroid function by controlling TSH release at the level of hypothalamus and by affecting T4-to-T3 conversion in the peripheral tissues , diabetes may cause alterations in the hypothalamic pituitary thyroid axis by reducing the levels of plasma thyroid releasing hormone and TSH, thereby affecting thyroid hormone production . Patients with diabetes may have an impaired TSH response to thyroid releasing hormone (TRH) stimulation with decreased T4-to-T3 conversion. [36]

T1DM may induce a "low T3" condition with low serum total and FT3. An abnormal thyroid hormone pattern associated with diabetes was attributed to the presence of binding inhibitor (THBI), an inhibitor of the extra thyroidal conversion enzyme (5'-deiodinase) of T4 to T3, and to the dysfunction of the hypothalamic pituitary thyroid axis .These features were exacerbated by stress and poorly controlled diabetes. [36]

Treatment of hypothyroidism

The approach to treatment of acquired hypothyroidism is similar to that of congenital hypothyroidism. Levothyroxine tablets are the treatment of choice for symptomatic overt hypothyroidism, administered once daily, 15 to 30 minutes prior to food consumption, avoiding co administration with calcium, iron, and soy products. [37]

Levothyroxine dosing is based on body surface area (100 µg/m2/d) or on age and weight following the general pattern:

4 to 6 µg/kg/d for patients 1 to 3 years of age,

3 to 5 µg/kg/d for patients 3 to 10 years of age,

2 to 4 µg/kg/d for patients 10 to 16 years of age,

1.6 µg/kg/d for patients 17 years of age or older.

Additional thyrotropin and T4 samples should be obtained 6 to 8 weeks after initiating therapy. Once a therapeutic dose has been established, the clinician should check thyroid function every 4 to 6 months until the child achieves final height. The goals of treatment are to maintain clinical and biochemical euthyroidism and to ensure normal linear growth and development throughout childhood and adolescence ***(37)***

Aims of the study

- *To identify the distribution of hypothyroidism in type 1 diabetes mellitus*

- *To identify the correlation between type 1 diabetes mellitus control and it's duration with the development of hypothyroidism. And the significance of family history of both diabetes mellitus type 1 and hypothyroidism in it's development also .*

- *To identify the main frequent symptoms of hypothyroidism in type 1 diabetic patients and it's treatment .*

Patients and methods

Study design, setting and sample size

This study was a cross sectional retrospective study conducted from the 1st of February 2022 till the 30th of July 2022 from the archive files of the previous years (2015-2021) that were recorded in the endocrinology departments of pediatrics in Al-Imanain Al- Kadhumain Medical City and Child's Central Teaching Hospital in Baghdad .

The study include information were taken from the files of patients recorded in the department of pediatric endocrinology
It include 105 patients diagnosed with T1DM by signs, symptoms and by investigations, their ages ranging from 3-18 years ..
Those patients divided in to two groups , The first group those with T1DM only with normal Thyroid Function Test and the second group was for the patients with T1DM and hypothyroidism that diagnosed by thyroid function testwith or without symptoms (depending on delta trade company for investigation)..
Those two groups are also subdivided in to three groups according to the duration of T1DM to illustrate the effect of the duration of diabetes on hypothyroidism and the glycemic control (HbA1c)

Data collection tools

The data collection tools include the following

- *Age and gender of the patients*
- *Age at diagnosis of DM*
- *Age at diagnosis of hypothyroidism*
- *Duration of T1DM*
- *DKA at presentation*
- *Recurrent hypoglycemia*
- *HbA1c level*

- *Family history of T1DM/hypothyroidism*
- *Other autoimmune diseases*
- *Symptoms of hypothyroidism as recorded*
- *Treatment of hypothyroidism*
- *Body weight of the patients*

Inclusion and exclusion criteria

The patients who having the following inclusion criteria are included in the study

- *Fully recorded information and follow up*
- *Age <18yrs. And >1 yr.*
- *Having T1DM and on insulin therapy*

T1DM patients diagnosed according to the presence of symptoms plus random blood sugars ,or fasting blood sugar and confirmed by HBA1c, while the hypothyroidism diagnosed by the presence of symptoms with elevated TSH with or without decreasing T4 according to normal range of different age groups in pediatric (reference range) .

