A DISSERTATION

ON

"PREVALENCE STUDY OF THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS''

Submitted to

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY
CHENNAI

In partial fulfilment of the regulations
for the award of

M.D DEGREE IN GENERAL MEDICINE
BRANCH I

GOVERNMENT MOHAN KUMARAMANGALAM

MEDICAL COLLEGE, SALEM

APRIL 2016

Government Mohan Kumaramangalam Medical College Hospital

SALEM

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled **"PREVALENCE STUDY OF THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"** is a bonafide and genuine research work carried out by me under the guidance of ***Dr.S R Subramanian, M.D., Professor***, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamil Nadu, India.

Place: Salem

Date: 29/09/2015

Signature of the Candidate

DR. PRASANNAKUMAR

i

Government Mohan Kumaramangalam Medical College Hospital

SALEM

CERTIFICATE BY THE GUIDE

This is to certify that this dissertation **"PREVALENCE STUDY OF THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"** is a bonafide work done by **Dr. PRASANNAKUMAR P** in partial fulfillment of the requirement for the degree of M. D. in General Medicine, examination to be held in 2016.

Signature of the Guide

Place: Salem

Date: 29/09/15

Dr.*S R Subramanian*, M.D

Professor
Department of Medicine,
Government Mohan Kumaramangalam
Medical College Hospital,
Salem, Tamil Nadu.

ii

Government Mohan Kumaramangalam Medical College Hospital

ENDORSEMENT BY THE HEAD OF DEPARTMENT

This is to certify that this dissertation titled " **PREVALENCE STUDY OF THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS**" is a bonafide work done by **Dr. PRASANNAKUMAR P** under the overall guidance and supervision of ***Dr. S R Subramanian M.D., Professor and Head***, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital, in partial fulfillment of the requirement for the degree of M. D. in General Medicine, examination to be held in 2016.

Seal & Signature of the HOD

Dr. S. R. Subramanian M.D.,
Professor and Head
Department of General Medicine
Government Mohan Kumaramangalam Medical College Hospital
Salem, Tamil Nadu, India

iii

Government Mohan Kumaramangalam Medical College Hospital

SALEM

ENDORSEMENT BY THE DEAN OF THE INSTITUTION

This is to certify that this dissertation entitled **"PREVALENCE STUDY OF THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"** is a bonafide work done by **Dr. PRASANNAKUMAR P** under the guidance and supervision of Dr. **S.R. Subramanian M.D.**, Professor and Head, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital, in partial fulfillment of the requirement for the degree of M. D. in General Medicine, examination to be held in 2016.

29/9/15

Seal & Signature of the Dean

Dean
Government Mohan KumaramangalamMedical College and Hospital
Salem, Tamil Nadu, India

DEAN
Govt.Mohan Kumaramangalam
Medical College Hospital,
Salem - 636 001.

iv

Government Mohan Kumaramangalam Medical College Hospital

SALEM

COPYRIGHT

I hereby declare that THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI, Tamil Nadu, India shall have the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Place : Salem

Date: 29/09/15

Signature of the Candidate

DR. PRASANNAKUMAR P

© THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY ,CHENNAI, Tamil Nadu, India

v

ACKNOWLEDGEMENT

I am extremely thankful to **Prof.Dr.R.RAVICHANDRAN, MS, Mch,** Dean, Government Mohan Kumaramangalam Medical College Salem, for allowing me to utilize the hospital facilities for doing this work.

I would like to express my heartfelt gratitude to my mentor and teacher, **Prof.Dr.S.R.SUBRAMANIAN, M.D**., Professor, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital for his relentless encouragement and expert guidance throughout the period of the study and postgraduate course. His enthusiasm and immense encouragement have been responsible for easing out many shortcomings during this work.

I am deeply indebted to **Associate Prof.Dr.R.MANOHARI, M.D.**, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital, for her fathomless enthusiasm and motivation throughout the study.

Warmest and sincere thanks to **Professors Dr. S RAMASAMY, M.D, Dr.T.RAVIKUMAR, M.D,** and **Dr.S.SURESH KANNA, M.D, DR.V.SUNDARAVEL, M.D,** for all the help, encouragement and guidance during my post-graduation study period.

My warmest gratitude to **Dr.PRAKASH G M.D, D. Diab,** Department of medicine for his guidance in completing the study.

I would like to express my gratitude to **Dr.VASANTHKUMAR,** M.D, and **Dr. KALAISEZHIAN,** M.D, whose relentless encouragement inculcated in me a sense of confidence.

I am deeply grateful toall Assistant professors in the department of General Medicine for their immense help and guidance during my post-graduation course.

I extend my heartfelt thanks to all my colleagues and friends for their help rendered during my study.

I specially thank all my patients without whose cooperation; this dissertation would never have seen the light of the day.

TABLE OF CONTENTS

LIST OF TABLES

TABLE OF CHARTS

TABLE OF FIGURES

ABSTRACT

BACKGROUND:

Type 1 Diabetes Mellitus is a chronic endocrine disorder of children and early adults of autoimmune origin. It is often complicated by other autoimmune disorders especially autoimmune thyroid disease characterized by the presence of thyroid antibodies to peroxidase and thyroglobulin. Using these autoantibodies, organ-specific autoimmunity may be detected before the development of autoimmune clinical disease. Thus the aim of the study is to find the prevalence of thyroid disorder and thyroid autoimmunity status in type 1 diabetes mellitus.

METHOD:

Data were collected from 100 type 1 Diabetic patients. They were tested for thyroid profile (TSH, total T3 and T4) and thyroid autoimmunity (thyroid peroxidase antibodies).

RESULTS:

The prevalence of thyroid disorder and thyroid autoimmunity was found to be 14% and 18% respectively in T1DM. Out of 18 thyroid peroxidase positive patients, 14 were hypothyroid and 4 were euthyroid. Over the 14 hypothyroid, only 3 were overt hypothyroid and the remaining 11 were subclinical hypothyroid. There was female preponderance for thyroid

autoimmunity in T1DM. There is also significant association T1DM and development of thyroid autoimmunity.

CONCLUSION:

There is higher incidence of thyroid disorder in type 1 diabetes mellitus which is usually subclinical. Coexisting thyroid disorder in type 1 diabetes may have a poor outcome on glucose control. Thus there is a need for periodic screening of thyroid profile in type1 diabetes mellitus.

INTRODUCTION

Type 1 Diabetes mellitus is a chronic autoimmune disorder of children and early adulthood due to destruction of beta pancreatic cells resulting in absolute insulin deficiency leading to both microvascular and macrovascular complications in due course of time.

As Type 1 diabetes mellitus is a common endocrine disorder associated with aberrant immune responses to specific β-cell autoantigens including autoantibodies to glutamic acid decarboxylase (GAD), to islet cell (ICA) and to insulin (IAA), these patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia[1]. Using these autoantibodies, organ-specific autoimmunity may be detected before the development of clinical disease.

The most common autoimmune disease associated with T1DM is autoimmune thyroid disorder, which is characterized by the presence of thyroid antibodies especially thyroid peroxidase and thyroglobulin[2].

In type 1 DM, the prevalence of thyroid antibodies in children is 8 to 50% from various studies in different nations due to variation in age, sex, and ethnic origin of the people.

Most patients with thyroid autoimmunity are asymptomatic. Even if symptomatic, symptoms may be attributed to diabetes. So, the diagnosis of thyroid dysfunction in

diabetic patients based solely on clinical manifestations can be difficult[3].As both conditions involve a dysfunction of the endocrine system, thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders affect the management of diabetes in patients[4].Subclinical hypothyroidism is associated with an increased risk of symptomatic hypoglycaemia in diabetic patients while hyperthyroidism worsens glycemic control.

Because of this high prevalence, lack of clinical features and the impact on morbidity, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease[2].

AIMS AND OBJECTIVES

- To study the prevalence and pattern of thyroid disorders in Type 1 Diabetic patient.
- To find out thyroid autoimmune status among them.
- To correlate thyroid autoimmunity with thyroid dysfunction.
- To assess any age/gender/diabetes duration difference.

REVIEW OF LITERATURE

DIABETES MELLITUS

BACKGROUND OF DIABETES MELLITUS

Diabetes Mellitus is a metabolic disorder of multiple aetiology, characterised by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The long-term effects of diabetes cause damage and dysfunction of almost all organs of body in the form of both microvascular and macrovascular complications. Microvascular complications include progressive development of retinopathy with potential blindness, nephropathy that may lead to renal failure, neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. Macrovascular complications include myocardial infarction, cerebrovascular accident and peripheral vascular accident.

HISTORY

The first mention of diabetes as a condition causing 'polyuria' was first made about 1500 B.C. in Papyrus Ebers found at Luxor in Egypt. A report from China indicated that the urine of diabetic patients was so sweet that dogs were attracted to it and a little later, around 400 B.C., the sweetness was referred to as “honey urine”

The word diabetes was first used by Aretaeus of Cappadocia in the second century AD. It comes from the Greek word meaning Siphon. Clinical description of polyuric states resembling diabetes mellitus was described in Ebers papyrus of Egypt (15 century BC)

PREVALANCE

DM is an epidemic disease seen throughout the world, but is more observed in developed countries. The Asian and African countries will have the major disease burden by 2030.In 2011, according to Indian Council for Medical Research, there are 62.4 million diabetics and 77.2 million prediabetics in India. The diabetic prevalence is expected to increase from 171 million in 2000 to 366 million in 2030 globally with India sharing the major disease burden. The increase in incidence in developing countries is due to urbanization and lifestyle changes, perhaps most importantly the "Western-style" diet. Type 2 diabetes mellitus amongst Indians occurs at a younger age, the age at diagnosis being a decade earlier than in the west. Body mass is lower by 4 kg/m^2 for males and 6 kg/m^2 for females. However abdominal obesity with increased weight to hip ratio is more common in Indian population

CLASSIFICATION OF DIABETES

In 1979, a uniform terminology and a functional classification of diabetes was developed classifying diabetes into insulin dependent diabetes mellitus and non- insulin dependent diabetes mellitus by the National Diabetics Data Group in USA[5]. This was later modified by the WHO Expert Committees in 1980 and 1985.The present classification and diagnostic criteria were proposed by an International Expert Committee[6], working under the sponsorship of the ADA in 1997 which was later accepted by WHO.

