STUDY ON THE PREVALENCE OF THYROID DYSFUNCTION IN TYPE 1 DIABETIC CHILDREN

Dissertation submitted to

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of degree of

M.D DEGREE (PEDIATRICS) BRANCH VII

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN MADRAS MEDICAL COLLEGE APRIL 2013

CERTIFICATE

This is to certify that the dissertation titled, "***Study on the prevalence of thyroid dysfunction in Type 1 Diabetic children***

submitted by ***Dr.A.Jagadeesh,*** *to the Faculty of Pediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfillment of the requirements for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2010-2013.*

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Prof.M.Kannaki,M.D.,DCH
Director and Superintendent,
Institute of Child Health and Hospital for Children,
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Professor of paediatrics,
Unit Chief, Research Guide,
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and Hospital for Children,

DECLARATION

I, **Dr.A.Jagadeesh**, solemnly declare that the dissertation titled **"**Study on the prevalence of thyroid dysfunction in Type 1 Diabetic children" has been prepared by me.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

Dr.A.Jagadeesh

Place : Chennai

Date :

SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.V.Kanagasabai, M.D.,** Dean, Madras Medical College, Chennai for permitting me to utilize the clinical materials of the hospital for the successful execution of my study.

ACKNOWLEDGEMENT

I express my heartfelt gratitude to **Prof.M.Kannaki, M.D.,DCH.,** Director and Superintendent, Institute of Child health and Hospital for children, Madras Medical College, Chennai for his guidance and support in the execution of this study.

I am very grateful to my unit chief, **Prof. Dr.P.S.Muralidharan, M.D., DCH.**, Professor of Pediatrics, for their constant guidance and encouragement, that made this study possible.

I express my gratitude to the Assistant Professors of Diabetology Department **Dr.S.Parivathini, MD.,DCH**and **Dr. V.Poovazhagi, MD.,DCH** and assistant professors of my medical unit, **Dr.D.Velmurugan,M.D., Dr.D.Prabakar M.D.,** and **Dr. Sridevi Narayan, M.D.,** for their invaluable help and support throughout the study process.

I am extremely thankful to **Dr. K.Nedunchelian,MD.,DCH.,** for his valuable suggestions and guidance during this study.

I am extremely thankful to **Dr. S. Srinivasan, DCH.,** Medical Registrar, for his valuable suggestions and guidance during this study.

I sincerely thank all the children and their parents who have submitted themselves for this study.

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. A. Jagadeesh
PG in MD Paediatrics
ICH / Madras Medical College, Chennai -3.

Dear Dr. A. Jagadeesh

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Prevalence of thyroid dysfunction in type 1 diabetic children at ICH & HC, Madras Medical College, Chennai " No. 29082011.

The following members of Ethics Committee were present in the meeting held on 16.08.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai, MD Dean, Madras Medical College, Chennai-3,	-- Deputy Chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
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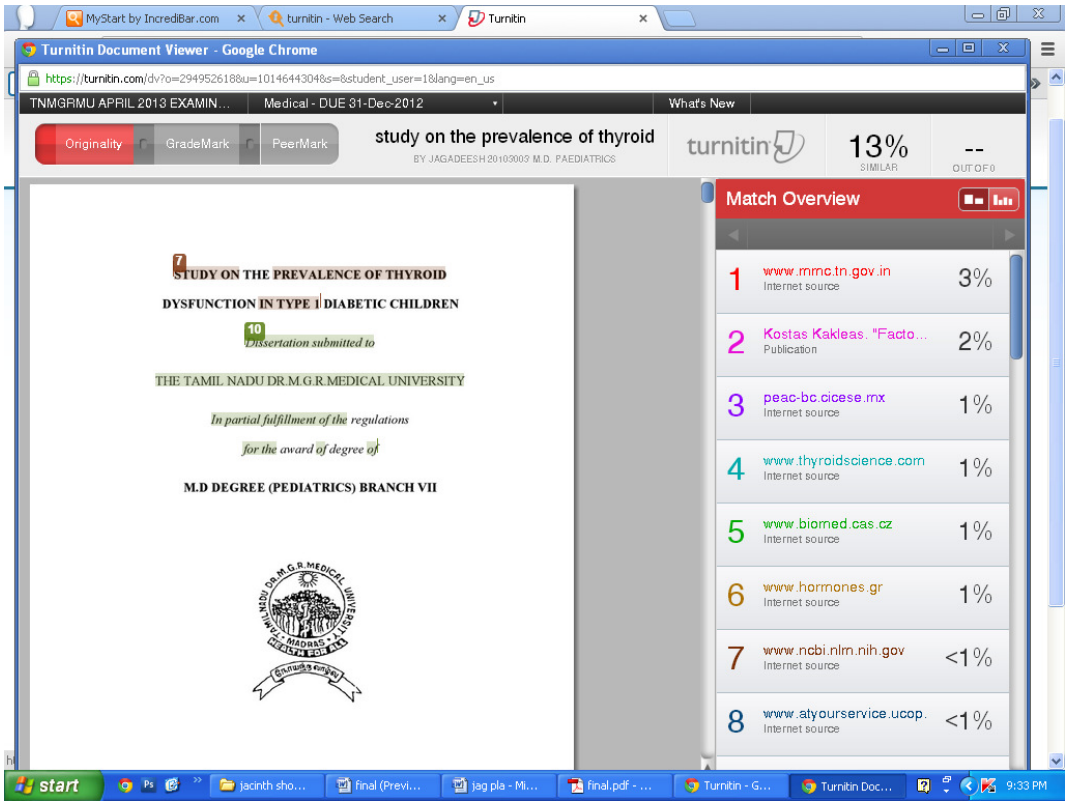
6.	Prof. C. Rajendiran, MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
7.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
8.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
9 .	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee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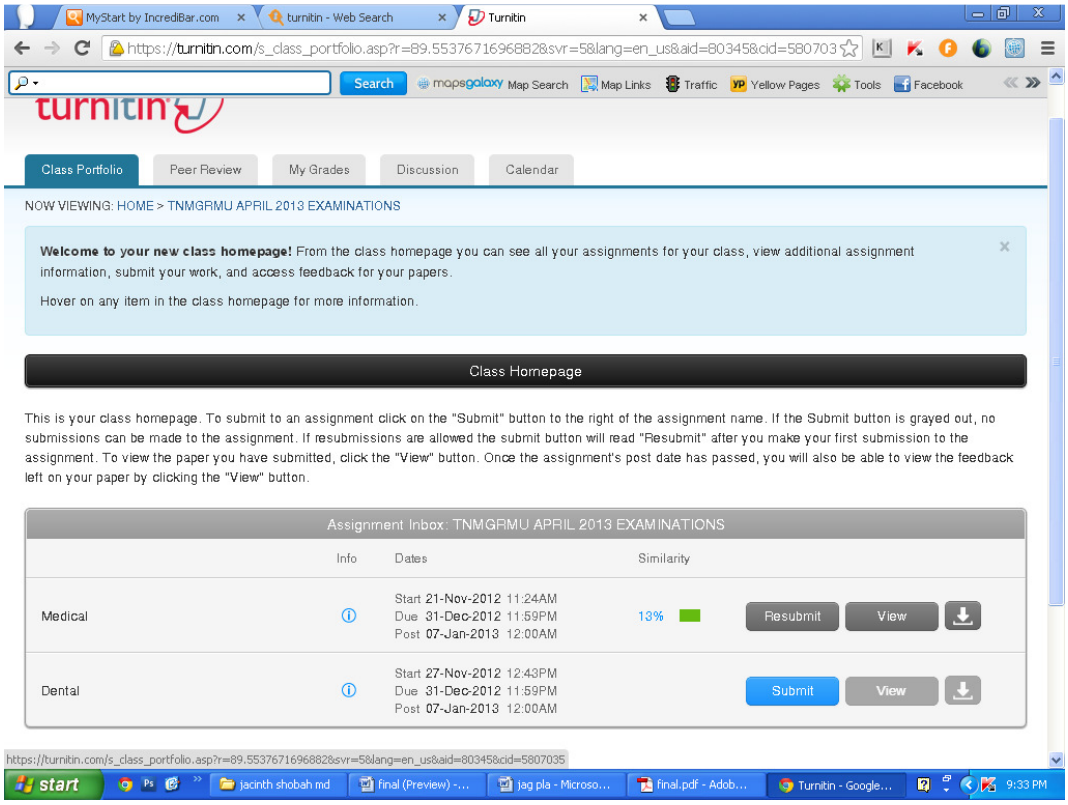
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STUDY ON THE PREVALENCE OF THYROID DYSFUNCTION IN TYPE 1 DIABETIC CHILDREN

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease resulting in insulin deficiency. In the recent two decades, the world wide prevalence of diabetes mellitus (DM) has increased significantly.[1] There is a genetic predisposition towards T1DM. This also predisposes these individuals to other autoimmune diseases such as thyroid disease, celiac disease and adrenal insufficiency. Of all the above mentioned diseases autoimmune thyroiditis (AIT) is the most frequently encountered one.[2, 3] According to various studies, 15-30% of T1DM patients have AIT,[4-7] 4-9% have celiac disease and 0.5% have Addison disease.[7]

AIT is the most frequent autoimmune disease seen in diabetic children. To diagnose AIT, thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG) antibodies are measured. The prevalence of these antibodies depends mainly on sex, age at onset of

hypothyroidism and duration of diabetes . Geographic location is an important determining factor and the prevalence is high in areas with higher iodine intake (De Block *et al.* 2001).

AIT is often clinically silent but it may progress to overt or subclinical hypothyroidism or hyperthyroidism[8]. When compared to the general population the positivity of anti-thyroid antibodies was found to range from 2.9% - 3.4%[9,10] while in T1DM children it was between 18.5% - 24.6%.[11-13] These thyroid antibodies may be seen just temporarily also.(Vondra *et al*1996).

According to previous studies age and sex are important risk factors to develop AIT, [11,13,14,15,16] while there are very limited studies to correlate the age at thyroid diagnosis [11,14], duration of diabetes [14,16,17] and the development of thyroid antibody positivity.

EFFECT OF DIABETES ON THYROID FUNCTION

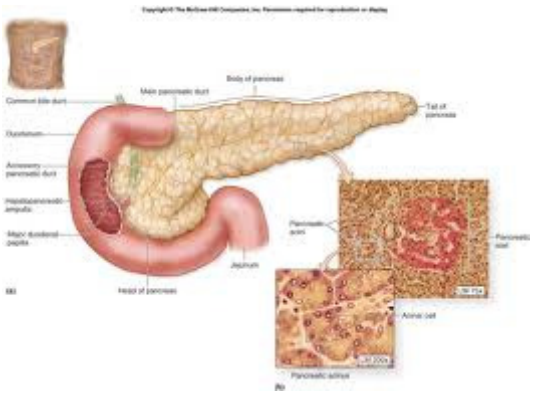
In T1DM children with normal thyroid function, the T3 and TSH levels may be strongly influenced by the glucose levels . T1DM which is poorly controlled may induce a low T3 state and it is the long term diabetic control that determines the T3 and TSH levels.[58]

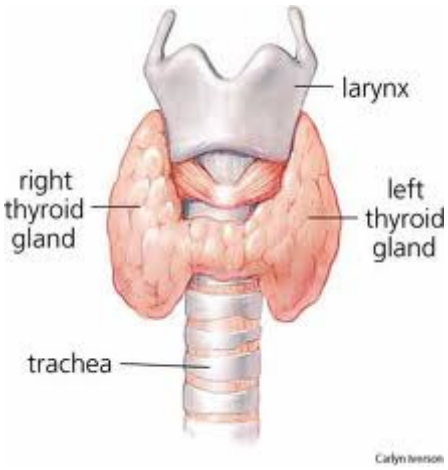
EFFECT OF HYPOTHYROIDISM ON DIABETES

In children with hypothyroidism the insulin synthesis is decreased. Gluconeogenesis is also reduced.It has been proposed that there is a postreceptor defect which explains the decrease in insulin stimulated utilization of glucose that occurs in peripheral tissues.This predisposes to hypoglycemia in these children.[59]

Clinical status	**Effect on blood glucose**	**Effect onThyroid function**
T1DM- With normal thyroid function		↓ T3 ↓ TSH
TIDM– in hyperthyroidism individuals	Poor control of glucose	↑ risk of ocular involvement
Hyperthyroidism – In euglycemic children	Glucose intolerance	Overt diabetes

Hyperthyroidism- In T1DM children	Poor control of diabetes	
Hypothyroidism- in diabetic children	Predisposes to recurrent hypoglycemia	
In Type 1 diabetic children		↑ Risk of thyroid disease





Both thyroid hormones and insulin are closely related that T1DM and thyroid dysfunction mutually influence the disease process of each other. In hyperthyroidism, it will be difficult to maintain the glycemic status thereby making the management of diabetes difficult. T1DM children with hyperthyroidism might need a increase in daily insulin requirement and hence there is increased risk of diabetic ketoacidosis.[18,19]

Hypothyroidism usually predisposes to hypoglycemia . Hypothyroidism as such causes growth retardation , increase in weight, menstrual irregularities, abnormal lipid elevations and it can also lead to cardiac complications in these T1DM children.[8]

In previous studies overt hypothyroidism occurs in 1-5% and hyperthyroidism occurs in 0.5-7% individuals.[3,20] Since the prevalence of AIT is increasing in T1DM children, these children should undergo screening either by using TSH or measurement of thyroid antibodies. Despite this fact, there is still no clear consensus regarding screening of AIT and thyroid function in T1DM.[21]

In AIT antibodies are produced against thyroglobulin (Tg), a colloid, and thyroid peroxidase (anti-TPO), which helps in the formation of thyroid hormones [23]

In T1DM children, the prevalence of anti TPO antibody was found between 10.3% and 28.4% whereas anti-Tg was found to range between 8.8% and 14.5%. [24,25,26,27] In the presence of both of these antibodies it was between 5.9%–7%. [24,26,27] These antibodies are usually not detected at diagnosis, but they may be seen after sometime in the course of the disease particularly in those children who are genetically predisposed. [11,17] In another study, 16.7% of the patients was found to have AIT at the onset of diabetes.[17]

In these children with AIT, family history of diabetes and family history of thyroid abnormalities should be taken into account. This is because AIT occurs more frequently in individuals with strong family history because of genetic predisposition in causing this autoimmunity.