Limitation of the study

The study is limited in that the patients may escape their visits to the hospital For a long time that we lose their follow up and they are not included in the study Some investigations are important in confirming the autoimmunity of the disease and they may be present before the development of the symptoms of both diabetes and hypothyroidism are not done to the patients

Ethical considerations and official approvals

The information were anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.
Administrative approvals were granted from the following
1. The Council of Iraqi Board of Medical Specialization.
2. Approval and agreement from Al-Imanain Al-Kadhmain Medical City and the Child's Central Teaching Hospital

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Chi square test was used to assess the association between age and gender and between diagnosis and both of age and gender. A level of P – value equal or less than 0.05 was considered significant.

The results

From the total number of patients involved in the study (105), 17 of them (16.1%) diagnosed to have hypothyroidism .

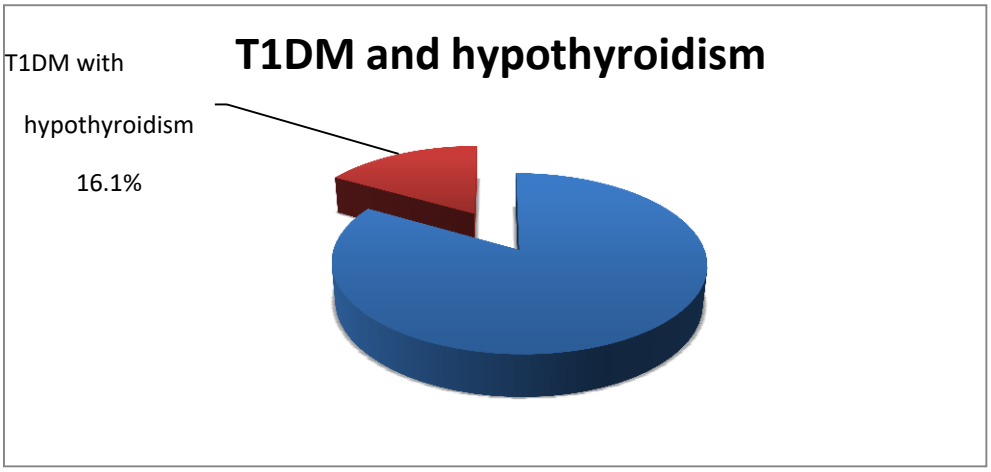

Figure 1 Distribution of hypothyroidism in T1DM Patients

In table 1 the patients stratified in to three groups according to the duration of T1DM. And compared according to the development of hypothyroidism with gender differentiation in each group

The result of sex distribution is that females being affected more than males, (12/17) in hypothyroid pt. Which is statistically significant & (50 /88) in euthyroid patients which is also significant (p- value of 0.05).

Table 1 also shows the distribution of cases according to DM duration (mean age for the diabetes is 8.6 yr. while for hypothyroid patients is 13 yr.) and the result is that the highest distribution of euthyroid diabetic patients in < 5 years duration (44 / 88) while the highest distribution of hypothyroidism is in 5-10 years duration (9/ 12) .

Table 1 distribution of cases according to gender and DM duration

T1DM duration	***hypothyroidism + T1DM***		***Total no.***	***OnlyDM1***		***Total No.***
	male	***female***		***male***	***female***	
<5 years No.47	*1*	*2*	***3 (2.8%)***	*21*	*23*	***44 (42%)***
5-10 years no.39	*3*	*6*	***9 (8.6%)***	*14*	*16*	***30 (28.5%)***
>10 years no. 19	*1*	*4*	***5 (4.7%)***	*3*	*11*	***14 (13.3%)***
Total No. 105	***5***	***12***	***p-value 0.05***	***38***	***50***	***p-value 0.05***

In table 2 there is a comparison of HbA1c between the euthyroid and hypothyroid diabetic patient (which indicate the glycemic control) which is higher in hypothyroid pts.