TABLE 1 ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

I. Type 1 diabetes
(beta cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated B. Idiopathic

II. Type 2 diabetes
(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

IV. Gestational diabetes mellitus

Genetic defects of betacell function
- Chromosome 20, HNF-4alpha (MODY1)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 12, HNF-1alpha (MODY3)
- Chromosome 13, IPF-1 (MODY4)
- Chromosome 17, HNF-1beta (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Chromosome 2, KLF11 (MODY7)
- Chromosome 9, CEL (MODY8)
- Chromosome 7, PAX4 (MODY9)
- Chromosome 11, INS (MODY10)
- Chromosome 8, BLK (MODY11)
- Mitochondrial DNA
- Permanent neonatal diabetes
- Transient neonatal diabetes
- Others

Genetic defects in insulin action
- Leprechaunism
- Lipoatrophic diabetes
- Rabson-Mendenhall syndrome
- Type A insulin resistance
- Others

Diseases of the exocrine pancreas
- Cystic fibrosis
- Fibrocalculouspancreatopathy
- Hemochromatosis
- Neoplasia
- Pancreatitis
- Trauma/pancreatectomy
- Others

Endocrinopathies
- Acromegaly
- Aldosteronoma
- Cushing's syndrome
- Glucagonoma
- Hyperthyroidism
- Pheochromocytoma
- Somatostatinoma
- Others

Drug- or chemical-induced
- Alpha-interferon
- Atypical antipsychotics
- Beta-adrenergic agonists
- Diazoxide
- Dilantin
- Glucocorticoids
- Highly Active Antiretroviral Therapy (HAART)
- HMG CoA reductase inhibitors (statins)
- Nicotinic acid
- Pentamidine
- Thiazides
- Thyroid hormone
- Vacor (rodenticide)
- Others

Infections
- Congenital rubella
- Cytomegalovirus
- Others

Uncommon forms of immune-mediated diabetes
- Anti-insulin receptor antibodies
- "Stiff-man" syndrome
- Others

Other genetic syndromes sometimes associated with diabetes
- Down syndrome
- Friedreich ataxia
- Huntington chorea
- Klinefelter syndrome
- Laurence-Moon-Bardet-Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Turner syndrome
- Wolfram syndrome
- Others

DIABETES MELLITUS TYPE 1

Type 1 diabetes is one of the most common metabolic disorders which occurs due to an absolute insulin deficiency. The disease shows an acute onset, with severe symptoms including weight loss. Positive family history of diabetes is rare and ketonuria is common. The patients are dependent on exogenous insulin for metabolic control and survival.

T1 DM develops in people who are genetically predisposed. In addition, certain environmental triggers start the process of autoimmune destruction leading to complete β cell destruction and insulinopaenia that is characteristic of type 1 DM.

It is estimated that 50% to 90% of type 1 DM patients have evidence of auto-antibodies and they are labeled as type 1A DM or autoimmune type 1 DM while the remaining are called type 1B DM or idiopathic type 1 DM. The prevalence of type 1B DM is reported to be 5% to 10% in Caucasian populations.

Markers of the immune destruction of the ß-cell include islet cell autoantibodies, autoantibody to insulin, autoantibody to glutamic acid decarboxylase GAD, and autoantibody to the tyrosine phosphatases IA-2 and IA-2ß. One and frequently more of these autoantibodies are present in 85– 90% of individuals when fasting hyperglycemia is initially detected**.** These antibodies can be measured in the majority of patients, and may help determine which individuals are at risk for developing T1DM.

In type 1 diabetes, the rate of ß-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first

manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. These patients are also having a tendency to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, celiac sprue, and pernicious anemia.

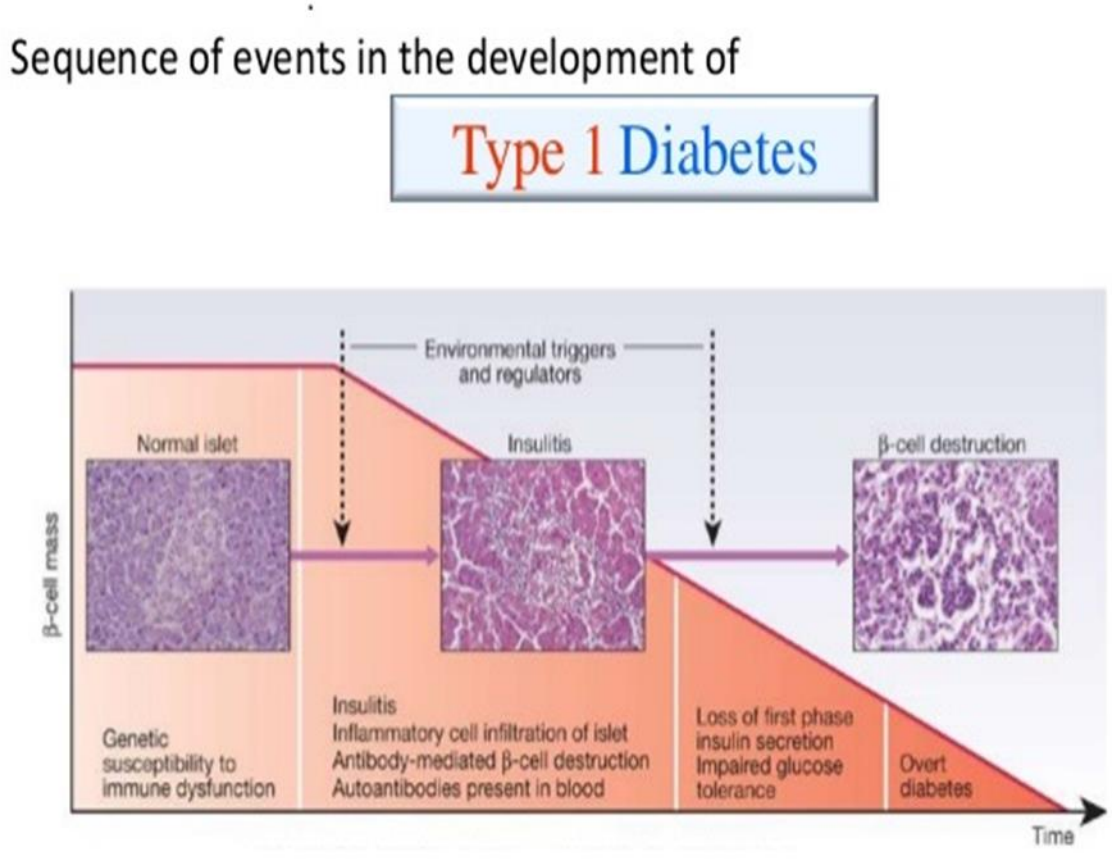


FIGURE 1: PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

DIABETES MELLITUS TYPE II

This type of diabetes, which accounts for 90% of those with diabetes, previously referred to as non-insulin-dependent diabetes, or adult-onset diabetes which usually diagnosed in patients >45 years but can occur in children and early adulthood. Type 2 diabetes is caused by the interaction of certain genetic abnormalities with adverse environmental factors.Type 2 diabetes is a polygenic disorder, caused by a cluster of susceptibility genes. These patients have relative insulin deficiency due to insulin resistance.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Unlike type 1 diabetes ketoacidosis seldom occurs spontaneously in this type of diabetes. It usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless such patients are at increased risk of developing macrovascular and microvascular complications. Insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently

in women with prior GDM and in individuals with hypertension or dyslipidemia and its frequency varies in different racial/ethnic subgroups.

GESTATIONAL DIABETES MELLITUS

Glucose intolerance that develops during pregnancy and typically resolves with delivery, occurs in about 7% of all pregnancies. This occurs because of insulin resistance due to pregnancy, overweight, obesity and genetic predisposition. It is a strong risk factor for later development of type 2 Diabetes

DIABETES MELLITUS SYMPTOMS

The symptoms of uncontrolled diabetes are related to high blood glucose levels, and loss of sugar in urine. Elevated glucose in urine causes increased urination leading to dehydration which in turn increases thirst and water consumption. The inability to utilize glucose energy eventually leads to weight loss despite an increase in appetite. Type 1 Diabetics have abrupt onset of signs and symptoms of hyperglycemia: increased thrist and hunger, frequent urination, weight loss, and fatigue and are more prone to develop ketoacidosis. Type 2 Diabetics are not prone to ketoacidosis until late in course or with prolonged hyperglycemia. They may also have blurred vision, delayed healing, numbness and tingling of the hands and feet, recurring fungal infection. Elevated glucose levels can also lead to lethargy and diabetic coma.

DIABETES MELLITUS DIAGNOSIS

The American Diabetes Association (ADA) criteria for the diagnosis of diabetes are any of the following for non-pregnant adults of Type 1 and Type II

Table 2 – American Diabetes Association diagnostic criteria for diabetes

Test[a]	Threshold	Qualifier
Hemoglobin A_{1c} or	≥ 6.5%	Lab NGSP-certified, standardized DCCT assay
Fasting glucose or	≥ 126 mg/dL (7.0 mmol/L)	No caloric intake for at least 8 hours
2-hour glucose or	≥ 200 mg/dL (11.1 mmol/L)	After 75 g of anhydrous glucose
Random glucose	≥ 200 mg/dL (11.1 mmol/L)	Plus classic hyperglycemia symptoms or crisis

NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial.

[a] Results must be confirmed by repeated testing.

AUTOANTIBODIES AS MARKERS OF DM

T1DM is an autoimmune disease, as pancreatic ß cells are destroyed. The strongest evidence to support autoimmunity as the ultimate pathogenesis comes from the presence of insulitis (presence of inflammatory cells consisting of T lymphocytes, B lymphocytes, and macrophages) around the islets in recently diagnosed patients of type 1 DM. Fifty per cent to ninety per cent of type 1 DM patients have presence of antibodies against, islet cells (ICA), Glutamic Acid Decarboxylase (GAD), and IA2. Moreover type 1 DM has a strong association with other autoimmune disorders, like Hashimoto's thyroiditis, Grave's disease, pernicious anaemia, coeliac disease, etc.