In girls particularly in adolescents, history of menstrual irregularities should be asked for, since both delayed and precocious puberty is well known to occur. Also features of any specific syndrome (Eg: Down syndrome) should be looked for, since AIT is more common along with T1DM in these children.

Intake of specific drugs triggering AIT and T1DM should be noted. Any stressful event in the form of trauma, infection, exanthematous illness also to be looked for.

Nearly one third of all T1DM children have co-existent AIT and a high prevalence of thyroid dysfunction which is predominantly hypothyroidism (clinical or subclinical) whilst a very few have hyperthyroidism. Since the prevalence of thyroid dysfunction in T1DM children is high, the importance of screening for AIT have been emphasized.

DEFINITIONS :

Overt hypothyroidism: was defined as elevated TSH and low T4,

Subclinical hypothyroidism as elevated TSH and normal T4,

AutoImmuneThyroiditis (AIT)

Positivity of at least one antibody either TPO or Tg, or pathological evidence was considered to be having AIT.

REVIEW OF LITERATURE:

Ardestani et al

Objective: Studies in different populations have shown great variation in the prevalence of thyroid diseases in individuals with T1DM. The objective was to study the prevalence of thyroid disorders such as autoimmunity of thyroid (AIT), thyroid dysfunction, and goiter in children with T1DM

Findings: The prevalence of subclinical hypothyroidism was high in both groups (18%). T1DM patients had lower frequency of goiter (21% vs. 38%), and higher prevalence of positive AIT (22% vs 8%), anti-TPO Ab positivity (19.2% vs. 5.2%), anti-Tg Ab (11.1% vs. 6.4%)

Conclusion: Results demonstrated the high prevalence of AIT and thyroid dysfunction in patients with T1DM and regular thyroid function and antibody testing was suggested.

Kostas kakleas et al

Anti-TPO was seen in 17.3% while anti-Tg was 11.1%, and of both anti-thyroid antibodies (10.4%). The presence of anti-thyroid antibodies had a positive association with age, duration of diabetes, and TSH levels. In general there is a female preponderance for AIT. Though the prevalence of AIT was more common in middle aged women, it still may start in early childhood. Hence early recognition forms an important aspect in the long term management of these children.

Ismael et al Diabetic care:

Study period: 2001

Study design: Descriptive study

.*Sample size*: 17,749 patients

Conclusion: 15% patients had AIT. Increase positivity were seen during the second decade.

More common in women. Treatment may be initiated if the antibody levels are too high, so that complications of hypothyroidism can be prevented.

Kordonouri et al, BMJ

Study period: 1990 - 2003

Study design: Longitudinal study

Study population: Children with Type 1 diabetes.

Methodology: Antithyroid antibodies were done in TIDM children and correlated with age, gender and duration of diabetes

Results:

When screened initially, 15.4% of patients were positive for anti-TPO and 14.4% were positive for anti-Tg. The incidence of AIT after a decade was significantly higher particularly after 12 years of age.

Individuals with AIT had poor glycemic control and frequent admissions. Also the lipid parameters were significantly elevated. Already individuals with T1DM are more prone for metabolic syndrome complications, and AIT still more worsens it.

Guillermo et al, Diabetic care

Study period:1983-2001

Study design: Randomized control trial

Sample size: 58 individuals

Results: 18 patients developed AIT, and 1 of them developed hyperthyroidism. AIT was seen more in females (41%). No significant association was found in BMI, lipid parameters, and glycemic control in individuals with AIT.

Those individuals with AIT who were promptly managed had less complications in terms of cardiovascular, metabolic, menstrual irregularities when compared to those individuals who didn't take treatment.

Pasupathi et al

The main objective was to investigate the effect of diabetes on thyroid hormone levels and other biochemical variables. The study population had 200 subjects who were divided into two groups: diabetic and non-diabetic. A significant increase in the levels of blood glucose, HbA1C, cholesterol, triglyceride were observed in diabetic patients compared to non-diabetic subjects. TSH levels was significantly decreased whereas T_4 and T_3 levels were significantly increased in diabetic patients when compared to controls.

However, the T_4 and T_3 levels did not differ significantly between the two groups. Of the 100 diabetic patients, 27% had low thyroid hormone levels, 16% had high thyroid hormones, and 55% had normal levels. This study demonstrated high incidence of abnormal thyroid hormone levels among the diabetics. To conclude ,the detection of abnormal thyroid hormone levels in the early stage of diabetes mellitus will help the patients to detect the complications associated with it.

Pranzy et al

The aim of this study was to detect subclinical AIT. The presence of antibodies was correlated with the control of diabetes. Fifty-one type 1 diabetic patients (mean age 37±11 years, mean duration of diabetes 16±13 years) were included into this study. TPO , Tg and TSH were measured by RadioImmunoAssay.

11 new cases of thyroid dysfunction (22 % of patients) were detected by the estimation of thyroid antibodies and TSH. Two new cases of hyperthyroidism were diagnosed during the study. In both patients with hyperthyroidism the control of diabetes initially worsened and improved after treatment. The screening of antibodies in type 1 diabetic patients revealed subclinical cases of AIT . Subclinical forms of these disorders have no influence on the control of diabetes . It was suggested to follow-up the patients with positive antibodies because further deterioration of the thyroid function can be expected.

STUDY JUSTIFICATION:

Finding of hypothyroidism in our TIDM children attending diabetic clinic when they are routinely screened for the same and unavailability of clear data regarding the prevalence of autoimmune thyroiditis in these T1DM children prompted us to do the study. We have a separate diabetic clinic where the patients are being followed up. In their routine screening we found a significant number of cases to overt hypothyroidism. In order to have a data for our own diabetic children and to demonstrate the autoimmunity we have decided to do this study.

Although it is generally agreed that because of increasing prevalence of AIT in T1DM children, screening for AIT in all T1DM is justified,[4,5] it is still not agreed which is the best method and how often to perform. The American Diabetes Association [6] [7,8] have recommended to use TSH as a screening tool in T1DM children once a year., as autoantibodies may still persist for many years without thyroid dysfunction.

However, the American Diabetes Association have suggested that the presence of thyroid autoantibodies increases the risk for thyroid disease. These evidences clearly show that the incidence of autoimmune thyroid disease is highly increased in T1DM children when compared to the general population[7,8] But controversy still remains regarding the management when antibodies alone are positive.

From previous studies it is clear that the prevalence of thyroid antibodies in patients with type 1 diabetes increases with age, female sex and duration of diabetes.[18,19]

Hence we confirm the recommendation that thyroid testing be done at diagnosis and annually in children with type I diabetes.[30,31] Also there are a very few studies which have analysed the risk factors to relate AIT with T1DM[3,30] . It is noteworthy that there are limited studies to demonstrate the influence of AIT on BMI of children with T1DM. Hence we decided to study the effect of AIT on the BMI of children with T1DM and glycemic control in patients with thyroid dysfunction. Also the effect of thyroid dysfunction in these individuals was also correlated.

AIM OF THE STUDY:

- To study the prevalence of thyroid dysfunction among children with newly diagnosed Type 1 diabetic children attending Diabetic clinic at Institute of Child Health from August 2011 to october 2012.

- To correlate the effect of thyroid dysfunction on age, gender, duration of diabetes, glycemic control, lipid abnormality and BMI in these T1DM children.

SUBJECTS AND METHODS:

1.Methodology

a) Study design:

Descriptive study design

b) Place:

Diabetic clinic,

Institute of Child Health ,Egmore, chennai

C) Period of study:

August 2011 – October 2012

D) Study population

Case definition:

Diabetes: Children with history of polydipsia, polyphagia, polyuria and

Fasting blood glucose ≥126 mg/dl

Random blood glucose ≥200 mg/dl

Inclusion criteria: All children attending diabetic clinic at ICH who were diagnosed with T1DM.

Exclusion criteria:

I. Children diagnosed to have secondary diabetes, secondary to drugs.(Drugs include steroids, asparaginase, phenytoin)

II. Children with dysmorphic or syndromic facies.

III. Patients found to be having hypothyroidism prior to diagnosis of diabetes

IV. Neonatal diabetes and in infants less than 1 year.

Sample size: 142 patients (All consecutive subjects were included)

Institutional Ethical Committee approval was obtained. Informed consent was obtained from each parent before recruitment

2.Manouvres :

- Clinical examination of thyroid gland and Goiter grading was done according to WHO/UNICEF/ ICCIDD classification [32]
- Thyroid profile which includes serum T3, T4,TSH levels

Serum T3 and T4 concentrations were measured using Competitive chemiluminescent immunoassay.

Normal range for T3 level: 60 - 200 ng/dl

T4 : 4.5 – 12 microgram/dl.

Serum TSH concentrations were determined with ultrasensitive sandwich chemiluminescent assay.

Normal range for TSH level : 0.3-5.5 microU/ml.

Overt hypothyroidism was defined as elevated TSH and low T4, subclinical hypothyroidism as elevated TSH and normal T4, overt hyperthyroidism as low TSH and elevated T4 and subclinical hyperthyroidism as low TSH and normal T4.

Serum anti-TPO antibody and anti-Tg antibody were measured by solid phase enzyme assay.

Anti-Tg antibody > 325 IU/ml

Anti-TPO concentrations >50 IU/ml, respectively, were considered positive.

Positivity of at least one antibody was considered as having AIT.

Thyroid ultrasonography was done in children with positive anti-thyroid antibodies, with or without elevated TSH . AIT was diagnosed when there is thyroid enlargement [33] with diffuse hypoechogenicity and/or diffuse micronodules [34]

AIT was diagnosed when TSH is elevated (>5 μIU/mL), associated with the presence of at least one thyroid autoantibody, with or without ultrasonographic evidence of thyroiditis.[34]

Clinical hypothyroidism is said to be present when there is low T4 and TSH levels with or without goitre.

- Lipid profile : S. Cholesterol & S.Triglycerides were done.

  S.cholesterol > 200, S.Triglycerides > 150 was taken as abnormal.[20]

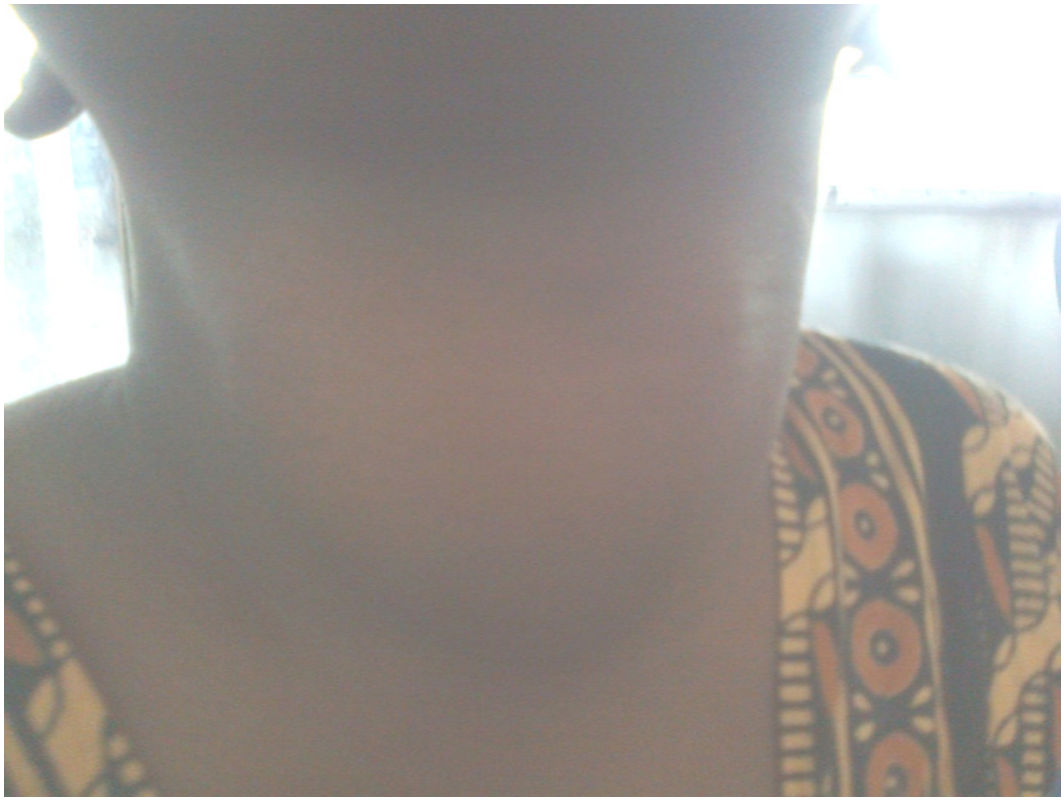
- USG of thyroid gland: Diffuse hypogenecity was suggestive of AIT.