The mean level of HbA1c is 7.7±2.1 SD for the euthyroid patients & 10.7±2.2 SD for the hypothyroid patients, with significant p value (0.01)

Table 2 correlation between HbA1c ,T1DM duration and hypothyroidism

Duration of T1DM	*HbA1c of T1DM& hypothyroidism*	*HbA1c of T1DM only*	*p-value*
< 5 years	*9.8 ±2 SD*	*8.5 ± 2 SD*	***0.01***
5-10 years	*10.5 ± 2.8 SD*	*7.7 ± 1.8 SD*	
>10 years	*12 ± 1.5 SD*	*7.1 ± 2.5 SD*	
Mean +SD	***10.7 ± 2.2 SD***	***7.7 ± 2.1 SD***	

In table 3 there is higher percentage of DKA at presentation in T1DM & HT (70.6 %) , while about (65.9 %) having DKA at presentation in patients with T1DM only, with p - value of 0.5 which is statistically non-significant !!

In the same table, there is higher percentage of repeated hypoglycemia in hypothyroid group compared to the euthyroid group 76.5% vs. 51.1% with a statistical significance p- value 0.005.

Table 3 association of acute diabetic complication (DKA at diagnosis and recurrent hypoglycemia) with hypothyroidism

.

	T1DM only	*percentage*	*T1DM & hypothyroidism*	*Percentage*	*p- value*
DKA at presentation	*58/88*	***65.9%***	*12/17*	***70.6%***	***0.5***
Hypoglycemia	*45/88*	***51.1%***	*11/17*	***76.5%***	***0.005***

Table 4 shows the distribution of family history of T1DM & hypothyroidism as recorded in the files of the patients. in euthyroid diabetic patients (20.5%) have positive family history of DM1 and (4.5%) have positive family history of hypothyroidism , while those with T1DM & hypothyroidism (29.4%) having family history of T1DM and (11.8%) having family history of hypothyroidism . there is a significant correlation between family history of T1DM and hypothyroidism and the development of hypothyroidism .

Table 4 distribution of the cases according to family history of T1DM &HT.

	T1DM only	*%*	*T1DM & hypothyroidism*	*%*	*p-value*
FH of DM1	*18/88*	***20.5%***	*5/17*	***29.4%***	***0.01***
FH of HT	*4/88*	***4 %***	*2/17*	***11.8 %***	***0.0005***

In table 5 of the study the total hypothyroid pt. are 17, 11 of them are asymptomatic (65%) followed by increasing body weight 4 / 17 (23.5%) then 3/17 (17.6%) having nonspecific symptoms (poor appetite and lethargy) while those who suffering from poor school performance accounts for 12% (only 2 /17 patients) the least presentation is the short stature (as recorded by the growth chart which was below 5th centile) just one patient (5.9%)

Table 5 frequency of symptoms of hypothyroidism in T1DM patients

symptoms	***frequency***	***percentages***
Free of symptoms	*11*	*65%*
Overweight	*4*	*23.5%*
Lethargy &poor appetite	*3*	*17.6%*
Poor school performance	*2*	*12%*
Short stature	*1*	*5.9%*

In table 6 the study shows that most of the diabetic patients with thyroid dysfunction (hypothyroidism) having normal body weight 12 out of 17 followed by those with overweight 4 out of 17 then the lowest is those underweight just one patient,
While the patients who have T1DM only 69/88 have normal body weight followed by underweight 11/88 then the overweight 8/88

Table 6 distribution of the cases according to body weight in hypothyroid diabetic patients

	T1DM with HT	*T1DM only*	***p- value***
Normal B.W	*12 (70.5%)*	*69 (78.5 %)*	
Overweight	*4 (23.5%)*	*8 (9%)*	***0.2***
underweight	*1 (6%)*	*11 (12.5%)*	
Total no.	***17***	***88***	

In table 7 comparing the cases by the age of patients between the two groups (T1DM with and without hypothyroidism). The result is that the highest distribution of T1DM only between the ages of 3-7 years 51/88, while the highest distribution of cases of T1DM with HT is in the age exceeds 10 years 14/17 .