Subjects with genetic predisposition to type 1 DM, if exposed to certain environmental trigger, autoimmune destruction of β-cells starts. These antibodies can be detected in the subject long before development of type 1 DM as insulitis is slowly progressive disease. However, all subjects with ICA or GAD – Ab do not necessarily develop type 1 DM.

Insulin antibodies carry a very small risk of type 1 DM, but its presence along with ICA increases the 5-year risk of type 1 DM to 50% to 70% particularly in childhood type 1 DM below 5 years of age. Presence of two or more antibodies suggests a greater risk of type 1 DM. Approximately 80% of patients with type 1 DM express two or more autoantibodies.

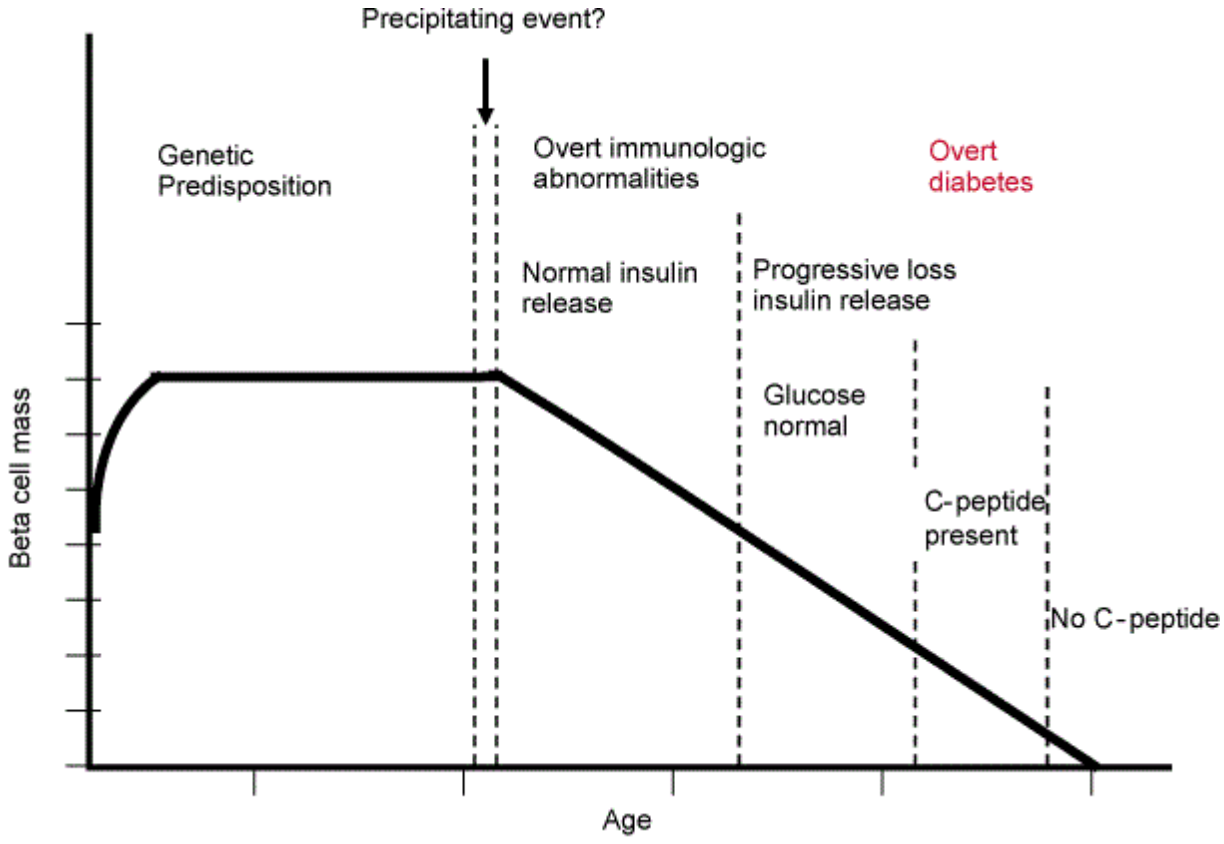


FIGURE 2: STAGES IN DEVELOPMENT OF TYPE 1 DIABETES

THYROID GLAND

ANATOMY

The thyroid is one of the largest of endocrine organs, weighing about 15 to 20 gm in adults, with each lobe being approximately 4 cm (height) × 2 cm (width) × 2 to 2.5 cm (thickness). The two lobes are connected by the isthmus. The gland is formed of follicles, which are filled with colloid. From the apex of follicular cells, numerous microvilli extend into colloid. It is at or near this surface of the cell that iodination, exocytosis and the initial phase of hormone secretion occur. Colloid contains Thyroglobulin molecules in which thyroid hormones are present.

REGULATION OF THYROID

The production of T4 and T3 in the thyroid gland is regulated by the hypothalamus and pituitary gland (figure 3). To ensure stable levels of thyroid hormones, the hypothalamus monitors circulating thyroid hormone levels and responds to low levels by releasing thyrotropin releasing hormone (TRH). This TRH then stimulates the pituitary to release thyroid stimulating hormone. When thyroid hormone levels increase, production of TSH decreases, which in turn slows the release of new hormone from the thyroid gland.

The thyroid gland needs iodine and the amino acid L-tyrosine to make T4 and T3. T3 is the biologically active form of thyroid hormone. The majority of T3 is produced in the peripheral tissues by conversion of T4 to T3 by a selenium-dependent enzyme.

Ninety-nine percent of circulating thyroid hormones are bound to carrier proteins, rendering them metabolically inactive. The remaining "free" thyroid hormone, the majority of which is T3, binds to and activates thyroid hormone receptors, exerting biological

activity. Very small changes in the amount of carrier proteins will affect the percentage of unboundhormones.