- HbA1C > 10 was taken as having poor control. [27]

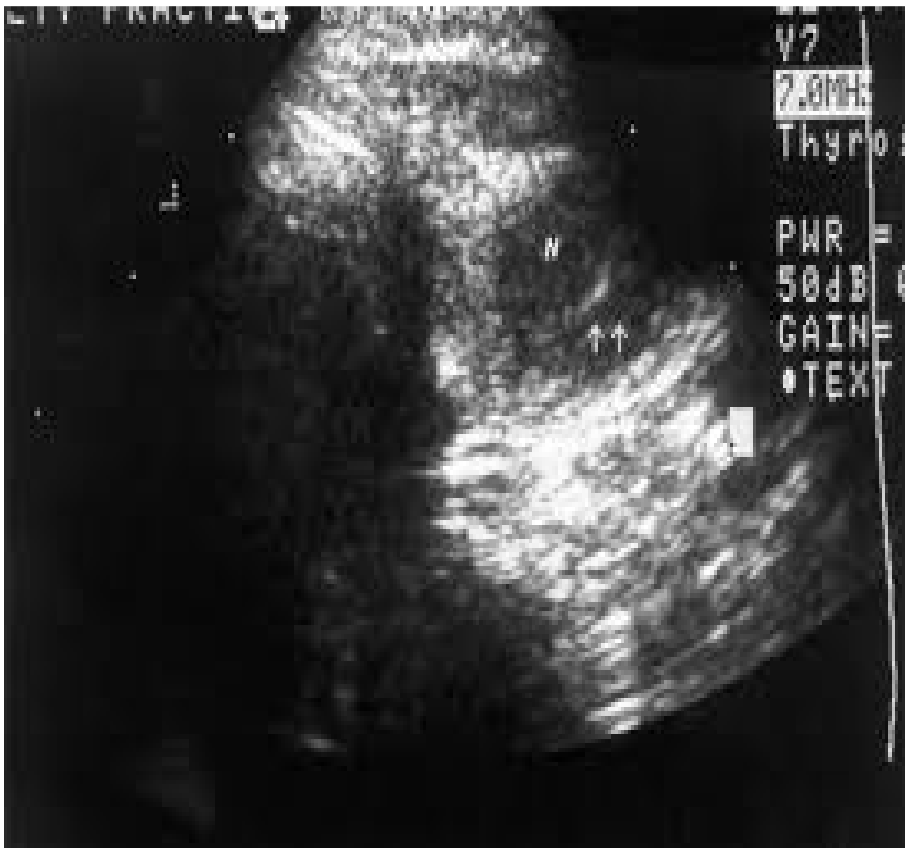
- Hypoglycemic episodes : It was taken as significant when it is symptomatic. (sweating, palpitations and seizures)

- BMI > 22 was taken as overweight and >25 as obese. [27]

DIABETIC CHILD WITH GOITRE



ULTRA SONOGRATHY OF THYROID SHOWING HYPOECHOGENECITY



3. Statistical analysis

- Descriptive data was be used to calculate the prevalence.

- Correlation of thyroid dysfunction on the age, gender, duration of diabetes, glycemic control, effect on BMI and lipid abnormality will be calculated using

  A) Univariate analysis

  B) Multivariate analysis

Quantitative variables are presented as mean±SD .

Qualitative variables were compared by Chi-square test. Correlation between quantitative variables was calculated by *P*-value and <0.05 was considered statistically significant.

Data analysis was done using SPSS 16.0 version.

OBSERVATIONS:

One hundred and forty two children with T1DM were enrolled into the study.

- 23 (**16%**) of the diabetic children had overt hypothyroidism.
- 12 (**8%**) children with T1DM had subclinical hypothyroidism.

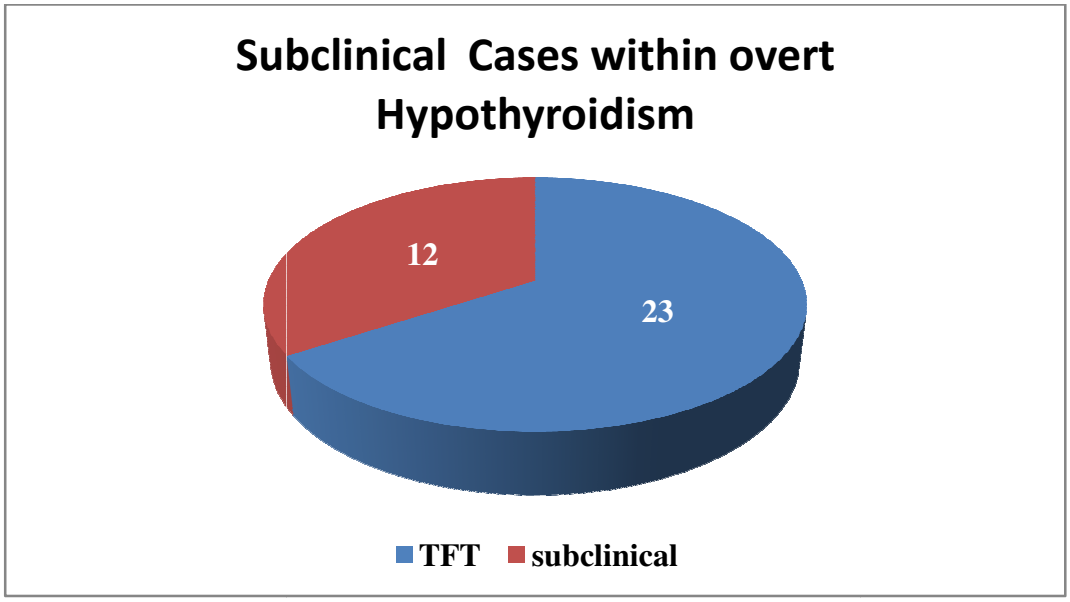


Fig 1

- Subclinical hyperthyroidism and overt hyperthyroid disease was not detected in any case with T1DM .
- Among the diabetic children 30 (**21%)** were found positive for Anti-TPO antibodies and 21(**14%**) were positive for Anti Tg antibodies. 19 (**13%**) children were found positive for both anti-TPO and anti-Tg antibodies.

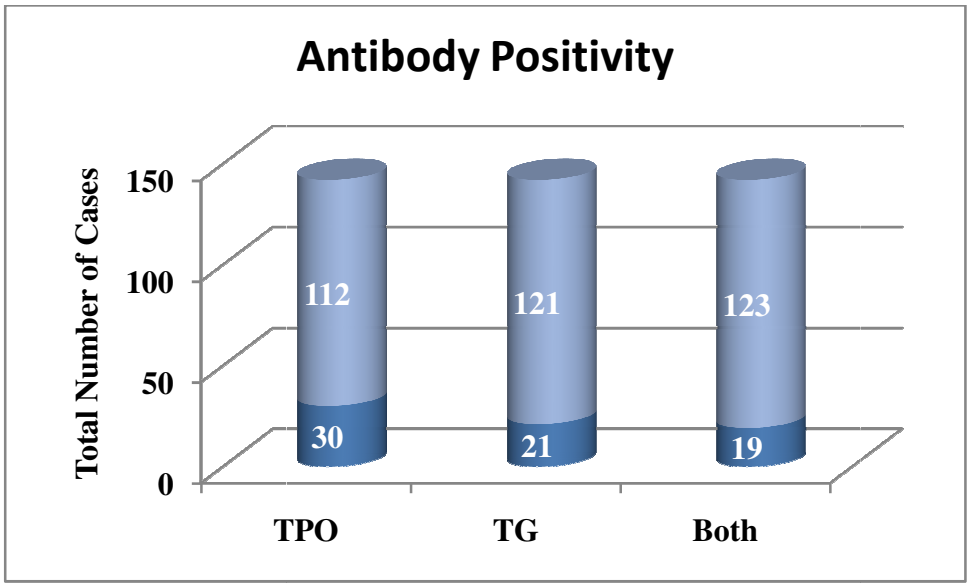

Antibody Positivity
Total Number of Cases
150
100
50
0
112
30
121
21
123
19
TPO
TG
Both

Fig 2:

- The overall prevalence of AIT based on the positivity of any one of these antibodies in diabetic children was 32 (**22.5%**) .
- Diabetic children with AIT had higher prevalence of thyroid dysfunction 23 (**16%**). Association of autoimmnune antibodies and hypothyroidism was significant (p- 0.002).
- Among the children with overt hypothyroidism 17 (73%) were positive for TPO antibodies, 12 (52%) were positive for TG antibodies and 11(47%) for both of these antibodies.

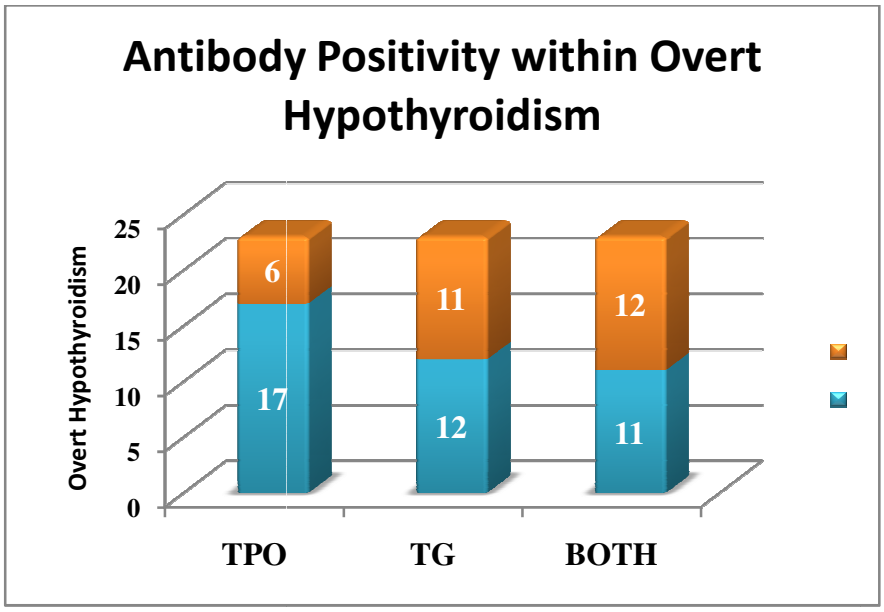

Antibody Positivity within Overt Hypothyroidism
Overt Hypothyroidism
25
20
15
10
5
0
6
17
11
12
12
11
TPO
TG
BOTH

Fig 3:

- 5 (**3.5%**) children had lab evidence of hypothyroidism but negative for antibodies.
- 12 (**8.4%**) children were positive for antibodies but no lab evidence for hypothyroidism.
- None had the clinical features of hypothyroidism.

In these TIDM children with presence of any of these antibodies (anti-TPO and anti-Tg) correlation was done with sex, duration of diabetes, age at onset of hypothyroidism, lipid profile including cholesterol and triglycerides, glycemic control using HbA1C, presence of thyroid enlargement, presence of thyroid echogenecity on USG, and subclinical hypothyroidism. BMI was compared in these individuals with and without AIT.

- In 2 of these 32 children (**6.2%**) were positive for AIT at the onset of diabetes.
- Anti-TPO antibodies were found positive at **3.01 ± 3.5** years after the onset of diabetes. Anti-Tg were positive **3.5 ± 2.5** years after the onset of diabetes. Both anti-TPO and anti-Tg were found positive **3.6 ± 2.5** years after the onset of diabetes.
- The mean ± SD age at onset of hypothyroidism with positive TPO antibodies was **6.97 ± 3.53** years , with Tg antibodies it

was **6.64 ± 3.4** . The mean ± SD BMI of the children without AIT was **15.8 ± 1.5** while the mean BMI in children with AIT was **18.5 ± 2.6**.

- The prevalence of goiter in the study group with positive TPO antibodies was 16 (**94%**), with TG antibodies it was 13(**76.5%**) and it was 12 (**70.6%**) when positive for both antibodies.