Table 7 distribution of cases according to age group

Age group	T1DM only		T1DM with ***hypothyroidism***		p- value
3-7 yrs.	51	58%%	0		
7-10 yrs.	21	24%	3	18%	0.05
>10 yr.	16	18%	14	82%	
Total no.	88		17		

figure 2, shows that from the 17 diabetic patient who are hypothyroidism 6 of them (35%) taking l-thyroxin treatment & the remaining 11 child (65%) don't taking treatment & on follow up by thyroid function test .

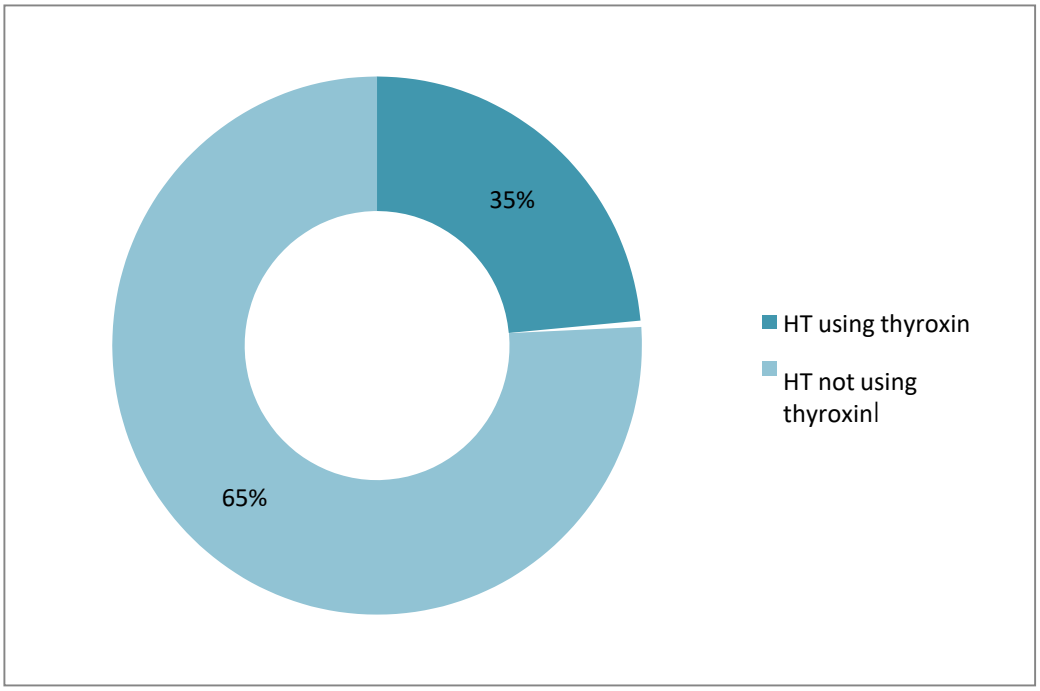

Figure 2. The percentage of using treatment in hypothyroidpatient with T1DM

In the last figure (fig. 3) of the study 30 /105 having other autoimmune disease, (17 / 30) having T1DM & hypothyroidism , (8 / 30) having T1DM & celiac disease , (3 / 30) having T1DM & autoimmune hepatitis , (1 / 30) having T1DM & hyperthyroidism & T1DM& polyglandular autoimmune syndrome (PAS)