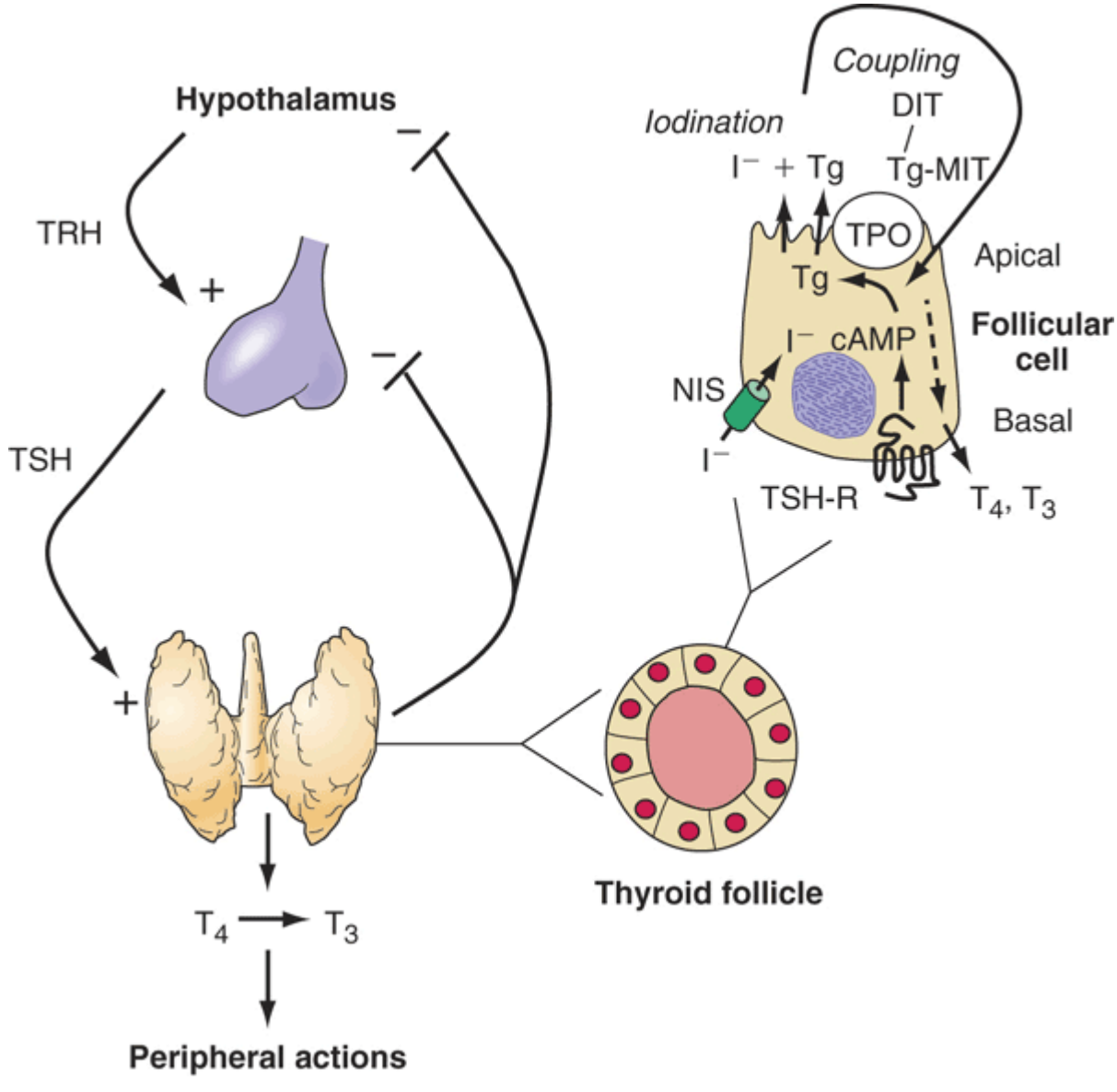


FIGURE 3: REGULATION OF THYROID HORMONE

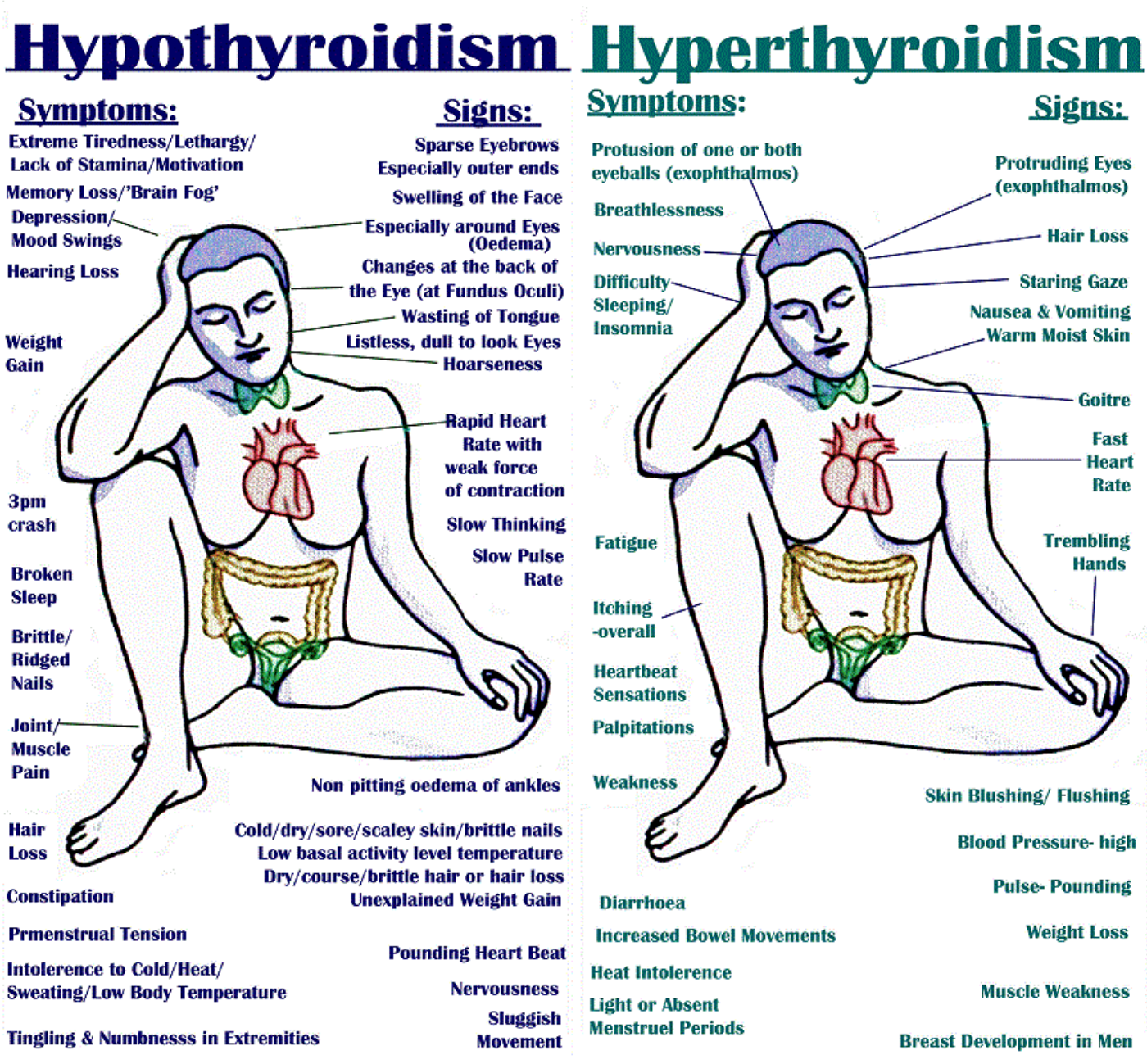


FIGURE 4: CLINICAL MANIFESTATION OF THYROID DISORDER

THYROID AUTOIMMUNITY

AUTOANTIBODIES AS MARKERS OF THYROID AUTOIMMUNE DISEASES

Thyroid autoantibodies is useful in disease prediction as it reflects the underlying disease activity and progression. Thyroid peroxidase and thyroglobulin are the most important autoantibodies associated with thyroiditis. Autoimmune thyroid disease (AITD) is the most common organ specific autoimmune disorder associated with both hypothyrodism and hyperthyroidism.

Autoimmune thyroid disease causes cellular damage through cell mediated destruction by sensitized T-lymphocytes and/ or autoantibodies binding to thyroid cell membranes leading to cell lysis and inflammatory reactions. Functional alterations in thyroid gland occur due to the action of stimulating or blocking autoantibodies on cell membrane receptors. The principal thyroid autoantigens are thyroid peroxidase (TPO), thyroglobulin (TG) and the TSH receptor.

Thyroid peroxidase (TPO) was initially known as ‘thyroid microsomal antigen’ and thyroid peroxidase antibodies are the hallmark of autoimmune thyroid disease as they are associated with all cases of Hashimoto's thyroiditis, 60% of patients with postpartum thyroiditis and 75% of patients with Graves' hyperthyroidism.

Three principal thyroid autoantigens namely TPO, TG and the TSH receptor are involved in AITD**.** It was found that the high TAA titres are consistently associated with AITD.

It was found that that the autoantibodies to TG and TPO are characteristic serum markers of thyroid autoimmunity in humans and Abs to both autoantigens are mostly present in the same subjects. Thus, TG and TPO may share common Abs epitopes which suggest the presence of bispecific TgPO Abs in thyroid autoimmunity. TgPO Abs are reported to be detectable in most patients with high titres of TG Abs and TPO Abs but absent in patients without TG Abs

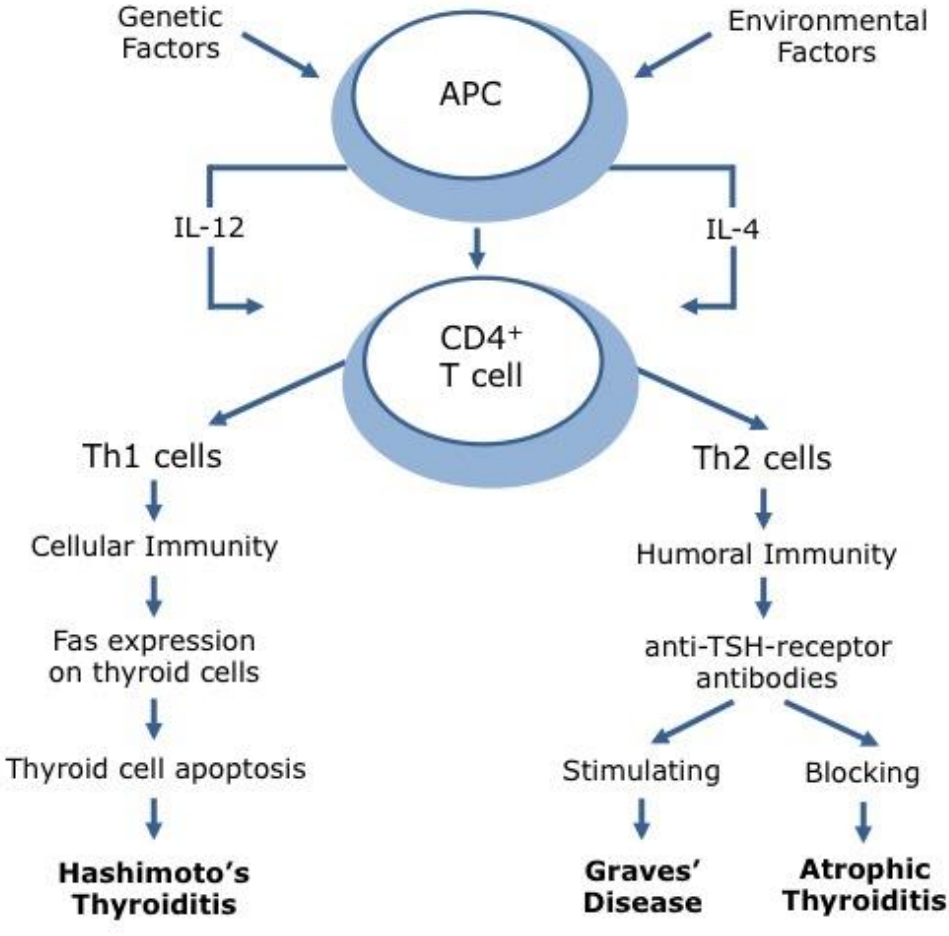


FIGURE 5: PATHOGENESIS OF THYROID AUTOIMMUNITY DISORDERS

ASSOCIATION BETWEEN IMMUNE MEDIATED (TYPE 1) DIABETES MELLITUS AND AUTOIMMUNE THYROID DISEASES

Type 1 diabetes mellitus is a chronic illness of children caused by insulin deficiency due to destruction of the insulin – producing pancreatic beta cells. The Onset commonly occurs in childhood but one - fourth of cases present in adults. Type 1 diabetic Patients with autoimmune mediated destruction of pancreatic beta cells are referred as type1 A which is approximating 85 percent7.Patients who are clinically T1DM but without autoantibodies are referred as having T1 B diabetes which is approximately 15 percent.

As T1DM is characterized by selective pancreatic β-cell destruction, the histopathology of T1DM is defined by a decreased β-cell mass with infiltration of mononuclear cells into the islets of Langerhans, which was described in 1901 by Opie[8]. This was known as 'insulitis', and is the characteristic of type 1 diabetes mellitus. In 1965, insulitis was seen in 70% of acute onset T1DM and found to be caused by a beta cell specific autoimmune process as reported by Gepts[9]. In 1970s, Nerup demonstrated cellular autoimmunity in type 1 diabetics utilizing lymphocytic infiltration in islets[10], therefore suggesting that an important role in the pathogenesis of T1DM was played by cell-mediated immunity. Because type 1A diabetes is an immune-mediated illness that develops in a genetically susceptible person, it is not surprising that most patients with type 1A diabetes have one or more additional autoimmune diseases. The most common associated disorders are thyroid autoimmunity (Graves' disease or Hashimoto's thyroiditis) and celiac disease[11]

The increased incidence of thyroid autoimmunity in type 1 diabetes was first reported in 1963[12].In the 1980s, Riley et al. reported that thyroid function tests of young diabetic patients revealed that about 1% had Grave's disease (autoimmune hyperthyroidism) and about 7% had Hashimoto's disease (autoimmune thyroiditis). Again, another 10% of patients tested positive for thyroid microsomal autoantibodies without concurrent evidence of clinical disease [13]. This frequency of antithyroid autoantibodies is about five times that found in healthy children of a similar age [14].The exact prevalenceof AITD among Indian adolescents with type 1 diabetes is still unknown.