Multivariate logistic regression analysis was done to correlate age at onset of hypothyroidism, gender, duration of diabetes, against AIT. The effect of AIT on the glycemic control, lipid abnormality, BMI were analysed. In children with AIT, the presence of thyroid enlargement and sonographic evidence of AIT were also analysed. (Table 1,2,3,4,5)

Table 1: Univariate analysis showing comparision of factors with TPO positivity

			n=30		
CHARCTERISTICS	N	POSITIVITY	%	P-VALUE	RESULT
SEX					
Male	52	3	5.8		
Female	90	27	30.0	**0.002**	Sig
HYPOGLYCEMIC EPISODE					
No episode	100	23	23.0		
1 or more	42	7	16.7	0.399	NS
CHOLESTROL					
Normal	119	18	15.1		
Abnormal	23	12	52.2	**0.003**	Sig-f
TRIGLYCERIDES					
Normal	120	20	16.7		
Abnormal	22	10	45.5	**0.002**	Sig-f
BOTH					

Normal	128	22	17.2		
Abnormal	14	8	57.1	**0.002**	Sig-f
HbA1C					
Fair	101	17	17.0		
Poor	41	13	31.7	**0.049**	Sig
GOITRE					
Present	17	16	94.1		
Absent	125	14	11.2	**0.001**	Sig-f
USG-AIT					
Present	18	17	94.4		
Absent	124	13	10.5	**0.001**	Sig-f
SUBCLINICAL HYPOTHYROIDISM					
Absent	133	26	19.5		
Present	9	4	44.4	0.077	NS

CHARCTERISTICS	n	POSITIVITY	P-VALUE	RESULT
		MEAN(S.D)		
BMI	30	15.7(1.5)	0.252	NS
DURATION	30	3.01(2.48)	**0.001**	Sig
BMI1	30	18.55(2.64)	0.465	NS

$P < 0.05$, statistically significant- chi square test, f-fischer test

Table 2: Univariate analysis showing comparision of factors with TG positivity

CHARCTERISTICS		POSITIVITY	%	P VALUE	RESULT
SEX					
Male	52	1	1.9	**0.001**	Sig
Female	90	20	22.2		
HYPOGLYCEMIC EPISODE					
No episode	100	15	15.0		
1 or more	42	6	14.3	0.913	NS
CHOLESTROL					
Normal	119	13	10.9	**0.007**	Sig-f
Abnormal	23	8	34.8		

TRIGLYCERIDES					
Normal	120	13	10.8	**0.005**	Sig-f
Abnormal	22	8	36.4		
BOTH					
Normal	128	14	10.9	**0.001**	Sig-f
Abnormal	14	7	50.0		
HbA1C					
Normal	101	12	11.9	0.126	NS
Abnormal	41	9	22.0		
GOITRE					
Present	17	13	76.5	**0.002**	Sig-f
Absent	125	8	6.4		

USG-AIT					
Present	18	14	77.8	**0.023**	Sig-f
Absent	124	7	5.6		
SUBCLINICAL HYPOTHYROIDISM					
Absent	133	19	14.3	0.622	NS
Present	9	2	22.2		

CHARCTERISTICS	n	POSITIVITY	P Value	RESULT
		MEAN(S.D)		
BMI	21	15.8(1.5)	0.594	NS
DURATION	21	3.5(2.4)	**0.004**	Sig
BMI1	21	18.7(2.5)	0.304	NS

$P < 0.05$, statistically significant- chi square test, f-fischer test

Table 3: Univariate analysis showing comparision of factors with Both TPO and TG positivity

TPO and TG

CHARCTERISTICS		POSITIVITY	%	P value	RESULT
SEX					
Male	52	1	1.9	**0.002**	Sig
Female	90	18	20.0		
HYPOGLYCEMIC EPISODE					
No episode	100	14	15.0		
1 or more	42	5	14.3	0.913	NS
CHOLESTEROL					
Normal	119	12	10.1	**0.009**	Sig-f
Abnormal	23	7	30.4		
TRIGLY					
Normal	120	12	10.0	**0.006**	Sig-f
Abnormal	22	7	31.8		
BOTH					
Normal	128	13	10.2	**0.001**	Sig-f
Abnormal	14	6	42.9		

HbA1C					
Nor	101	10	9.9		NS
Abn	41	9	22.0	0.056	
GOITRE					
Present	17	12	70.6	**0.021**	Sig-f
Absent	125	7	5.6		
USG-NECK					
Present	18	13	72.2	**0.003**	Sig-f
Absent	124	6	4.8		
SUBCLINICAL HYPOTHYROIDISM					
Absent	133	18	13.5	0.836	NS
Present	9	1	11.1		

CHARCTERISTICS	N	POSITIVITY	P value	RESULT
		Mean(S.D)		
BMI	19	15.8(1.5)	0.617	NS
DURATION	19	3.6(2.5)	**0.002**	Sig
BMI1	19	18.8(2.5)	0.25	NS

$P < 0.05$, statistically significant- chi square test, f-fischer test

Logistic regression analysis to estimate the risk factors associated with autoantibody positivity in T1DM children

Table 4: TPO positivity

		P value	OR	95% C. I
1.	Sex	0.299	0.104	0.029 – 0.376
2.	Cholesterol	**0.057**	7.827	0.940 – 65.197
3.	Triglycerides	0.553	0.361	0.012 – 10.488
4.	Both	**0.023**	6.003	3.454 – 8.491
5.	HbA1C	0.482	2.225	0.239 – 20.670
6.	Goitre	**0.003**	4.044	2.001-5.992
7.	USG	**0.003**	5.84	4.802 – 5.920

$P < 0.05$, statistically significant- chi square test,

OR- odds ratio, CI- confidence interval

Table 5: Tg positivity

		P value	OR	95% C. I
1.	Sex	0.154	8.432	0.449 – 158.38
2.	Cholesterol	0.499	2.356	0.197 – 28.259
3.	Triglycerides	0.520	0.244	0.003-17.941
4.	Both	0.884	0.682	0.002 – 1.043
5.	HbA1C	0.354	1.234	0.008 – 1.432
6.	Goitre	**0.002**	4.470	3.04- 6.558
7.	USG	**0.002**	5.168	4.056 – 6.091

$P < 0.05$, statistically significant- chi square test,

OR- odds ratio, CI- confidence interval

- In children with TPO positivity nearly 27(90%) were females and 3(10%) were males. Among the Tg positive children 20(95%) were females and 1(5%) were males. When both antibodies are positive 18(94.7%) were seen in females and 1(5.3) were seen in males. Thus overall there was a female preponderance among antibody positive T1DM children. Both univariate and multivariate analysis showed statistical significance between thyroid antibody positivity and female gender. (Table 1,2,3,4,5).

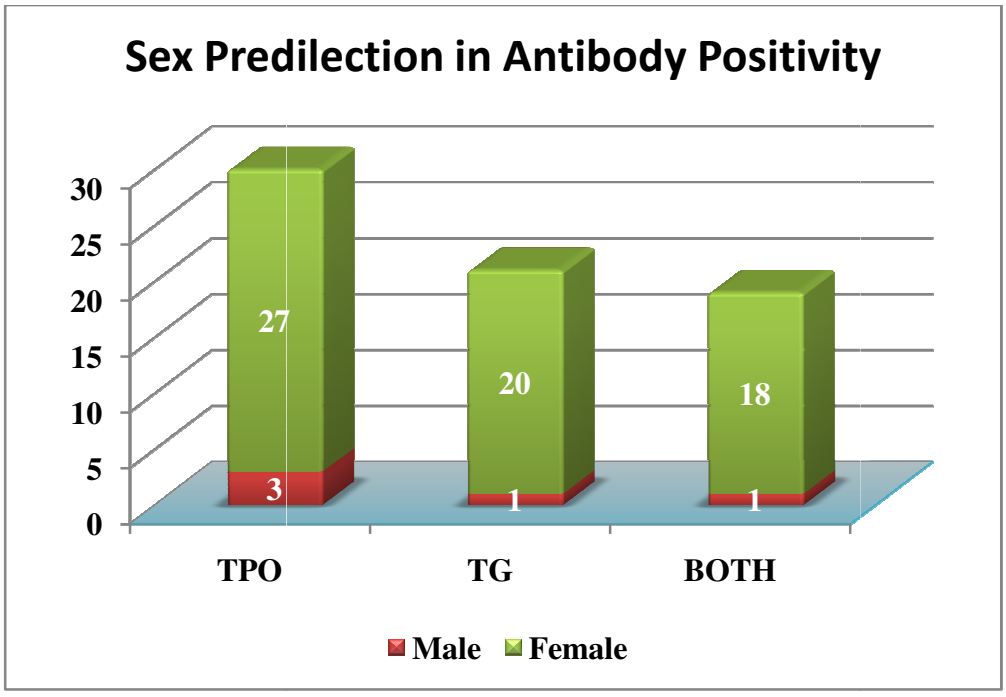


Fig 4:

- In children with positive TPO antibodies,16 (53.3%) developed thyroid enlargement (goitre) (P= 0.001, OR 1.004 , 95% CI 0.001 – 1.992) and 17 (56.7%) children showed diffuse hypoechogenicity on ultrasonography (P=0.002, OR 2.84 , 95% CI 2.01-3.774). In children with positive TG antibodies 13 (53.3%) showed thyroid enlargement (goitre) (P= 0.001, OR 1.004 , 95% CI 3.04-6.558) and 17 (56.7%) children had sonographic evidence of AIT.(P=0.002, OR 5.168 , 95% CI 3.24-5.78). In children with both antibodies positive, goiter was seen in 12(63.2%, p=0.003) children and sonographic evidence of AIT was seen in 13 children(68.4%)

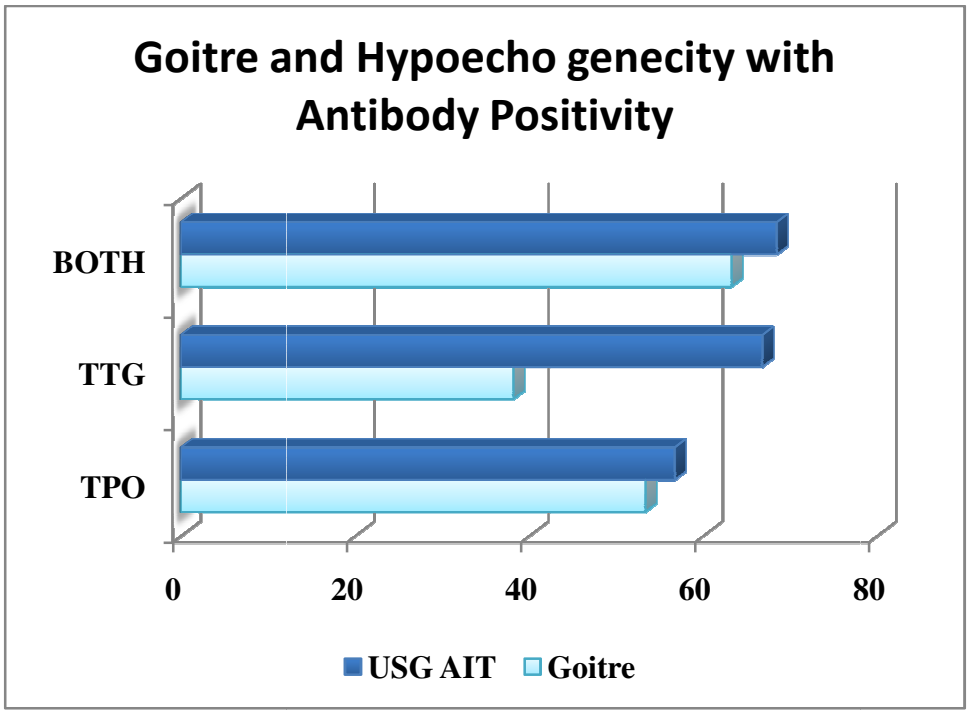


Fig 5:

- In patients with positive TPO antibodies only 4 (13.3%) had subclinical hypothyroidism. (p= 0.077). In children with positive Tg antibodies only 2 (9.5%) had subclinical hypothyroidism. (p=0.622). In children with both antibodies positive only 1(5.3%) had subclinical hypothyroidism.

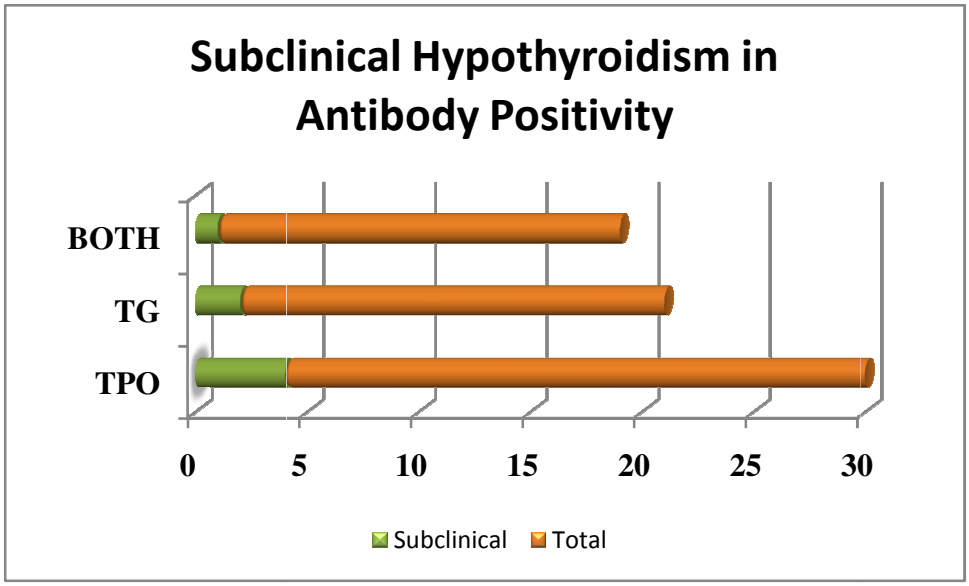


Fig 6

- Hypercholesterolemia was seen in 12(40%) children with positive TPO antibodies(p=0.002) while it was 8(38.1%) with positive Tg antibodies(p=0.007) and 7 (30.4%) in children with both antibodies positive(p=0.009). Hypertriglyceridemia was seen in 10(33.3%) children with positive TPO antibodies(p=0.001) while it was 8(36.4%) with positive Tg antibodies(p=0.005) and 7 (36.8%) in children with both antibodies positive(p=0.001). Both hypercholesterolemia and hypertriglyceridemia was seen in 8(26.7%) children with positive TPO antibodies (p=0.002) while it is 7(33.3%) with positive Tg antibodies (p=0.001) and 6 (31.6%)in children with both antibodies positive(p=0.001).