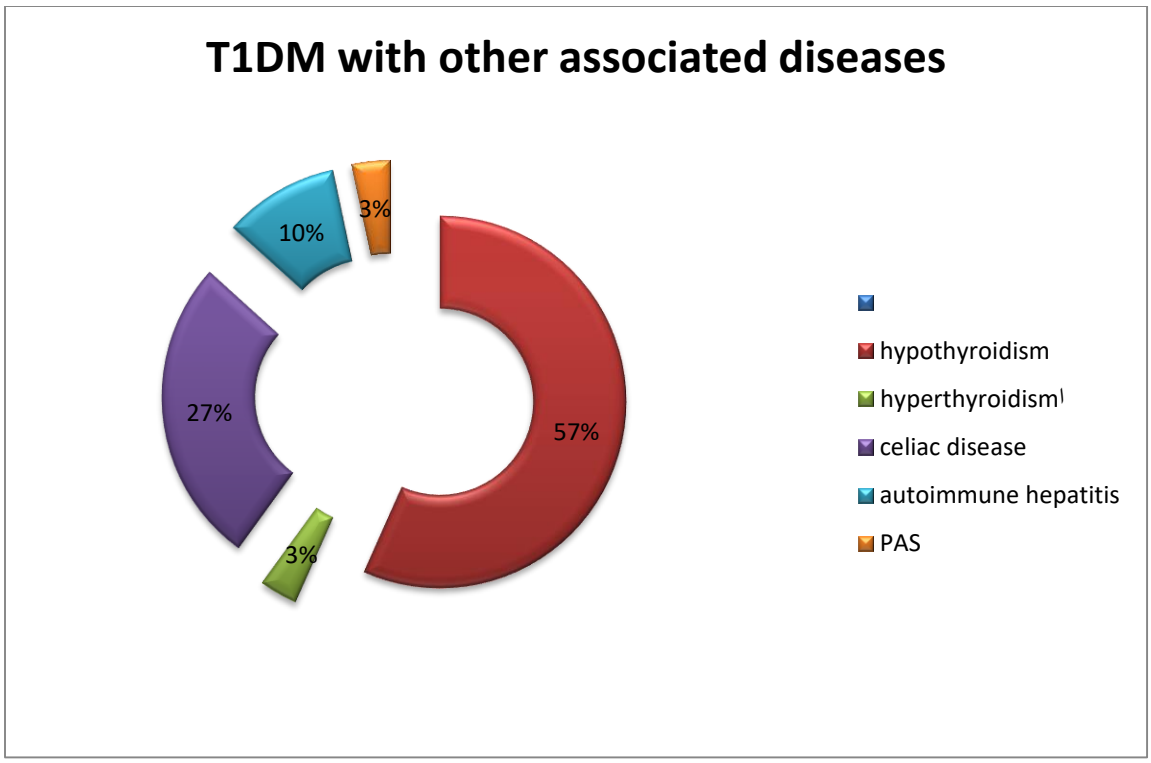

Figure 3 distribution of other autoimmune disease with T1DM

Discussion

In figure 1 the distribution of hypothyroidism in the current study was (16.1%),.

Comparing this with a study done in Cairo by Elmenshawi , and the result was that from 100 patients with T1DM 31% of them having hypothyroidism [38]

The lower percentage of hypothyroidism in our study may be due the difference in the variables (diabetic duration and control) that may affect the development of hypothyroidism or bias in selecting the cases .

females affected more than males in both euthyroid (12:5) and hypothyroid (50:38) groups with a significant p value.

Comparing this to a study which was done in Iran by Ardestani that include 18 diabetic patients with hypothyroidism female :male (11 :7), the second group consisting of 65 diabetics patients without hypothyroidism (36 :29) the female : male ,both of the two groups having higher number of females ,but with no significant value . [39] *Which may be due to bias in sample selection*

T1DM mostly seen < 5 years duration (44 / 88) 42% while hyopthyrod diabetic pt. mostly seen in 5-10 years duration (9 /17) 8.6% .

In a study that was done in Cuba, by Valdés Alonso MC, which involve 54 patients 25 of them with hypothyrodism (46.3%) & 29 without HT…

It shows highest percentage of euthyroid patients in less than 5 years duration 3 / 4 (12%) and hypothyrodism seen mostly in 5-10 years duration 10 / 13 (40%) patient. [40] Both of the studies have the similar results .