In general, T1DM associated endocrinopathies are more common in patients with expressing HLA-DR3[15]. These individuals are dormant for a longer period of time before developing diabetes, presumably due to slower pace or later onset of beta cell destruction and are also positivefor anti-islet cell antibodies, compared with patients expressing HLA-DR4, who are younger at time of diagnosis, positive for anti-insulin antibodies, and are less likely associated with other autoimmune endocrinopathies.

Up to 20 percent of patients with type 1 diabetes have positive antithyroid antibodies (anti-thyroid peroxidase and/or anti-thyroglobulin), and 2 to 5 percent of patients with type 1 diabetes develop autoimmune hypothyroidism[16-21]. The prevalence of autoimmune thyroiditis is higher in girls with diabetes compared with boys, and it increases with age[21,22].

Children with beta cell autoantibodies (glutamic acid decarboxylase: antiGAD) appear to have a higher risk of developing anti-thyroid antibodies [21-23]. The presence of

anti-thyroid antibodies at diagnosis of T1D predicts the development of future thyroid disease [20]. Patients with anti-thyroid antibodies are 18 times more likely to develop thyroid disease than patients without anti-thyroid antibodies [21].Specific HLA subtypes (for example HLA-DQB1*0302) have also been associated with greater risk of developing autoimmune thyroid disease [17,24]. One study reported thatDR3-DQ2/DRB1*04:01-DQ8 is a susceptibility genotype for T1DM with autoimmune thyroiditis, while DRB1*11:01-DQA1*05:05-DQB1*03:01 and DRB1*15:01-DQA1*01:02-DQB1*06:02 genotypes are protective [25].

Patients with circulating antibodies may be euthyroid, or they may be hypothyroid and require thyroid hormone replacement therapy[16,26]. Rarely, they may be hyperthyroid with a reported prevalence of 1 to 2 percent in patients with type 1 diabetes.

The peak incidence of thyroid autoimmunity in young people occurs during early to mid-puberty, while in adults the risk is highest in middle-aged women . In children at genetic risk of Type 1 diabetes, seroconversion to thyroid peroxidase antibodies peaks around the time of puberty, at which time the thyroid gland undergoes remodelling. This is later than seroconversion to islet autoimmunity, suggesting that thyroid autoimmunity has different environmental trigger(s).

Biochemical thyroid dysfunction may present at diagnosisof Type 1 diabetes or may be detected after several decades of diabetes. There may be a prolonged period of thyroid autoimmunity prior to the development of thyroid dysfunction, but it is unknown whether

progression to clinical disease is more rapid in Type 1 diabetes than in the general population.

Type 1diabetes may be seen in association with hypothyroidism in Down's syndrome and also in patients with congenital rubella. Insulin requiring diabetes in association with primary hypothyroidism is sometimes seen in cases of haemochromatosis. Autoimmune polyglandular syndrome type 2 (APS 2) which is more common in women and occurs in early to middle adulthood is characterized by autosomal dominant inheritance and presence of autoimmune Addision's disease, autoimmune thyroid disease and immune mediated diabetes.

TABLE 3: THYROID DISORDER ASSOCIATED WITH T1DM

S.NO	
1	HASHIMOTO THYROIDITIS • Euthyroid • Hypothyroid
2	GRAVES DISEASE
3	POSTPARTUM THYROIDITIS
4	POLYGLANDULAR AUTOIMMUNE SYNDROMES(PAS) • PAS 1 • PAS 2
5	CO-OCCURENCE WITH COELIAC DISEASE, ADDISON'S DISEASE

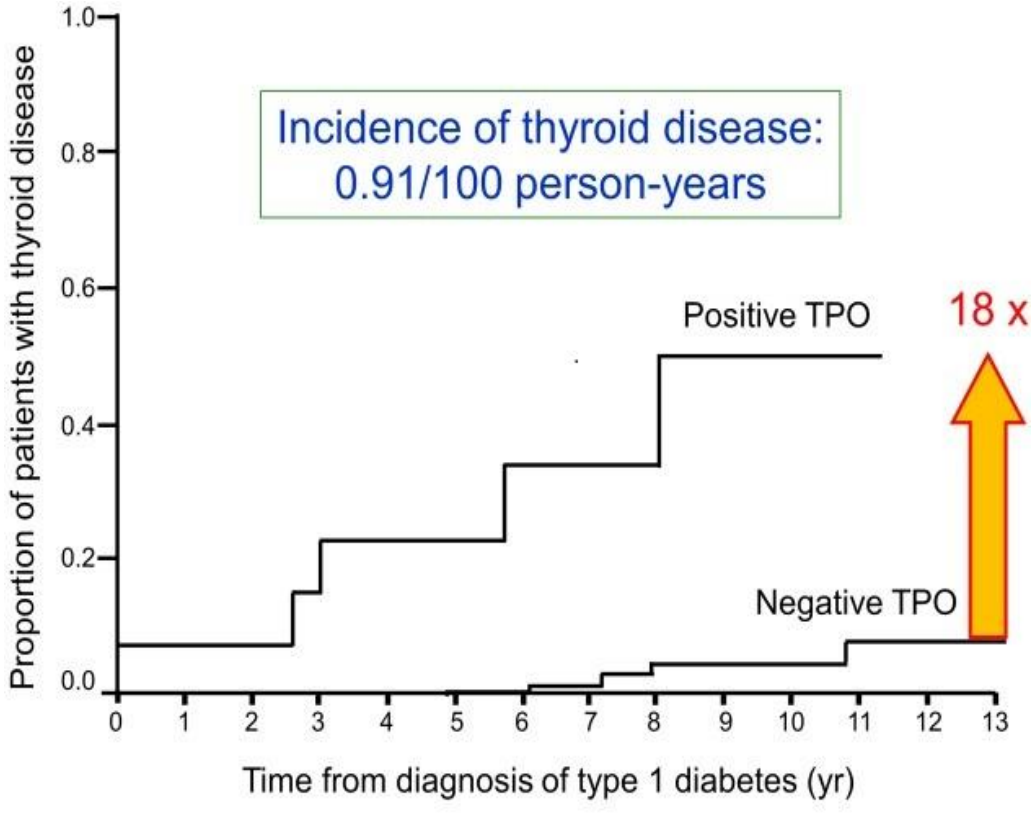


FIGURE 6: ASSOCIATION BETWEEN DURATION OF T1DM AND AITM

TABLE 4: GENES ASSOCIATED WITH T1DM, CD AND AITD

GENES	ASSOCIATED DISEASE
HLA • DR3-DQ2,DR4-DQ8 • DR3,DR5 • DR3-DQ2 • DR3-DQ2,DR4-DQ8	T1DM AITD CD AD
MIC-A	T1DM,CD,AD
PTPN22	T1DM,AITD,AD
CTLA-4	T1DM,AITD

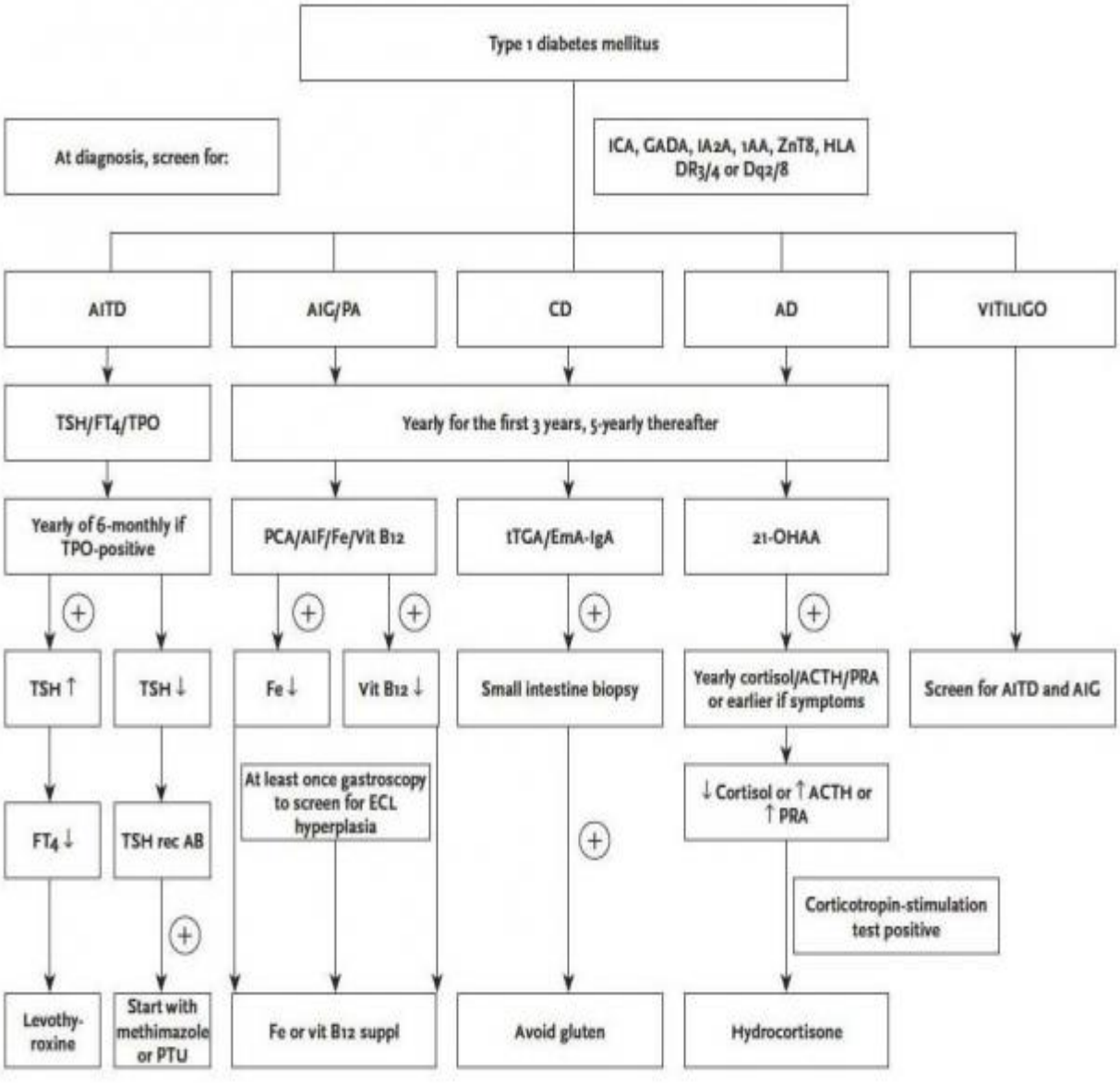


FIGURE 7: SCREENING OF OTHER AUTOIMMUNE DISORDES IN T1DM

THYROID REGULATION OF GLUCOSE HOMEOSTASIS

Thyroid hormone has profound effect on the regulation of glucose metabolism which exerts its effect on the circulating levels of insulin and counter regulatory hormones, hepatic output and peripheral utilization of glucose[27].