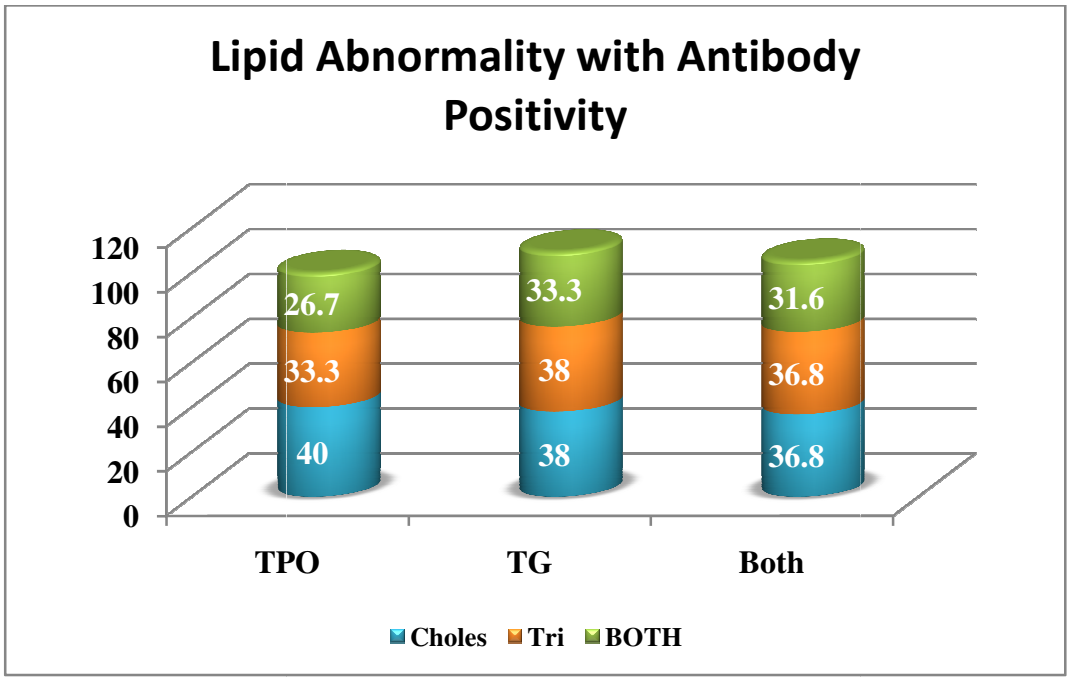

Lipid Abnormality with Antibody Positivity
120
100
80
60
40
20
0
26.7
33.3
40
33.3
38
38
31.6
36.8
36.8
TPO
TG
Both
Choles
Tri
BOTH

Fig 7:

- Poor glycemic control with positive TPO antibodies was seen in 13(43.3%, p=0.049) while with positive Tg antibodies it was seen in 9(42.9%, p=0.126). In children with both antibodies positive poor glycemic control was seen in 9(47.4%, p=0.056).

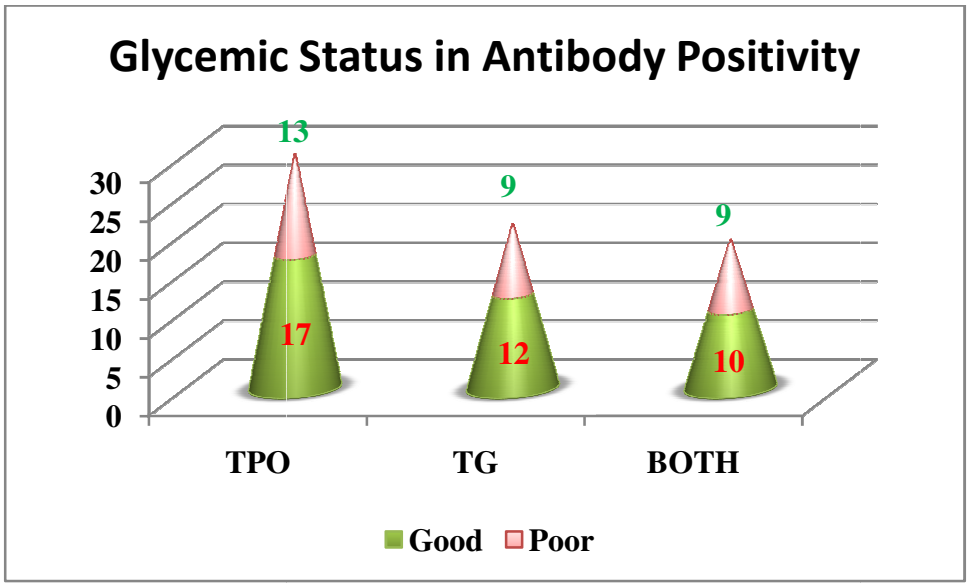


Fig 8:

- In children with positive TPO antibodies, 7(26.3%) had hypoglycemic episodes (p=0.399) while with positive TTG antibodies 6(28.6%) had hypoglycemic episodes (p=0.913). In children with both antibodies positive 5(26.3%) had hypoglycemic episode (p=0.913).

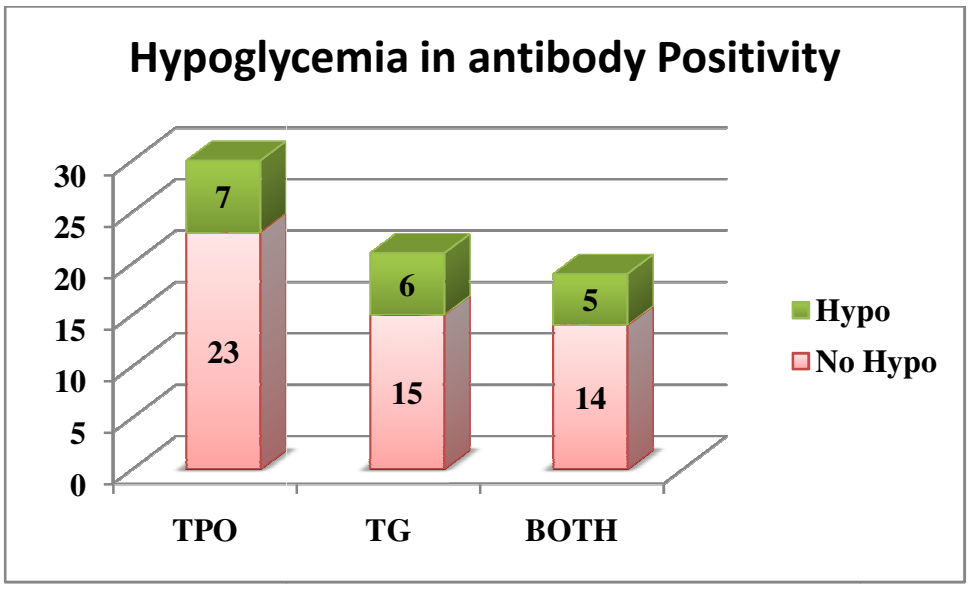


Fig 9:

- BMI of the children with AIT positive children was compared with BMI in children without AIT. Statistical significance was not observed for AIT and BMI.(table 1,2,3,4,5)

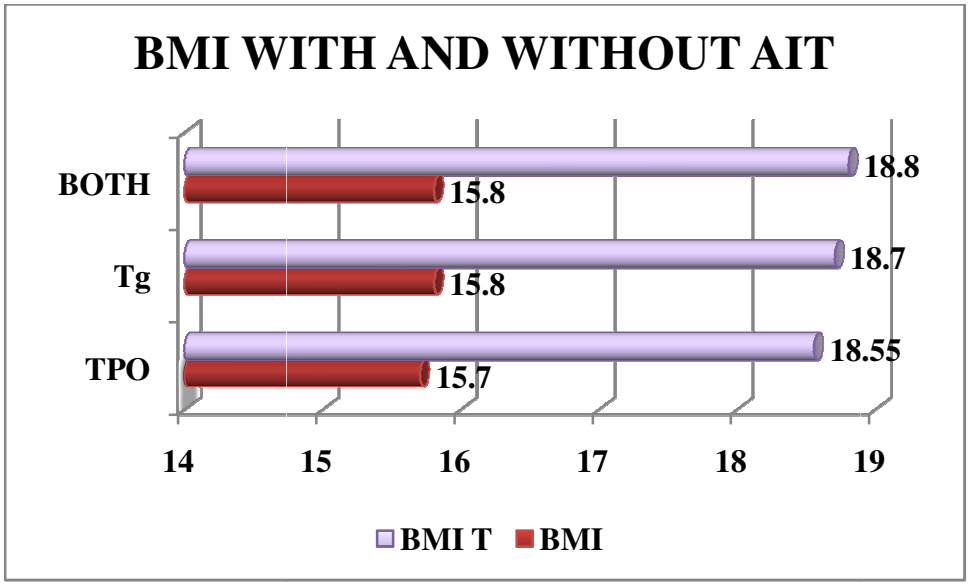


Fig 10:

DISCUSSION

The present study showed that children with T1DM had high levels of both anti-TPO and anti-Tg antibodies. AIT is the most prevalent autoimmune disorders associated with T1DM[20,35]. The reason for the high prevalence of some autoimmune disorders in these patients still remains undetermined. It may be due to a increased tendency to act against specific antigens, or loss of self recognition particularly when there is genetic or environmental trigger.[36].

According to some studies, HLA[30,31] or some genetic component outside the HLA (i.e., CTLA4 and PTPN22) might be a reason [37,38] in the occurrence of AIT in T1DM patients. Moreover, environmental triggers such as any stressful event, infection, trauma may also play a role. Both T1DM and AIT are diseases which occurs as a result of autoimmunity mediated through T-cell pathway. [39].

In the present study, the prevalence of positivity for anti-TPO Antibody, anti-Tg antibody, and the prevalence of positivity for both antibodies and AIT (at least one positive antibody) in children with T1DM were 21%, 14%,13% and 22.5% respectively (Fig 2). In other

studies, the prevalence of positive anti-TPO antibody in T1DM patients was reported to be 5.5-46.2% and that of anti-Tg antibody ranged from 2.1 to 40%. Thus like in previous studies TPO antibody has higher positivity.The wide range of these data can be explained by the difference in genetic factors, age, and sex of the studied population,[40] as well as the different methods of measurement of antibodies.[8]

Most studies that have reported low prevalence of AIT were conducted 10-20 years ago,which shows the low sensitivity of the lab tests. Meanwhile, this finding might also be a result of increase in the prevalence of AIT during the recent decades[8] along with increasing TIDM cases. Epidemiologic studies have shown higher incidence of AIT after elimination of iodine deficiency in endemic areas.[39] The lower prevalence of AIT in our study could be explained by the different age group of studied individuals in our study. However, the present study was conducted on children and showed comparable results with other studies performed in similar age group. Age dependent increase of AIT incidence has been described previously.[42]

From previous studies the prevalence of clinical and subclinical thyroid dysfunction in T1DM patients is suggested to be 13.4-20% [40] whilst the prevalence of hypothyroidism and hyper-thyroidism in the normal population is 5-10% and 1%,respectively.[7]

A significant percentage of them were found to have AIT very early after the onset of diabetes. In the present study, there was no case of clinical thyroid dysfunction. However, there was lab evidence of hypothyroidism and also thyroid enlargement were seen in those cases which has overt or antibody positive hypothyroidism (Fig 3,5). Subclinical hypothyroidism was present in 8% (Fig 1). In our study, the prevalence of subclinical hyperthyroidism in T1DM patients was 0%, which is consistent with the findings of previous studies.[3]

We found that diabetic patients with AIT had higher prevalence of thyroid hormones, which was statistically significant.(Fig 3). Therefore, the higher prevalence of subclinical hypothyroidism in T1DM patients could be explained by the high prevalence of AIT (22.5%) in these patients.

Unfortunately, iodine status of the studied population was not evaluated and as a result, we could not investigate the role of iodine deficiency in the high prevalence of subclinical hypothyroidism. In the present study, the prevalence of goiter in T1DM was 11.2 % . The lower prevalence of goiter in T1DM patients is in contrast with previous studies,which showed increase in goiter prevalence in T1DM patients.[43-45]. However in our study there is higher prevalence of goiter in T1DM patients with AIT(94%) (Fig 5) which is statistically significant. Urine iodine concentration in T1DM patients was previously reported to be high (46). Goiter was made by inspection and palpation. All the cases clinically suspected to have goiter were confirmed by thyroid ultrasonography.

In our study, the prevalence of AIT in female patients with T1DM was higher than that in male T1DM patients which is consistent with many studies with higher prevalence of positive thyroid autoantibodies in females[47] though some studies reported similar prevalence in both genders. [48,49] In T1DM children with AIT, oestrogen were found to increase the risk of autoimmunity by acting through the T cell pathway, while androgens usually protects against this.[56]

In our study, the prevalence of AIT is increased with age and duration of diabetes. These observations in our study are similar to previous studies[11,54]. This has lead to the suggestion that autoimmunity is the end result which started with self recognition, then passes through immunity followed by appearance of antibodies finally leading to autoimmune disease.[56] In our study, in children with AIT, duration of diabetes was found to have statistical significance in the univariate analysis. As the duration increases the prevalence of AIT increases. Thus strongly reinforces that along with initial screening, these children with AIT should have a long term follow up.

In contrast to previous studies[5], in the current study, we found a relationship between HbA1c, a measure of metabolic control in diabetic patients, and AIT or thyroid dysfunction. In TPO positive children there was a statistical significance, while in Tg and both antibody positivity there was no statistical significance. (Tab 1,2,3; Fig 8). This clearly points out that children with AIT might have fluctuating glycemic control and diabetic management can be made difficult. Another explanation that can be given for no statistical significance is that cut off of 10 was taken as to be having poor control. But ideally < 6 is normal and for good control it should be

atleast 6-8. It is well known fact that T1DM children with AIT are prone to have poor glycemic control.

In TIDM children with AIT, there is significant elevation in lipid parameters including both cholesterol and triglycerides.(Fig 7; Tab 1-5) which is in consistent with previous studies. Here there is a statistical significance for both cholesterol and triglycerides when compared for both the antibodies which is an extremely important finding. As such the long term morbidity is increased, hence these should be looked into while managing these children. Also we have found a significant elevation in a very early age. Hence they should be regularly followed up to avoid other cardiovascular complications.