In this study there is lower HbA1c 7.7 ± 2.1 SD (better glycemic control) for euthyroid patients & higher level 10.7 ± 2.2 SD for the hypothyroid patients which is significant (p value 0.01) .

which compared to a study which was done in Iran by Ardestani SK , which also shows higher level of HbA1c in the diabetic patients with hypothyroidism (8.88) compared to diabetic patients without hypothyroidism (8.24) [39]

Another study which was done in Egypt by Shuhoub, A, which shows the difference in the HbA1c between the diabetic patients with and without hypothyroidism (11.37 ± 2.10 vs. 10.02 ± 1.89) with a significant p- value of 0.01 [42]

In those two studies, there is higher level of HbA1c in the hypothyroid patient with T1DM. Which is similar to the results of the current study that confirm the relation of poor glycemic control accelerate the hypothyroidism development and increase it's occurrence and lack of thyroid hormone associated with insulin resistance and treatment of hypothyroidism was reported to improve insulin sensitivity .

there is higher DKA in hypothyroid patients than T1DM. Only. 70.6% vs. 65.9%. with p - value of 0.5 (statistically non-significant!)

Comparing this to a study which was done n Zagazig ,Egypt by Shuhoub, A , which shows 68% of hypothyroid patients with T1DM. Presented with DKA compared to 36.3% euthyroid pts., which is statistically significant p – value of 0.002. [41]

In spite of higher percentages of DKA in hypothyroid patients with T1DM in both studies, but the DKA in the euthyroid diabetic children of the current study is higher than the Egyptian study which may be due to unawareness of the family about the signs and symptoms of T1DM in their children who are susceptible to get the disease and delay seeking medical advice until it presents as a DKA which exaggerated by any stress condition like infection

The current study also shows higher recurrent hypoglycemia in hypothyroid group (11/17) compared to that of euthyroid group (45/88) with a statistical significance (p- value 0.005) ,

Compared this to study which was published by A. Mohn S , in which there were a 13 / 31 patient diagnosed to have hypothyroidism with T1DM and the hypothyroid patients had significantly more recurrent symptomatic hypoglycemia with a p- value of 0.05. (significant) also. [42]

Regarding the family history of T1DM. &hypothyroidism. of this study, The euthyroid pts. Have (20.5%) positive family history of T1DM. And (4 %) positive family history of hypothyroidism, while those with hypothyroidism (29.4%) having family history of T1DM. And (11.8%) having family history of hypothyroidism …

In a study which was done in Tehran ,Iran by Fatourechi A, Ardakani HM, Sayarifard F, Sheikh M. , they found that from 298 patient who have T1DM only 15.1% have positive family history of T1DM & 11% have positive family history of hypothyroidism , while 32 patient have hypothyroidism 31.2% have positive family history of T1DM & 18.7% have positive family history of hypothyroidism . [43]

the variation in the percentage of T1DM only group it is higher in our study regarding family history of T1DM & lower in family history of hypothyroidism , which may be, belong to the variations and differences in the sample size between the two studies & poor screen in our society to other members of the family who are asymptomatic …

In studying the frequency of symptoms of hypothyroidism as recorded in patient's files there result was as the following 65% asymptomatic followed by increasing body weight 23.5% then 17.6% having nons pecific symptoms (like poor appetiteand lethargy) while those who suffering from poor school performance accounts for 12% and the least presentation is the short stature 5.9% ..

Comparing those results to another study which was done by Murillo-Vallés, M., Martinez, S., Aguilar-Riera, C. et al. which shows that about 41.5% of patients with hypothyroidism. are discovered by routine investigations (means asymptomatic) ,13.8% having obesity ,12.3% having short stature and 18.4% having other symptoms ..[44]

Which have the same sequence of our study from the highest to lowest frequent symptoms asymptomatic , obesity followed by other non-specific symptoms and lastly the short stature ..

While the distribution of cases according to body weight in the study shows that most of the hypothyroid patients having normal body weight (70.5%) followed by those with overweight /obesity (23.5%) then the lowest percentage is the underweight /asthenia (6%).

Comparing this to another study which was made in Cuba by Valdés Alonso MC,. in which it involve 25 patients with AIT diseases most of them having normal body weight 80% followed by excess weight 16% and

the lowest percentage for those who are underweight 4% [40] this results agree with the results of the current study…

In table 7 the highest distribution of diabetic cases only with the age between 3-7 years (58%) while the highest distribution of hypoyhyroid cases is within the age of more than 10 yrs.