Thyroxine stimulates liver gluconeogenesis and also improves peripheral glucose utilization in skeletal muscle and adipose tissue. It acts through direct and indirect mechanisms. Direct effect is by liver gene transcription and indirect effect by activating sympathetic pathway. But the central target is 5' adenosine monophosphate-activated protein kinase[27,28]. Thyroid hormones also modulate the gene expression of uncoupling proteins in brown adipose tissue thus altering thermoregulation.

Thyroid hormone nuclear receptors and type 4 melanocortin receptor are both expressed in the hypothalamus by TRH neurons. In hyperthyroid, T3 has a repressive effect on expression of MC4R thus conserving energy as of MC4R reduces food intake and increases energy expenditure[28].

EFFECTS OF THYROID HORMONE AT HEPATIC TISSUE

T3 mainly targets genes involved in gluconeogenesis and glycogen metabolism

1) Pyruvate carboxylase, the gluconeogenic enzyme involved in the formation of oxaloacetate through carboxylation of pyruvate in the mitochondria

2) Phosphoenolpyruvate carboxykinase (PEPCK), the enzyme that catalyzes the rate-controlling step of gluconeogenesis by decarboxylation and phosphorylation of oxaloacetate to produce phosphoenolpyruvate[27,28].

Thyroid exerts antagonistic insulin effect through decrease in protein kinase B expression which inturn decreases glycogen synthesis inactivating glycogen synthase kinase 3. Thyroid hormones facilitates glycogenolytic and gluconeogenic effects of epinephrine and glucagon through stimulation of β2-adrenergic receptor mRNA and suppression of inhibitory G protein (Gi) RNA of the adenylate cyclase pathway

EFFECTS OF THYROID HORMONES AT PERIPHERAL TISSUES

In skeletal muscle, the main site of insulin-mediated glucose disposal, glucose transporter GLUT4 is induced by thyroid hormone.

EFFECT OF DIABETES ON THYROID FUNCTION

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process. In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status. Poorly controlled diabetes, both Type 1 and Type 2, may induce a “Low T3 state” characterized by low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations. Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5’ monodeiodination reaction. Studies indicate that it may be the long term diabetic control

that determines the plasma T3 levels. Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak. TSH responses and "low T3 state" may normalize with improvement in glycemic status but even with good diabetes control, the normal nocturnal TSH peak may not be restored in C-peptide negative patients i.e. those with totally absent pancreatic beta cell function.

Diabetes mellitus influences the assessment of thyrotoxicosis by falsely decreasing the blood levels of thyroxine (T4) and triiodothyronine (T3) during severely uncontrolled hyperglycemia.

METABOLIC EFFECTS OF THYROID DYSFUNCTION ON DIABETES

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, increased insulin degradation, and probably increased insulin resistance. Indeed, thyrotoxicosis may unmask latent diabetes.

In practice, there are several implications for patients with both diabetes and hyperthyroidism. First, in hyperthyroid patients, the diagnosis of glucose intolerance needs to be considered cautiously, since the hyperglycemia may improve with treatment of thyrotoxicosis. Second, underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia. Third, in diabetic patients with hyperthyroidism, physicians need to anticipate possible deterioration in glycemic control and adjust treatment accordingly.

Restoration of euthyroidism will lower blood glucose level. Although wide-ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestation of these abnormalities is seldom conspicuous. The synthesis and release of insulin is decreased but there is reduced rate of insulin degradation that may lower the exogenous insulin requirement. The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis.

The net effect is an increased risk of recurrent hypoglycemia in a diabetic individual. More importantly, hypothyroidism is accompanied by a variety of abnormalities in plasma lipid metabolism, including elevated triglyceride and low-density lipoprotein (LDL) cholesterol concentrations. Even subclinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in diabetes and further increase the risk of cardiovascular diseases.

TABLE 5: DIABETES MELLITUS – THYROID DISEASE INTERACTION

CLINICAL CONDITION	**EFFECT ON GLYCEMIA**	**EFFECT ON THYROID FUNCTION**
Diabetes Mellitus-In euthyroid Individuals		↓ Serum T3 ↑ rT3 ↓ TSH response to TRH impaired noctural TSH peak
Hyperthyroidism-In euglycemic individuals	Glucose intolerance-in 50% cases overt diabetes in 2-3%	
Hyperthyroidism- in diabetic individuals	Deterioration of diabetic control	
Hypothyroidism-in diabetic individuals	Predisposition to recurrent hypoglycemia. Exacerbation of symptoms.	

CONCLUSIONS

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process. Hyperthyroidism results in deterioration of diabetic control while hypothyroidism increases the susceptibility to hypoglycemia in diabetic patients thereby complicating the diabetic management in these individuals.

Nearly one third of all newly detected Type 1 diabetes mellitus patients have co-existent thyroid autoimmunity (TAA) and a high prevalence of thyroid dysfunction which is predominantly hypothyroidism (clinical or subclinical) whilst a few have hyperthyroidism. The high prevalence of thyroid dysfunction emphasizes the importance of routine screening for TAI in all newly detected Type 1 diabetes mellitus patients followed by annual TSH assay in case TAA is positive.

Thyrotropin, also known as thyroid stimulating hormone (TSH), is the most useful screening test. In general, TSH should be tested several weeks after the diagnosis of type 1 diabetes, when metabolic control has been established. This is because at least 20 percent of patients will have transient abnormalities of thyroid function when type 1 diabetes is first diagnosed, which resolve as the diabetes is treated . However, thyroid laboratory studies should be performed more promptly (within a few days of resolution of initial diabetes symptoms) in newly diagnosed children with clinical suspicion of thyroid disease because of thyroid enlargement or symptoms of hypo- or hyperthyroidism.

- If the TSH level is abnormal, free T4 is measured.
- If the TSH level is normal, patients should have a repeat measurement every one to two years. Additional thyroid function testing should be obtained whenever thyroid dysfunction is suspected or thyromegaly is detected.
- Patients with elevated TSH levels should be treated with thyroid hormone replacement therapy. The American Diabetes Association (ADA) suggests that antibodies to thyroid peroxidase (TPO) and thyroglobulin should be measured at diagnosis. An alternative strategy is to measure these antibodies only if abnormalities of thyroid function are detected.
- If Graves' disease is suspected, then the thyrotropin receptor antibody should be measured.
- If the initial antibody screening is positive, the patient should be monitored closely by screening with TSH annually and if any symptoms of hyper- or hypothyroidism develop. Repeat antibody testing is not needed

STUDIES ON TYPE 1 DIABETES AND THYROID DYSFUNCTION

Fuji *et al.* (1981) investigated thyroid hormone abnormalities in serum in 47 patients with diabetes mellitus and reported that no significant differences in T4 but significantly higher reverse T3 (rT3) and lower T3 levels were found between diabetics and healthy controls. Moreover, patients in diabetic ketoacidosis showed markedly high rT3 with low T3 levels. They found that with insulin treatment, these levels returned to normal in several days.

Gray *et al.* (1981) investigated the clinical features of diabetics with coexisting Graves' disease, or primary hypothyroidism and found that those with Graves' disease developed thyroid dysfunction and diabetes at an earlier age than patients with primary hypothyroidism. There was, however, no difference between the two groups in respect of sex ratio or proportion of subjects requiring insulin treatment. They found a strong correlation between age at diagnosis of diabetes and that of hyperthyroidism or hypothyroidism.

Bagchi (1982) found several alterations in thyroid function in diabetes mellitus.The most profound changes occur in patients with insulin-dependent diabetes. Plasma T4 is normal, plasma T3 is diminished, and the plasma level of rT3 is elevated in diabetic ketoacidosis or in patients with severely uncontrolled diabetes. They suggested that these changes arise from alterations in the monodeiodination pathways of T4 and both hypo- and hyperthyroidism occur

with increased frequency in diabetes. Also there is an increased prevalence of thyroid autoantibodies in insulin-dependent diabetes.

Cardoso *et al.* (1995) determined thyroid function and the prevalence of thyroid autoimmunity in IDDM Africans and the results were compared with those of a nondiabetic group and a group with non-insulin dependent diabetes mellitus (NIDDM). Thyroid hormone levels were significantly lower in IDDM patients than in the control population and the NIDDM population. Subclinical hypothyroidism was present in 21 % of the 28 IDDM patients, whereas one patient was hypothyroid and another hyperthyroid. Of the 60 NIDDM patients, 5 (8.3%) had subclinical hypothyroidism. Forty-six percent of the IDDM patients had significant levels of serum thyroid autoantibodies (TAA). This was significantly higher than the 1.4% and 1.7%, respectively in the controls and NIDDMs. Presence of TAAB in the patients was strongly associated with thyroid dysfunction, female preponderance, and duration of diabetes mellitus.