Though the hypoglycemic episodes did not have statistical significance in our study (Tab 1-5, Fig 9) it is an important complication known to occur in diabetic children with hypothyroidism. Again here hypoglycemic episodes were taken as significant when there is documented low sugar along with other manifestations like palpitations, sweating or seizures. It is a known fact these children are more prone for hypoglycemia. Hence proper counseling need to be given regarding recognition of symptoms.

Another important observation of our study was that the influence of AIT on BMI, showed no statistical significance like in other studies.[11,29]. But, Chase et al [28] has observed decreased growth in T1DM children with AIT. But difference was noted in children with and without AIT. (Fig 10) Thyroxine if given early leads to improved growth in these children. This observation has highlighted the significance of the early identification and treatment of AIT in these individuals. Though BMI didn't had statistical significance these children should be followed in long term basis to exactly arrive at a conclusion.

It was also observed that in the presence of both thyroid antibodies, the autoimmune process is more vigorous, causing AIT. Among both the antibodies, TPO were found to be more specific to detect AIT.[11]

COMPARISION OF AIT IN VARIOUS STUDIES:

Ardestani et al	22%
Kostas kokleas et al	Tpo-17.3%, Ttg-11.3%, both 10.4%
Ismael et al	15%
Kordonouri et al	Tpo 15.4%, Ttg 14.4%
Guillermo et al	17.91%
This study	Tpo-21%, Tg-14%, both- 13% 0verall-**22.5%**

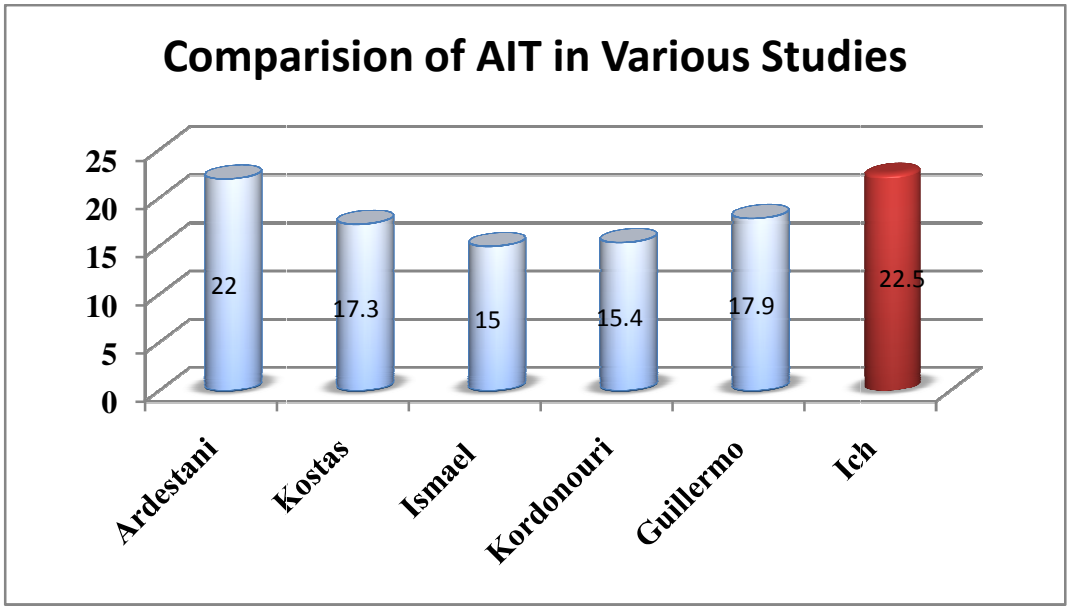
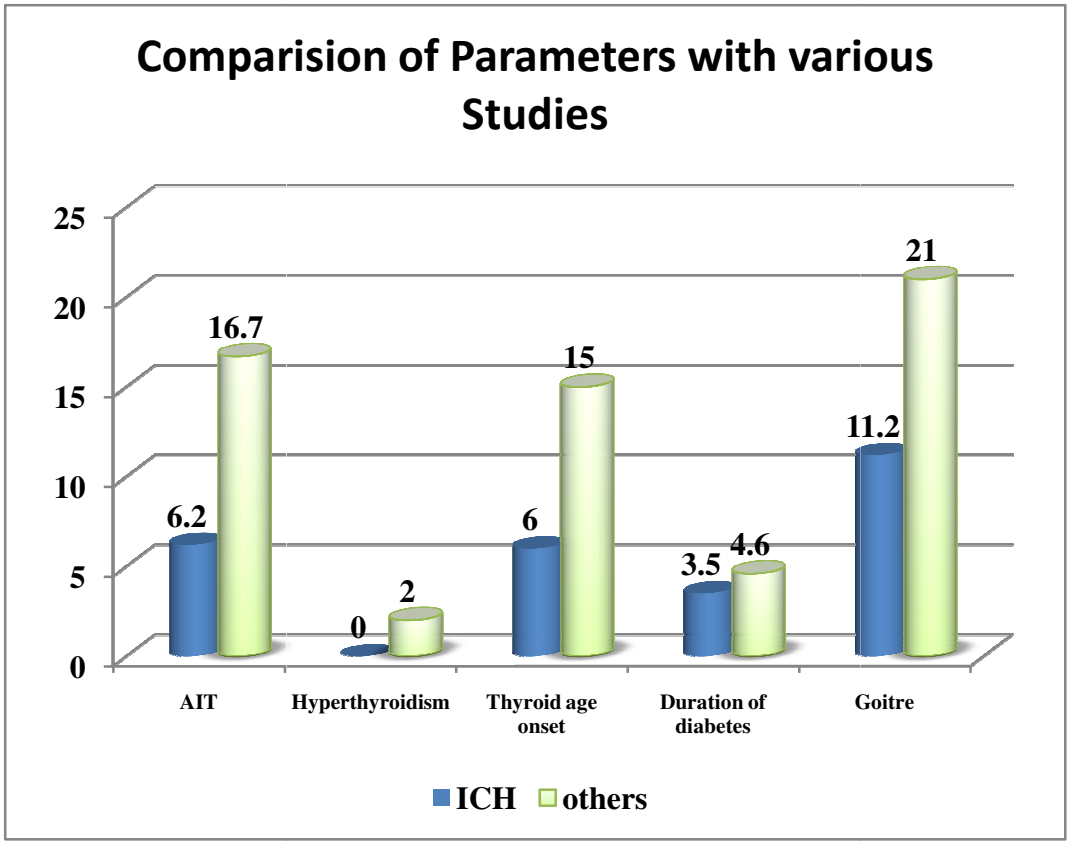

Comparision of AIT in Various Studies
25
20
15
10
5
0
22
17.3
15
15.4
17.9
22.5
Ardestani
Kostas
Ismael
Kordonouri
Guillermo
Ich

Fig : 11

Parameters	**This study**	**Previous studies**
AIT at the diagnosis of diabetes	6.2%	16.7 (Guillermo et al)
Hyperthyroidism	0%	1-2% (Ardestani et al)
Mean age at onset of AIT	6 years	15 years (Pranzy et al)
Mean duration of diabetes	3.5 years	4.6 years (Kostas et al)
Prevalence of goiter	11.2%	21% (Ardestani et al)


Comparision of Parameters with various Studies
25
20
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5
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15
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21
11.2
AIT
Hyperthyroidism
Thyroid age onset
Duration of diabetes
Goitre
ICH
others

CONCLUSION

Hypothyroidism is predominantly autoimmune in T1DM children. Mostly it is asymptomatic. This emphasizes the need for regular thyroid screening in diabetic children. Children with T1DM had higher prevalence of AIT. To conclude, the presence of thyroid antibody positivity was common among our T1DM children. Important among the risk factors for AIT to develop in these children include increasing age , female sex, longer duration of diabetes.

Importantly AIT significantly affects lipid status of the body which increases the long term morbidity in these children. Presence of AIT makes the glycemic control difficult, predisposing these individuals to hypoglycemia. Though AIT has not been found to affect the growth of T1DM children it is extremely important in long term to monitor BMI .

Hence it is recommended that all patients with T1DM should undergo screening for AIT at the time of diagnosis of diabetes and then yearly or atleast 2-3 yearly. If thyroid antibody is positive they should be followed up regularly. Presence of thyroid antibody is not

an indicator to start treatment. Current recommendation is that treatment is decided based on the level of TSH.

Importance of diagnosing AIT lies in the fact that these individuals are more prone to develop thyroid dysfunction and that early diagnosis aids to initiate treatment early. To summarize, the antibodies should be screened in T1DM children to find AIT, but its value to predict the progression of the clinical manifestation is limited. These patients with positive antibodies should be followed up because further deterioration of the thyroid gland may occur.

RECOMMENDATION:

- Screening for thyroid disease in type 1 diabetic children should be initiated at diagnosis.
- Preferably it should be checked annually, or at least every 2-3 years.
- The preferred method of screening is using TSH.
- Other method of screening includes thyroid peroxidase antibody.
- Thyroid antibody positivity alone is not an indication for treatment in these children, but they have a increased risk to develop thyroid dysfunction.

LIMITATIONS OF THE STUDY:

- Iodine status of our diabetic children was not estimated
- Prevalence of AIT in normal children was not assessed and hence could not be compared with our T1DM children.

TIME SCHEDULE

Protocol finalization – July 2011

Study period – August 2011- Oct 2012

Manuscript preparation – November 2012

Manuscript Submission – December 2012

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ABBREVIATIONS

TIDM – Type 1 diabetes mellitus

TPO – Thyroid peroxidase

TG - Thyroglobulin

AIT - Autoimmune thyroiditis

USG - Ultrasonography

BMI - Body Mass Index

INFORMATION SHEET

Place of study: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN, Diabetic OPD

Name of Investigator :

Name of Participant age: sex:

Hospital No: Diabetic No:

Study title : Study on prevalence of thyroid dysfunction in type 1 diabetic children

• We are conducting a study on prevalence of thyroid dysfunction in type 1 diabetic children.

We request you to participate in the study

• The purpose of this study is to study the prevalence of thyroid dysfunction in type 1 diabetic children.

• The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

• Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

• The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

INFORMED CONSENT FORM

Study place: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN, Diabetic OPD

Title of the study: study on the prevalence of thyroid dysfunction in type 1 diabetic children.

Name of the investigator

Name of the Participant: Age: Sex:

Hospital number: Diabetic no:

1. I have read and understood this consent form and the information provided to me regarding the participation in the study.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have informed the investigator of all the treatments I am taking or have taken in the past

including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.*

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer

unusual symptoms. *

8. I have not participated in any research study in the past.

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason

and this will not affect my future treatment in this hospital. *

11. I am also aware that the investigator may terminate my participation in the study at any time, for

any reason, without my consent. *

12. I hereby give permission to the investigators to release the information obtained from me as result

of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I

understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing

this consent form I attest that the information given in this document has been clearly explained to me

and understood by me, I will be given a copy of this consent document. For adult participants:

Name and signature / thumb impression of the participant /parents/guardian

Name _____ Signature_____
Date_____

Name and Signature of impartial witness:

Name _____ Signature_____
Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு:

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

எனது குழந்தைக்கு சர்க்கரை நோய் உள்ளது என்பதால், தைராய்டு பிரச்சனை ஏற்படுவதற்கு வாய்ப்பு அதிகம் உள்ளது என்பதை மருத்துவர் மூலம் அறிவேன். இதனை முன்கூட்டியே அறிந்து கொள்வதற்கு எனது குழந்தையின் இரத்தத்தை எடுத்து பரிசோதனை செய்து கொள்ள எனக்கு பரிபூரண சம்மதம்.