Comparing this to a study which was done by Magdy A. Omar , which found that the highest distribution of diabetic patients 60 % at age > 10 yrs. , While the hypothyroid pts. 50% within the age between ages 5-10 yrs [45]

This may be due to bias in selection of cases or due to difference in compliance or adherence to the management plans .

The current study shows that 35% (6/17) taking l-thyroxin treatment & the remaining 65% do not taking treatment & on follow up just.

this study was compared to another study which was done by Kordonouri O, Hartmann R, Deiss D, Wilms M, Grüters-Kieslich in Berlin , Germany , the result of this study was that during the study period 62 out of 659 patients (9.4%) required treatment with l-thyroxin . [46]

This difference in the percentage of treatment use may be due to huge difference in sample size between the two studies.

In figure 3 Other autoimmune diseases ,

we find that 57% having T1DM & hypothyroidism, 27% having T1DM & celiac disease, 10% Having T1DM & autoimmune hepatitis, 3% having T1DM & hyperthyroidism & T1DM & 2 other diseases (PAS)

While in a study which was done at Germany , by Frommer L, and

Kahaly GJ the study showed that hashimoto thyroiditis presented in 56.84% of those with T1DM patients ,43.68% having graves diseases,15.75% celiac disease & 3.15% with autoimmune hepatitis .[47]

Another study which was done by Ben-Skowronek I, Michalczyk A, Piekarski R, Wysocka-Łukasik B, Banecka B which showed that 14.5% of children with DM1 have type 3 PAS [48]

The two studies having higher percentages of the hypothyroidism but variable other AID which may belong to the bias in selectiing patients .

Conclusion

- *16.1% is the distribution of hypothyroidism in T1DM in the study .*
- *Females' are affected more than males in both T1DM. & hypothyroidism groups.*
- *There is a significant correlation between T1DM duration and the development of hypothyroidism*
- *There is a significant correlation between glycemic control (HbA1c) and the development of hypothyroidism in patients with T1DM.*
- *Most of the hypothyroid patients in T1DM. are asymptomatic and need just follow up*
- *Most of them have normal body weight*
- *There is no significant correlation between DKA at presentation of T1DM and development of hypothyroidism.*
- *There is significant correlation between recurrent hypoglycemia and the development of hypothyroidism .*
- *There is significant correlation between family history of T1DM & hypothyroidism . and the development of hypothyroidism .*

Recommendations

Screen all T1DM. not only for their secondary prevention but at times also for primary prevention and early diagnosis and treatment.

Our society having higher DKA presentation than the expected. so increase community awareness about the signs and symptoms of diabetes and not post ponding taking medical advice especially for those who are young children because they will have nonspecific unusual symptoms or asymptomatic .

Family education about signs & symptoms of hypoglycemia, DKA, and early medical consultation with adherence to the treatment with the use of newer insulin regimes to control the diabetes

The massage is that good controlling of DM and good follow up may lead to delay hypothyroid occurrence.

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Appendices

Questionnaire

Name

Sex

Age of T1DM/Hypothyroidisms

Duration of DM

DKA at presentation

Recurrent hypoglycemia

Weight

Family history of T1DM/ hypothyroidism

Symptoms of hypothyroid diabetic patients

Treatment of hypothyroid patients

Other autoimmune diseases

الخلاصه

الخلفية *يعود داء السكري من النوع الأول إلى تدمير المناعة الذاتية الخلوي لخلايا البنكرياس البائية. يتم تعريفه بواحد أو أكثر من علامات المناعة الذاتية ، بما في ذلك الأجسام المضادة لخلايا البنكرياس والأجسام المضادة للأنسولين ، وللمرض ارتباطات قوية بـ مستضد الكريات البيض البشرية HLA كما أن المرضى معرضون أيضًا لاضطرابات المناعة الذاتية الأخرى مثل التهاب الغدة الدرقية هاشيموتو ومرض الاضطرابات الهضمية ومرض جريفز وغيرها.*