Lorini *et al.* (1996) assessed TAA thyroid autoantibodies (MsA and TgA) cross- sectionally in 212 children and adolescents (93 girls and 119 boys) aged 1.2-21 years with IDDM from 0-18 years, and longitudinally in 90/212 (43 girls and 47 boys) at diagnosis and during a 3-10 year follow-up. In the cross-sectional study, they found that TAA were present in 22/93 girls (23.7%) and 13/119 boys (10.9%). In the longitudinal study TAA were observed at diagnosis in 6 patients, and during the follow-up in 9 girls. In 11/15 TAA positive

patient's anti-nuclear antibodies were also present. Thyrotoxicosis also occurs with increased frequency in diabetic children than in the general population.

Chang *et al.* (1998) in their study among 243 type 1 diabetic patients found, 53 (21.8%) were positive for antiTPO. Among the type 1 diabetic patients with thyroid autoimmunity, anti-TPO tended to occur in those of older age or with long-standing disease. The frequency of anti-GAD was 45.6% (99 of 217), without gender preponderance (males: females, 18.0% vs 27.6%).Thus they reported that the presence of anti-TPO in 21.8% of type 1 diabetic patients confirmed the strong association of AITD and type 1 diabetes mellitus without ethnic differences.

Maugendre *et al.* (2000) during their study showed that thyroid peroxidase (TPO) antibodies were present in 45 of the 258 diabetic patients (17%) whereas thyroglobulin (Tg) antibodies were found in 19 patients (7%), including 13 cases with TPO antibodies. They found that prevalence of TPO antibodies were not influenced by such factors as gender, duration of disease, age at screening and at diabetes diagnosis, positivity of familial history. Thyroglobulin (Tg) antibodies were found in 19 patients (7%), including 13 cases with TPO antibodies. All patients without TPO antibody (n=213), including Tg-positive patients displayed TSH values in normal range. From the 45 TPO-positive patients they studied, 11 shows thyroid dysfunction. During their 5-year follow-up, only 2/45 patients became anti-TPO negative whereas

thirteen of the 45 patients developed subclinical or clinical thyroid diseases (4 Graves' disease and 9 thyroiditis with hypothyroidism).

Rattarasarn *et al.* (2000) in their study of 50 Thai type 1 diabetic patients found that thyroglobulin (Tg-Ab) and thyroperoxidase antibodies (TPO-Ab) were positive in nine (18%) and 15 (30%) patients respectively whereas eight patients (16%) were positive for both antibodies. None of 34 patients without thyroid antibodies had thyroid dysfunction. They followed up eight patients with positive thyroid antibodies but without clinical thyroid dysfunction and 21 patients without thyroid antibodies for up to 3 years and found that two patients of the first group developed hypothyroidism, whereas none of the latter developed thyroid dysfunction.

Kordonouri *et al.* (2002) in their multi center survey of 118 paediatric diabetic center in Germany and Austria reported the results of 7097 type1 diabetic patients and found that in 1,530 patients, thyroid antibody levels were elevated on at least one occasion, whereas 5,567 were antibody-negative during the observation period. Thyroid-stimulating hormone (TSH) levels were higher in patients with thyroid autoimmunity (3.34 pU/ml, range 0.0-615.0 pU/ml) than in control subjects (1.84.pU/ml, range 0.0-149.0 pU/ml) ($P < 0.001$). Even higher TSH levels were observed in patients with both anti-TPO and anti-TG (4.55 uU/ml, range 0.0-197.0 pU/ml).Thus they found that thyroid autoimmunity seems to be particularly common in girls with diabetes during the

second decade of life and may be associated with elevated TSH levels, indicating subclinical hypothyroidism.

Radaideh *et al.* (2003) investigated the prevalence of thyroid dysfunction and autoimmunity in 79 type 1 diabetic patients and compared with normal control. They found a significant difference in thyroid function variables between diabetics and controls. Among type 1 diabetic patients, 7 (9.2%) had thyroid autoantibodies, 5 with positive TPOAb only and 2 with positive TgAb, compared with 8 (6.3%) in the control group, 4 with positive TPOAb only and 4 with positive TgAb. Umpierrez*et al.* (2003) in cross sectional studies have reported that risk of thyroid dysfunction in patients with type 1 diabetes is two to three fold higher than in general population. They analyzed the incidence of thyroid dysfunction over time in a cohort of 58 patients (26 men and 32 women) and prospectively followed them for 18 years and reported that 18 patients had hypothyroidism, and 1 patient experienced transient hyperthyroidism. They found that hypothyroidism was more common in female (41 %) than in male (19%) subjects and in patients with positive TPO antibodies. Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89-82.54). There were no differences in BMI, lipid profile, and HbAlc between patients with and without thyroid dysfunction.

Shomon (2003) has confirmed the linkage between autoimmune thyroid disease and type 1 diabetes, suggesting that diabetic patients should receive regular screening for thyroid dysfunction.

Hawa*et al.* (2006) in their study evaluated disease-associated autoantibodies in both type 1 diabetes and thyrotoxicosis attending the Central Hospital of Yaounde in Cameroon. They collected samples from a total of 101 subjects, 47 of whom clinically had established type 1 diabetes, 18 had thyrotoxicosis and 36 normal subjects and tested for diabetes-associated glutamic acid decarboxylase (GAD) and tyrosine phosphatase (IA2) autoantibodies, thyroiditis-associated thyroglobulin (Tg) and thyroid peroxidase (TPO) autoantibodies .They reported that out of 47 patients with type 1 diabetes, 16 (34%) had GAD autoantibodies (Abs), 3 (6.4%) had IA2 Abs, and 2 (4.3%) had TPO Abs. Out of 18 patients with thyrotoxicosis, 4 (22.2%) had GAD Abs, 5 (27.8%) showed IA2 Abs, while 8 patients (44.4%) were TPO Abs positive. No patients in either group had TgAbs. Among normal subjects, 2 (5.6%) showed GAD Abs, and one of these was also IA2 Abs positive, but none had thyroid autoantibodies.

Volzke *et al.* (2007) studied the spectrum of thyroid disorders in 224 adult type diabetic subjects and compared them with results obtained from a sample of 3481 general adult population. They concluded that type 1 diabetic subjects had a higher risk of known thyroid disease, a lower risk of goiter and nodules and a higher risk of anti-TPO-Ab >200 IU/mL compared to the

reference population. Furthermore, diabetic subjects had lower serum FT3 levels than the non diabetic references.

Araujo *et al.* (2008) investigated the prevalence of thyroid autoantibodies in 214 children, adolescents, and young adult with type1 diabetes from north eastern Brazil as well as their significance for the development of thyroid disorder. They found that anti-TPO antibody test was positive in 54 out of the 214 patients studied, resulting in an overall prevalence of 25.2%,with females were predominance (72%) over males (28%). A total of 55.5% patients with positive anti-TPO antibodies had abnormal TSH levels.

Korner *et al.* (2008) investigated the prevalence of thyroid autoimmunity as well as the frequency of autoimmune thyroid disease in patients with type 1 diabetes mellitus and compared the prevalence of autoimmune thyroid disease in patients with type 1 diabetes mellitus and in those with type 1 diabetes mellitus and coeliac disease. Their results concluded that frequency of autoantibody positivity was significantly higher in diabetic patients suffering from celiac disease (type 1 diabetes mellitus: 43 (16%), type 1 diabetes mellitus + celiac disease: 16 (33.3%, $p < 0.01$). Hypothyroidism due to thyroiditis was also more prevalent in patients with type 1 diabetes mellitus and celiac disease.

Monajemzadeh *et al.* (2009) investigated the prevalence of thyroid dysfunction among children and adolescents with newly diagnosed type 1 diabetes in Iran for which they had compared 75 newly diagnosed type1 diabetic subjects with 105 healthy control children. They reported the

prevalence of thyroid dysfunction in diabetics was 14.6% (9.3% were subclinical hypothyroidism, 4% hypothyroidismand 1.3% subclinical hyperthyroidism) which were higher than normal controls.

Muralidhara Krishna *et al.* (2011) evaluates the levels of TSH, TmAb and lipid parameters in 36 type l diabetes cases and found that TSH was significantly elevated in cases and TmAb was identified in 7 of the 36 cases studied. Presence of TmAb and elevation in TSH were more pronounced in female cases. They also reported that serum total cholesterol as well as LDL-cholesterol levels were significantly elevated and serum HDL-cholesterol was significantly lowered in type 1 diabetics.

Joshap *et al.* (2011) assessed thyroid function at the diagnosis of type 1 diabetes and reported that 21/110 (19.0%) patients had abnormal thyroid function at diagnosis of TIDM. They found that abnormalities of thyroid function occurred more commonly in children with diabetic ketoacidosis (DKA) than those who did not have DKA(31.0% vs. 14.8%,).

MATERIALS AND METHODS

Study design:

Cross sectional observational study to analyse the prevalence of thyroid disorders and thyroid autoimmunity among Type 1 Diabetes.

Setting:

The study was carried at diabetic clinic of the Government Mohan Kumaramangalam Medical College Hospital, Salem

Approval:

The study was approved by the ethical committee of Government Mohan Kumaramangalam Medical College Hospital, Salem

Study population:

100 Patients were enrolled from the patient population who attended the outpatient clinic of Diabetology, from August 2014 to July 2015.

Inclusion criteria:

Established cases of Type 1 Diabete , diagnosed based on standard criteria.

- Symptoms of diabetes and casual plasma glucose 200 mg/dl (11.1 mmol/l) or
- Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l) or
- 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) and
- Patient on insulin from the time of diagnosis of diabetes

Exclusion criteria:

- Patients less than 14 years
- Pregnancy
- Evidence of other autoimmune diseases like Addisons disease, vitiligo, autoimmune hepatitis, rheumatoid arthritis, SLE.
- Multinodular goiter and known thyroid disease on medication
- Past history of thyroid surgery or radioiodine therapy.

CONSENT:

Patients were informed about the details of the test performed and blood sample were collected with consent.

SAMPLE COLLECTION:

Venous blood sample were collected after 8 hours fasting state. After serum separation, samples were sent for analysis.

METHOD OF TESTING:

- T3, T4, TSH – Radio ImmunoAssay.
- Thyroid peroxidaseAntibodies - Enzyme Linked Immuno Sorbent Assay.