இந்த ஆராய்ச்சியின் விபரங்களும் அதன் நோக்கங்களும் முழுமையாகவும் தெளிவாகவும் எனக்கு விளக்கப்பட்டுள்ளது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன். இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகின்றேன். நான் இந்த ஆராய்ச்சிலிருந்து எந்த நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்

Annexure : Patient data entry form

- Name of the patient:
- Present age:
- Age at onset of diabetes:
- Gender:
- Duration of diabetes:
- Palpation of thyroid gland
- Body mass index
- Biochemical parameters:

  Thyroid profile: T3,T4,TSH

  Thyroid peroxidase antibodies, Thyroglobulin antibodies

- Lipid profile
- No. of hypoglycemic episodes
- HbA_1C
- USG neck

sl no	D. No	age	sex	wt	ht	BMI	onset_age	age_hypo	interval	symptom	duration	severity	FHDM	FHHYP	insulin	wt	ht	BMI	Hypogly	cholesterol	triglycer	both	oth_illness	HbA1C	Menarc	Goitre	usg_neck	TFT	Subclinal Hypo	TPO	TTG	Both Ab'S positive
1	32	0.08	2	8	72	16.3	0.8	0	0	pu	30	mod	0	+	1	24	126	16.7	2	0	0	0	cmv.igm+	6	0	0	0	0	0	0	0	0
2	44	1.5	2	8	78	16.3	1.5	7	6	pu,pd,wl	30	severe	0	0	2	30	116	22.3	7	1	1	1	0	6.7	0	1	1	1	0	1	1	1
3	51	3	2	10	76	17.54	3	5	2	pu	30	mod	0	0	2	20	97	21.2	3	0	1	0	downs	6.3	0	0	0	1	0	0	0	0
4	71		2	15	101	15	4				30		0		1	27	123	18.7	0	0	0	0	0	6	0	0	0	0	0	0	0	0
5	79	3.8	2	14	92	17.2	3.8	0	0	pu,pd,ne	30	mod	0	moth-hyp	1.5	42	144	21.4	4	0	0	0	0	6.8	0	0	0	0	0	0	0	0
6	84	3.5	1	12	87	18.7	3.4	0	0	pu,pd,pp	30	mild	0	0	1.5	29	137	17.2	2	0	0	0	0	7	0	0	0	0	0	0	0	0
7	85	9.75	1	27	132	16	8.9	0	0	pu	30	severe	0	0	0.6	30	123	21.4	4	0	0	0	0	5.9	0	0	0	0	0	0	0	0
8	94	2.	1	10	86	15	3	0	0	pu,pd,pp	30	seve	0	0	1.2	16	94	19	2	0	1	0	0	6.3	0	0	0	0	0	0	0	0

		16				.6				,br		re						.7														
9	98	6	2	18	110	14.8	6	13	7	pu,pd	30	severe	0	0	1.3	35	134	21.8	3	1	1	1	0	6.1	0	1	1	1	0	1	1	1
10	100	6.41	2	17	112	14.2	6.41	10	4	pu,pd,br	30	severe	0	0	1.4	25	112	20.66	3	0	1	0	nephropathy	7	0	1	1	0	0	1	1	1
11	104	1.16	1	10	75	20.4	1.16	0	0	pu,pd	30	non	0	0	1.4	34	134	20.1	3	1	1	1	0	7.5	0	0	0	0	0	0	0	0
12	110	6.58	1	20	110	16.6	6.5	0	0	pupd	30	mild	0	0	1.5	30	132	17.7	5	0	0	0	0	7.3	0	0	0	0	0	0	0	0
13	121	11	2	29	141	15.2	11	0	0	pu,pd,v.i	30	mild	0	0	1.8	36	151	16	5	0	1	0	0	13	0	0	0	0	1	0	0	0
14	133	5.6	1	19	112	15.8	5.6	0	0	pu,pd,fev	30	severe	0	0	1.7	32	136	20	1	1	0	0	0	11	0	0	0	0	0	0	0	0
15	139	2	1	10	84	15.6	2	0	0	pu,pd,wl	30	non	0	0	1.1	20	110	16.6	2	0	0	0	0	10	0	0	0	0	0	0	0	0
16	150	7	1	29	132	18.1	7	0	0	pu,pd	30	severe	0	0	1.1	37	152	16.4	4	1	1	1	0	9.8	0	0	0	0	0	0	0	0
17	153	5	1	16	10	16	5	0	0	pu,pd,ab.	30	mil	0	0	1.3	29	13	17	1	0	0	0	0	8.4	0	0	0	0	0	0	0	0

					5					p		d					2	.1														
18	157	2	2	11	81	17.2	2	0	0	wl,pu,pd,br	30	severe	0	0	24	11	81	17.2	1	0	0	0	0	11.3	0	0	0	0	0	0	0	0
19	162	1.3	2	8.5	76	17.3	1.3	0	0	pu,pd	30	mod	0	0	1	34	134	21.2	5	0	0	0	0	12	0	0	0	0	0	0	0	0
20	167	5.66	1	17	113	14.2	5.6	0	0		30	mild	0	0	0.7	36	136	22.5	0	0	0	0	0	9.8	0	0	0	0	0	0	0	0
21	171	14.5	2	22	120	15.2	6.3	9.5	2.2	pu,pd,leth	30	severe	0	0	1.3	32	140	16.3	3	1	1	1	0	8.4	not attai	1	1	0	1	0	1	0
22	172	6	1	15	112	15	6	0	0	pu,pd,pp	30	severe	0	0	0.5	24	108	21.9	0	0	0	0	0	8.8	0	0	0	0	0	0	0	0
23	175	6.66	2	19.5	115	15	6.6	0	0	pu,pd,leth	30	non	0	0	1	41	150	18.2	0	0	0	0	0	7.7	not attai	0	0	0	0	0	0	0
24	177	7.5	2	17	119	14.2	6.16	0	0	pu,pd	30	mild	0	111	1.5	27		16	0	0	0	0	aque.ste	7.5	0	0	0	0	0	0	0	0
25	179	2.7	2	11	88	17.1	2.7	0	0	pu,pd,wl,vc	30	mod	0	0	0.9	25	128	17.8	0	0	0	0	0	8.6	0	0	0	0	0	0	0	0
26	185	7.0	2	24	116	20	6	0	0		30	severe	0	0	1			21	0	1	0	0	0	9	0	0	0	0	1	0	0	0

		8																													
27	187	7	2	19	111	15.7	7			pu,pd,a.p,loc	30	severe	0	0	1			18.4	0	0	0	0	0	7.3	0	0	0	0	0	0	0	0
28	189	4.6	2			16.5	4.6	0	0		30		0	0	1.6			19.3	0	0	0	0	0	8	not attai	0	0	0	0	0	1	0
29	198	14	2	20	125	14	5.7	0	0	pu,pd,pp,leth	30	non	0	0	0.8	40	138	23.6	0	0	0	0	neph	8.9	0	0	0	0	0	0	0	0
30	201	6.75	2	17	117.5	14	6.75	0	0	pu,pd	30	non	0	0	2	27	144	14.2	0	0	0	0	EHPVO	8.6	0	0	0	0	0	0	0	0
31	202	3.6	1	18	118	15	3	0	0	pu,pd,wl	30	mod	0	0	1.2	33	120	23.5	0	0	0	0	0	9.8	0	0	0	0	0	0	0	0
32	203	7.75	2	21	116	17.5	7	0	0	pu,pd,pp,wl	30	non	0	0	1.4	40	150	17.7	2	0	0	0	0	11.7	0	0	0	0	0	0	0	0
33	206	8.5	2	20	108	17.2	5.4	0	0	pupd	30	non	0	0	1.2	41	142	20.9	0	0	0	0	0	13.7	0	0	0	0	0	0	0	0
34	209	3.8	2	12	95	15.1	3.8	0	0	pu,pd	30	mod	0	0	1.6	23	123	16.4	0	0	0	0	0	11.27	not attai	0	0	0	0	1	1	1
35	216	0.7	2	6	67	16.	0.75	2.75	2	fev,pu	30	mod	0	0	1.2	14	79	22.	1	1	1	1	0	9	0	1	1	1	0	1	0	0

		5				7												5													
36	233	6.4	2	20	104	18.5	6.4	13	7	pu,pd	30	mild	0	0	1.2	34	129	23.6	0	1	1	1	0	12.5	not attai	1	1	1	0	1	1	1
37	240	5	1	18	102	17.3	5	0	0	pu,pd,pp,ne	30	mild	0	0	1.7	24	125	16.6	0	0	0	0	0	8.4	0	0	0	0	0	0	0	0
38	245	10	2	25	131	14.7	10	0	0	ap,pu,vo	30	severe	0	0	70	45	144	22.9	0	0	0	0	0	12.5	0	1	1	0	0	1	0	0
39	247	11	1	23	120	16	9	0	0	pu,pd,fev	30	severe	0	0	1.6	32	142	16.3	2	0	0	0	0	9.7	0	0	0	0	0	0	0	0
40	249	7	1	19	115	15.8	7	0	0	pu,pd,pp,vo	30	mod	0	0	1.4			17.4	0	0	0	0	0	8.3	0	0	0	0	0	0	0	0
41	254	6.9	2	20	110	16.6	6.9	0	0	pu,pp,a.p,brea	30	severe	0	0	0.7	29	130	17.1	0	0	0	0	0	7.9	not attai	0	0	0	0	1	1	1
42	258	6.75	2	19	106	16.9	6.75	11	4	low,itce.g	30	non	0	0	1	29	127	20.1	3	0	0	0	0	8.5	0	1	1	1	0	1	1	1
43	259	8.6	2	23	127	15.9	8.6	0	0	pu,pd,wl	30	severe	0	0	1	35	154	15.5	0	0	0	0	0	11.6	0	0	0	0	0	0	0	0
44	263	1.6	2	9	82	14	1.6	0	0	pu,fev,cou	30	severe	0	0	0.8	24	120	16.7	0	0	0	0	0	7.3	0	0	0	0	0	0	0	0

45	266	7.8	2	27	133	15.9	7.8	0	0	pu,pd	30	severe	0	0	1.6	52	155	23.1	0	0	0	0	0	11.2	0	1	1	0	0	1	1	1
46	267	14	2	34	136	20.1	6				30	non	0	0	1.4			22.7	1	1	0	0	0	10.2	0	0	0	0	0	0	0	0
47	271	8.7	2	21	120	14.5	8.7	0	0	pu,pd,fati	30	non	0	0	2.3	41	140	20.9	3	0	0	0	0	11.9	0	0	0	0	0	0	0	0
48	272	6	1	24	121	16.7	5	0	0	pu,pd,pp,a.p	30	mod	0	0	0.8	34	137	20.1	0	0	0	0	0	11.6	0	0	0	0	0	0	0	0
49	273	7	1	18	105	16.4	7	0	0	pu,pd,a.p	30	severe	0	0	1.7	24	124	16.7	10	1	0	0	addison	7	0	0	0	0	0	1	0	0
50	274	10	2	22	122	15.3	9	0	0	pu,pd	30	non	0	0	1.5	43	150	19.1	3	1	1	1	0	11.3	0	0	0	0	0	0	0	0
51	276	4.25	1	13.5	99	16.7					30		0		1.8			19.7	2	0	0	0	nephro	13.9	0	0	0	0	0	0	0	0
52	277	1.25	2	12	79	19.3	222			pu,pd,leth,br	30	severe	0	0	1.6	21	107	18.4	0	0	0	0	0	10.7	0	0	0	0	0	1	1	1
53	287	8.16	2	24	120	16.7	8.16	0	0	pu,pd,pp,wl	30	non	0	0	1			18.9	0	0	0	0	0	8.9	0	0	0	0	0	0	0	0
5	289	6	1	1	1	1	2.8	0	0	pu,p	30	se	0	m	1.	2	1	1	4	0	0	0	0	6.	0	0	0	0	0	0	0	0

4		.16		8	08	5.9				d,pp		vere		other	1	1	16	7.5						1							
55	290	2.8	2	13.5	92	16.6	2.8	0	0	pu,pd,pp	30	mild	0	0	1.1	17	97	18.1	0	0	0	0	0	11.8	0	0	0	0	0	0	0
56	292	6	1	16	88	25	6	0	0	pu,pp,loc	30	severe	0	0	0.9	28	128	19.4	0	0	0	0	0	10.5	0	0	0	0	0	0	0
57	294	7.41	2	20	120	13.8	7.4	0	0	pu,pd,br,a.p	30	severe	0	0	1.2	36	139	21.3	3	1	0	0	0	10.8	0	0	0	0	0	0	0
58	297	4.3	2	14	94	15.9	4.3	0	0	fev,pu,pd,a.p	30	mild	0	0	1.6	18	111	14.8	0	0	1	0	nephro	13.6	0	0	0	0	1	1	0	0
59	298	11	2	24	132	14.2	11	0	0	pu,pd,oralthr	30	severe	0	0	1.6	30	139	17.7	4	0	0	0	0	9.8	not attai	0	0	0	0	0	0	0
60	301	3.16	1	13.5	94	16.6	3.16	0	0	pu,pd,pp,leth	30	mild	0	0	0.8	20	110	16.5	0	0	0	0	0	9.7	0	0	0	0	0	0	0	0
61	303	7.6	1	18.5	118	15.2	7.6	0	0	pu,pp,pd	30	mild	0	0	1.1	27	138	15.9	0	0	0	0	0	9	0	0	0	0	0	0	0	0
62	304	11	1	26	139	15.3	11	0	0	pu,pd,noca.p	30	severe	0	0	0.8	28	142	14.2	2	0	0	0	0	8.9	0	0	0	0	0	0	0	0
63	305	4.	2	14	90	17	4.3	0	0	pp,pd,pu	30	non	0	0	0.6	14	82	21	0	0	0	0	0	10.	0	0	0	0	0	0	0	0

		3				.2												.8						3								
64	307	10	1	23	120	15.9	10	0	0	pp,pu,br	30	mod	0	0	1.8	39	148	19.8	1	0	0	0	0	11.8	0	0	0	0	0	0	0	0
65	312	11	2	23	136	13.6	11	0	0	pp,pu,pd	30	non	0	0	1.7	40	147	20.4	0	1	0	0	0	9.3	0	0	0	0	0	1	0	0
66	313	10	1	32.5	139	19.23	10	0	0	fev,leth,br	30	sev	0	0	0.9	32	139	19	2	0	0	0	0	7.3	0	0	0	0	0	0	0	0
67	316	5	2	15	91	18.75	5	0	0	pu,pd,leth	30	mild	0	0	1.9	15	91	18.7	0	0	0	0	0	7.8	0	0	0	0	0	0	0	0
68	318	8	2	19	124	13.2	8	0	0	pu,pd,w.l	30	non	0	other	1.5	35	147	17.8	0	1	1	1	0	7.6	0	0	0	0	0	1	0	0
69	319	10	2			18	8			pu,br	30		0	0	1			18.5	0	0	0	0	0	14	0	0	0	0	0	0	0	0
70	320	4	2	16	100	16	4	0	0	pp,pu,pd	30	mild	0	0	1.4	24	121	19.8	0	0	0	0	0	7.4	0	0	0	0	0	0	0	0
71	323	7	1	17	115	14	7	0	0	pu,pd,a.p	30	severe	0	0	0.8	30	132	17.7	0	0	0	0	0	10.2	0	0	0	0	0	0	0	0
7	324	1	1	2	1	1	11		sa	pu,p	30	se	0	0	1	3	1	1	0	0	0	0	0	1	0	1	1	0	0	1	1	1