أهداف الدراسة لتحديد العلاقة بين السيطرة على داء السكري من النوع 1 ومدته مع تطور قصور الغدة الدرقية وأهمية التاريخ العائلي لكل من داء السكري من النوع 1 وقصور الغدة الدرقية في تطوره أيضًا ، وتحديد الأعراض الرئيسية المتكررة لقصور الغدة الدرقية في مرض السكري من النوع 1 للمرضى وعلاجه

المرضى *دراسة استعادية مقطعية أجريت في أقسام الغدد الصماء لطب الأطفال في مدينة الإمامين الكاظمين الطبية ومستشفى الطفل التعليمي المركزي من 1 فبراير 2022 حتى 30 يوليو 2022 من ملفات أرشيفية للمرضى في السنوات السابقة من 2015 -2021. اشتملت الدراسة على مرضى السكري من النوع الأول الذين تم تقسيمهم إلى مجموعتين: المجموعة الأولى تشمل المرضى الذين ليس لديهم قصور الغدة الدرقية ، والمجموعة الثانية تشمل مرضى قصور الغدة الدرقية. درست المجموعتان أعمارهما ، ومدة الإصابة بمرض السكري ، ونسبة السكر التراكمي ، ونقص السكر في الدم المتكرر ، والحماض الكيتوني السكري عند ظهور الأعراض ، وأعراض قصور الغدة الدرقية وعلاجه ، والتاريخ العائلي لكلا المرضين ، وتطور أمراض المناعة الذاتية الأخرى.*

النتائج: بلغ إجمالي عدد المرضى 105 ، قصور الغدة الدرقية 16.1 % ، والإناث أعلى من الذكور في كلا المجموعتين بقيمة P 0.05 ، ومتوسط عمر الأطفال المصابين بالسكري 8.6 سنوات ، والأطفال الذين يعانون من قصور الغدة الدرقية 13 سنة ، وقصور الغدة الدرقية موزعة في الغالب على 5 - 10 سنوات من الإصابة بمرض السكري 8.6 % ، قصور الغدة الدرقية مع مرض السكري من النوع 1 يرتبط بنسبه أعلى للهيموغلوبين A1c مقارنة بمرضى السكري فقط بقيمة 0.01 p. يرتبط قصور الغدة الدرقية بشكل كبير بنقص السكر في الدم المتكرر ولكن ارتباط غير مهم مع الحماض الكيتوني السكري عند. التشخيص يرتبط قصور الغدة الدرقية بشكل كبير بالتاريخ العائلي لمرض السكري من النوع 1 في 29.4 % وقصور الغدة الدرقية في 11.8 %. تشكل نسبة اعمار المصابين بقصور الغدة الدرقيه الذين يتجاوزون العشر سنوات (82

%) بينما داء السكري من النوع 1 فقط (3-7 سنوات يشكلون 58 %) معظم مرضى قصور الغدة الدرقية يعانون من أعراض 65 % ولديهم وزن طبيعي 70.5 % و 35 % فقط يتلقون العلاج.

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الاستنتاج يرتبط قصور الغدة الدرقية ارتباطًا وثيقًا بضعف السيطرة على مرض السكري وطول مدة المرض ، وهناك ارتباط كبير بين تطور قصور الغدة الدرقية والتاريخ العائلي لكل من داء السكري من النوع 1 وقصور الغدة الدرقية ، ومعظم حالات قصور الغدة الدرقية في مرض السكري من النوع 1 هي أعراض تحتاج إلى متابعة وقليل منهم يحتاج إلى العلاج. وهناك ارتباط كبير بين التاريخ العائلي للإصابة بمرض السكري من النوع الأول ، وقصور الغدة الدرقية ، وتطور قصور الغدة الدرقية.

العلمي والبحث العالي التعليم وزارة

الطبية للاختصاصات العراقي المجلس

توزيع قصور الغدة الدرقية في عينة من الأطفال المصابين بالسكرى من النوع الأول

أطروحة

مقدمه الى

المجلس العراقي للاختصاصات الطبية كجزء من متطلبات نيل شهادة زميل المجلس العراقي للاختصاصات الطبية في طب الأطفال

من قبل

سجى جمعه ضمد

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اشراف

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قسم طب الأطفال

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