2		1		6	33	5.3			meti me	p,pd ,leth		vere				6	45	8.9						2.6								
73	325	7.4	2	13		16.5	7.4	0	0	pp,pu,pd	30	non	0	0	1.5	20	113	16.5	0	0	0	0	0	8.4	0	0	0	0	0	0	0	0
74	327	10.2	1	30	131	17.7	10.2	0	0	w.l, pu,pd	30	non	0	0	0.7	52	146	26.5	0	0	0	0	0	9.5	0	0	0	0	0	0	0	0
75	330	7.5	2	20	117	16.5	2	0	0	pu pd	30	seve re	0	0	1			17.3	0	0	0	0	0	8.3	0	0	0	0	0	0	0	0
76	328	5.5	1	15	102	15	5.5	0	0	pu,pd	30	mild	0	0	1.3	23	120	15.9	5	0	0	0	cp	9.1	0	0	0	0	0	0	0	0
77	334	8.75	1	30	134	17.7	8.75	0	0	tir,w .l,pu ,pd	30	non	0	0	0.7	39	153	17.3	0	0	0	0	0	7.7	0	0	0	0	0	0	0	0
78	339	7.3	2	17	116	14	7.3	0	0	pu,pd,ne, itc	30	mild	0	0	1.2	22	131	13	0	0	0	0	0	8.6	0	0	0	0	0	0	0	0
79	340	3.8	1	11	93	13.5	3.8	0	0	pu,pd	30	non	0	0	1.1	20	114	16.5	0	0	0	0	0	8.4	0	0	0	0	0	0	0	0
80	341	8.8	2	25	130	14.7	8.8	0	0	pu,pd,,ne ,w.l, le	30	non	0	0	0.8	25	130	14.7	0	0	0	0	0	6.7	0	0	0	0	1	0	0	0
81	342	3.9	1	26	131	15.	3.9	0	0	pu,pp,pd ,v,br	30	seve re	0	0	1.2	22	116	18.	0	0	0	0	0	7.4	0	0	0	0	0	0	0	0

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82	346	9.6	1	25	130	14.7	9.6	0	0	pp,pu,pd,w.l	30	non	0	0	0.7	24	130	14.2	1	0	0	0	0	6.5	0	0	0	0	0	0	0	0
83	348	5.5	2	18	107	18	5.5	0	0	pu, pd	30	severe	0	0	1.1	30	129	20.8	0	0	0	0	0	8.9	0	0	0	0	0	0	0	0
84	350	12	2	23	125	15.9	8.2	0	0	pu pd wl	30	non	0	0	1.1	36	137	21.3	0	0	0	0	0	7.5	0	0	0	0	0	1	1	1
85	352	10.5	1			16	8	0	0	pu pd	30	non	0	0	2			16.8	0	0	0	0	0	9.4	0	0	0	0	0	0	0	0
86	353	10	2			19	6	0			30	severe	0	0	1.4			18.7	0	0	0	0	0	8	0	0	0	0	0	0	0	0
87	354	8.16	2	20	125	13.8	8.16	0	0	pup dvof eabp a	30	mild	0	0	1.8			15	0	0	0	0	0	7.4	0	0	0	0	0	0	0	0
88	355	6	2	14	108	14	6	0	0	pu pd	30	mild	0	0	1.1	21	119	17.3	0	0	0	0	0	5.9	0	0	0	0	0	0	0	0
89	361		2	7.25		16.4	7	0	0	pu pd	30	non	0	0	1.7			17.5	1	0	0	0	0	6.4	0	0	0	0	0	0	0	0
90	362	3.5	1	14	97	17.2	3.5	0	0	pup dpp	30	mild	0	0	0.8	23	119	19	0	0	0	0	nephrop	7.42	0	0	0	0	0	0	0	0

91	363	4	1	13	96	16	4	0	0	pupd	30	non	0	0	15	13.5	97	16.6	0	0	0	0	0	7.8	0	0	0	0	0	0	0	0
92	365	11.3	2	27	141	13.7	11.3	0	0	pupd	30	mild	0	0	1.5			15.8	0	0	0	0	0	7	0	0	0	0	0	0	0	0
93	368	3.5	1	14	95	17.2	3.5	0	0	pupd wt loss	30	mild	0	0	2			19.4	0	0	0	0	0	6.8	0	0	0	0	0	0	0	0
94	369	5.6	1	14.5	109	14.5	5.6	0	0	pupd	30	mild	0	0	1.3	23		15.7	0	0	0	0	0	7.6	0	0	0	0	0	0	0	0
95	372	9.9	2	20	122	13.8	9.9	0	0	pupd	30	non	0	0	2	24	131	14.2	0	0	0	0	0	9.9	0	0	0	0	0	0	0	0
96	373	11	2	17	104	17	5.5	0	0	pupdwl	30	mild	0	0	1.5	21	116	17.3	0	1	1	1	0	6.4	0	0	0	0	0	1	1	1
97	375	4.5	1	16	103	16	4.5	0	0	pupdwl	30	severe	0	0	1.2	16	103	16	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0
98	376	12.42	2	23	137	14.3	12.4	10	-2	pupd	30	non	0	0	1.4	32	144	16.8	0	1	0	0	0	11	delayed	1	1	1	0	1	1	1
99	377	12.7	2	23.5	142	12.1	12.7	0	0	pupdap	30	severe	0	0	1.2	32	145	16.8	0	0	0	0	0	8.03	0	0	0	0	1	1	1	1
1	379	1	1	2	1	1	11.	12	1	pu	30	se	0	0	2	3	1	1	0	0	0	0	0	1	0	1	1	1	0	1	0	0

00		1.1		6	38	6.2	1			pdwl		vere			5	4	42	7.8						1.4								
101	380	11	2	22	130	13.7	11	0	0	pupdpp	30	severe	0	0	1.2	24	136	15	0	0	0	0	0	10.4	0	1	1	0	1	1	0	0
102	381	10.1	1	20	129	14.2	10.1	0	0	pupd	30	mild	0	0	1.3	22	123	15.7	0	0	0	0	0	9.5	0	0	0	0	0	0	0	0
103	383	4	2	16	101	16.1	4	0	0	pupp	30	severe	0	0	1.5			17	0	0	0	0	0	8.7	0	0	0	0	0	0	0	0
104	385	5	2	17	106	17	5	9	4		30		0		1.2	26	138	16.2	1	1	1	1	0	12.2	0	1	1	1	0	1	1	1
105	388	3	2	13	99	16	3	5	2	pupdap	30		0		32	16.5	105	16.5	0	1	1	1	SRNS	11.6	0	1	1	1	0	1	1	1
106	389	8.7	2	24	131	15	8.7	0	0	pupdpp	30	mild	0	0	1.4	26	130	16.2	0	0	1	0	0	9.4	0	0	0	0	1	0	0	0
107	396	4.7	2	16	107	16	4.7	6.7	2	pupd	30	non	0	0	14	20	115	16.6	0	1	0	0	0	9.6	0	0	0	0	1	1	0	0
108	398	5	1	20	106	20.1	1.42	0	0	pupdap	30	severe	0	0	1	25	123	17.3	0	1	1	1	0	6	0	0	0	0	0	0	0	0
10	399	6	2	26	14	13	6	0	0	puwl	30	non	0	0	1.3	31	14	16	0	0	0	0	0	13.	0	0	0	0	0	0	0	0

9					0	.6											3	.3						4								
110	400	6	1	20	122	13.8	6	0	0	pupd	30	severe	0	0	1.4	22	123	15.2	0	0	0	0	0	6.7	0	0	0	0	0	0	0	0
111	405	0.58	2			16.4	0.16				30		0	0	0.4			16	0	0	0	0	0	6.8	0	0	0	0	0	1	0	0
112	406	3.5	1	35	147	18.4	3.5	0	0	pupdap	30	mild	0	0	1	41	148	21.5	0	0	0	0	0	8.2	0	0	0	0	0	0	0	0
113	407	3.7	2	11	90	13.5	3.7	0	0	pupdwlvv	30	mod	0	0	1.2			14.3	0	0	0	0	0	9.7	0	0	0	0	0	0	0	0
114	408	6	2	16	110	13.3	0.04			pupp	30	non	0	0	0.6	25	128	17.3	0	0	0	0	0	7.7	0	0	0	0	0	0	0	0
115	409	5.5	2	14	103	14	5.5	0	0	pupdleth	30	mod	0	0	0.7	20	104	20	0	0	0	0	0	5.9	0	0	0	0	0	0	0	0
116	412	1.5	1	11	82	17.2	0.04	0	0		30		0	0	0.5			17.8	0	0	0	0	0	12.2	0	0	0	0	0	0	0	0
117	413	3.8	2	13	89	20.3	3.8	0	0	puppwl	30	mild	0	0	1	18	99	22.2	0	1	0	0	0	7.7	0	0	0	0	0	0	0	0
118	416	11.8	2	30	140	15.7	11.8	0	0	pupd	30	non	0	aunt	0.6	34	142	17.8	0	0	0	0	0	9.8	0	1	1	0	0	1	1	1

119	417	10.8	2	42	134	26.2	10.8	0	0	pupd	30	non	0	0	0.8	43	134	26.8	0	0	0	0	0	5	0	0	0	0	0	0	0	0
120	419	6	2	25	123	17.3	3	0	0	pu	30	mild	0	0	1.2			18	0	0	0	0	0	9	0	0	0	0	0	0	0	0
121	421	0.1	2	4	50	20	0.1	0	0	pu	30	mild	0	0	1.2			20.3	0	0	1	0	0	6.8	0	0	0	0	0	0	0	0
122	422	5	2	21.5	127	14.9	5	0	0	pupdvv	30	non	0	0	1.3	22	126	15.2	0	0	0	0	0	6.6	0	1	1	0	0	1	1	1
123	426	9	2	22	129	15.2	9	0	0	pupd	30	mild	0	0	1.1			16	0	0	0	0	0	7.1	0	0	0	0	0	0	0	0
124	437	9.7	2	27	131	16.8	9.7	0	0	pupdvi	30	non	0	0	1.7			17	0	0	0	0	0	6.9	0	0	0	0	0	1	0	0
125	438	10.2	2	31	130	19.3	10.2	0	0	pu	30	non	0	0	0.6	34	132	21.5	0	0	0	0	0	11.4	0	0	0	0	0	0	0	0
126	439	12.6	1	34	143	17.8	12.6	0	0	pupd	30	mod	0	0	0.8	37	144	19.4	0	0	0	0	0	7	0	0	0	0	0	0	0	0
127	441	5.7	2	15	103	15	5.7	0	0	pu	30	non	0	0	0.9	21	105	21	0	0	0	0	0	9.5	0	0	0	0	0	0	0	0
12	446	9.	2	20	12	13	9.1	0	0	pupd	30	mil	0	0	1.5	20	12	13	0	0	0	0	0	8.7	0	0	0	0	0	0	0	0

8		1			1	.8				vi		d					2	.8													
129	447	1.3	1	8.6	82	13.4	1.3	0	0	breath	30	severe	0	0	1.2	8.6	82	13.4	0	1	1	1	0	13	0	0	0	0	0	0	0
130	448	12.4	1	26	135	16.2	12.4	0	0	pu	30	mild	0	0	0.7	31	138	19.3	0	0	0	0	0	8.1	0	0	0	0	0	0	0
131	451	7.6	2	21	122	14.5	7.6	0	0	puvv	30	mild	0	0	1.4	25	125	17.3	0	0	0	0	0	12.7	0	0	0	0	0	0	0
132	452	10.8	2	25	135	15.6	10.5	0	0	pupd	30	severe	0	0	1.4	27	127	18.7	0	0	0	0	0	10.9	0	0	1	0	0	1	1	1
133	457	7.7	2	18	118	14.8	7.7	0	0	pupd lewl	30	non	0	0	1.1	18	118	14.8	0	0	0	0	0	7.5	0	0	0	0	0	0	0	0
134	458	10	2	25	147	13.1	10	0	0	ap le	30	mod	0	0	1.1	26.5	147	13.9	2	0	1	0	0	6	0	0	0	0	0	0	0	0
135	460	11	2	22	126	15.2	11	0	0	puap	30	non	0	0	1	24	126	16	0	0	0	0	0	5.4	0	0	0	0	0	0	0	0
136	463	3.3	1	13	93	16	3.3	0	0	pufe	30	sev	0	0	0.4	29.5	128	20.4	0	0	0	0	0	5	0	0	0	0	0	0	0	0
137	471	8.6	1	24.	124	17	8.6	0	0	pupdfe	30	mild	0	no	1.3	28	128	19.	1	0	0	0	0	16.4	0	0	0	0	0	0	0	0

				5														4														
138	472	2.4	2	14	97	17.2	2.4	0	0	pupd fe	30	severe	0	present	1.4	19	97	23.4	0	0	0	0	0	10.2	0	0	0	0	0	0	0	0
139	473	8	1	20.5	125	14.2	8	0	0	pupdno	30	non	0	0	1.2	26	136	16.25	0	0	0	0	0	15.5	0	0	0	0	0	0	0	0
140	482 abinaya	5	2	16	110	13.2	5	0	0	pupdpp	30	non	0	0	0.4	16	110	13.2	0	0	0	0	0	6.7	0	0	0	0	0	0	0	0
141	491	5	1	13	99	16	5	0	0	pupdpp	30	mild	0	0	1.5	15	101	15	1	0	0	0	0	7.2	0	0	0	0	0	0	0	0
142	492	9	2	27.5	130	17.1	9	0	0	pupd	30	non	0	0	1.3	31	130	19.3	1	0	0	0	0	6.1	0	0	0	0	0	0	0	0
											30		0																		