NORMAL RANGES:

- T3 -80 – 180 ng/dl
- T4 - 4.2 - 11 µg/dl
- TSH - 0.5 – 5 mIU/ ml
- TPOA <40 IU/ml

RESULT INTERPRETATIONS:

- Any T3 /T4 value above the upper limit of normal along with a lowTSH < 0.5 mIU/ml is considered as hyperthyroidism.
- Any T3 /T4 value below the lower limit of normal along with an elevated TSH > 5mIU/ml is considered as hypothyroidism.
- TSH > 5mIU/ml along with normal range T3, T4 is considered as subclinical hypothyroidism.
- TSH < 0.5 mIU/ml along with normal range T3, T4 is considered as subclinical hyperthyroidism.
- Thyroid autoimmunity is considered to exist if TPOA level is > 40 IU/ml and not to exist if it is lesser.

STATISCAL ANALYSIS:

Statistical analysis was done using standard formulae SPSS (Statistical Package for Social Sciences) in windows Dos version. Base line data like age, gender, duration of diabetes were collected. Patients were categorized based on their thyroid status and thyroid autoimmune status. The significance of difference between means in two groups was calculated using student t test and the significance of difference in proportions using chi-square test. Fisher exact test was used when any one of the values was less than 5 in chi-square test. 2 x 2 tables were constructed for each variable and chi square value for a degree of freedom calculated.Statistical significance at 5% levels was taken for p value < 0.05 and at 1% levels p < 0.001.

DISCUSSION

In this study, 100 type 1 diabetic patients were enrolled and tested for this study

Total number of patients : 100

Number of male : 54

Number of female : 46

Age range : 14 – 34

Mean age : 21.8 ± 5.5 years

Mean duration of diabetes : 9 ± 4.5 years

Total Number of hypothyroid :14

Male : 4

Female : 10

Number of overt hypothyroid :3

Number of subclinical hypothyroid :11

Total number of hyperthyroid patients : nil

Number of TPOA positive : 18

Male : 4

Female : 14

Number of TPOA positive with hypothyroidism :14

Male : 4

Female : 10

Number of TPOA positive with euthyroidism :4

Male : 1

Female : 3

Mean age of patients with AITD : 13.1 ±4.4YRS years

Mean duration of diabetes of patients with AITD : 25.5± 6.2 years

TABLE 6: THYROID STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS

THYROID STATUS	GENDER		TOTAL
	MALE	FEMALE	
EUTHYROID	50	36	86
HYPOTHYROID	4	10	14
HYPERTHYROID	NIL	NIL	NIL

On comparing the female and male ratio by chi square test, the p value is 0.077 which is > 0.05. So, the association between gender and hypothyroidism is not significant indicating that there is no significant gender difference among hypothyroid and euthyroid type 1 diabetics as per this study.

CHART 1: THYROID STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS

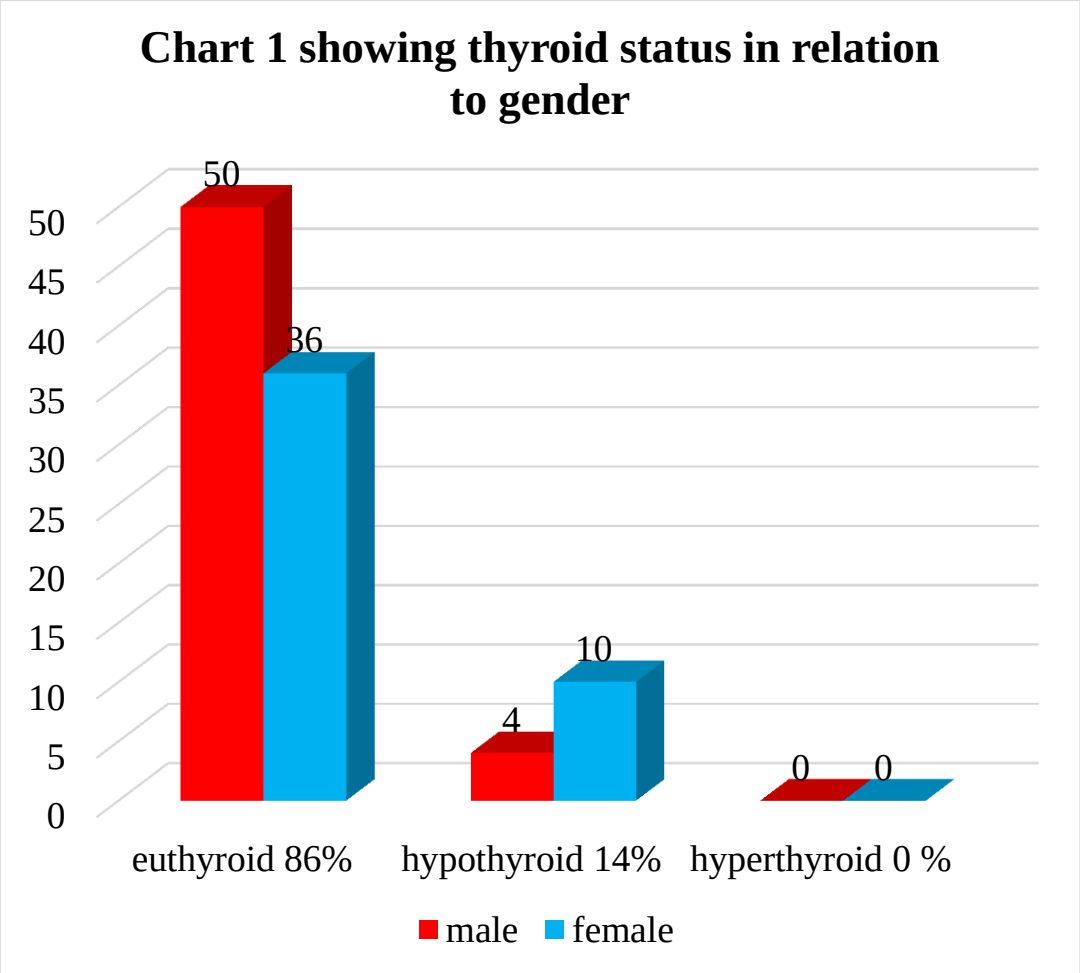


CHART 2: SCATTER PLOT DIAGRAM OF T3 VALUE OF ALL PATIENTS

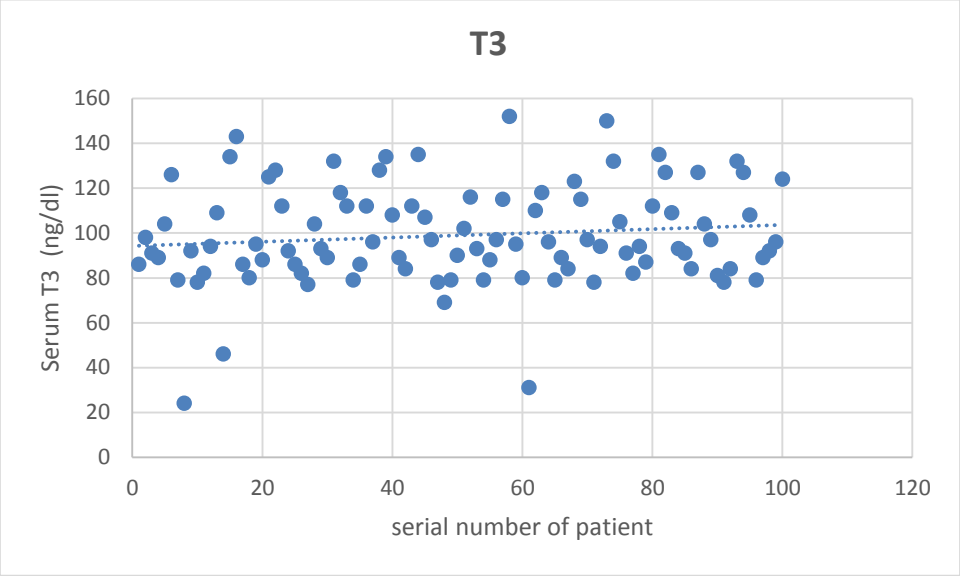


CHART 3: SCATTER PLOT DIAGRAM OF T4 VALUE OF ALL PATIENTS

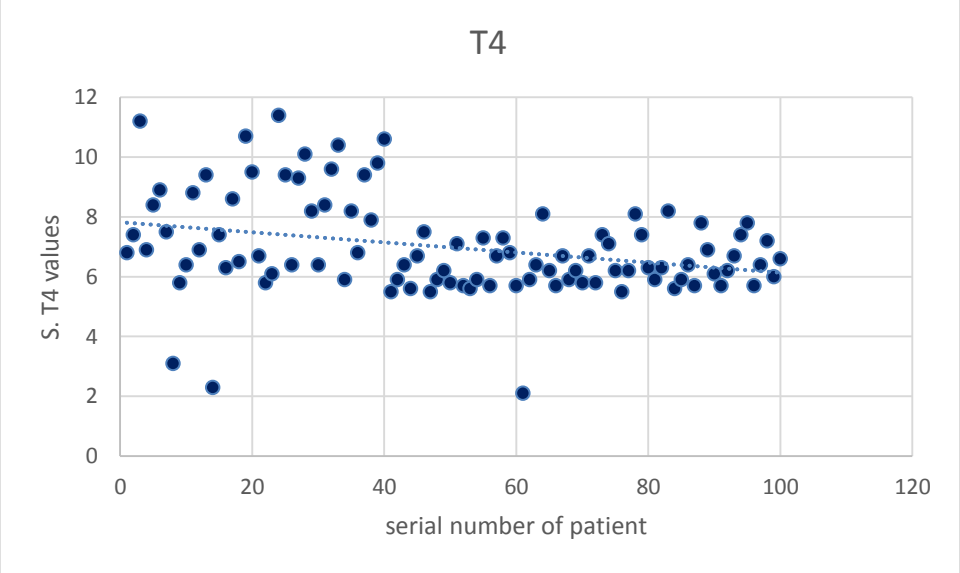
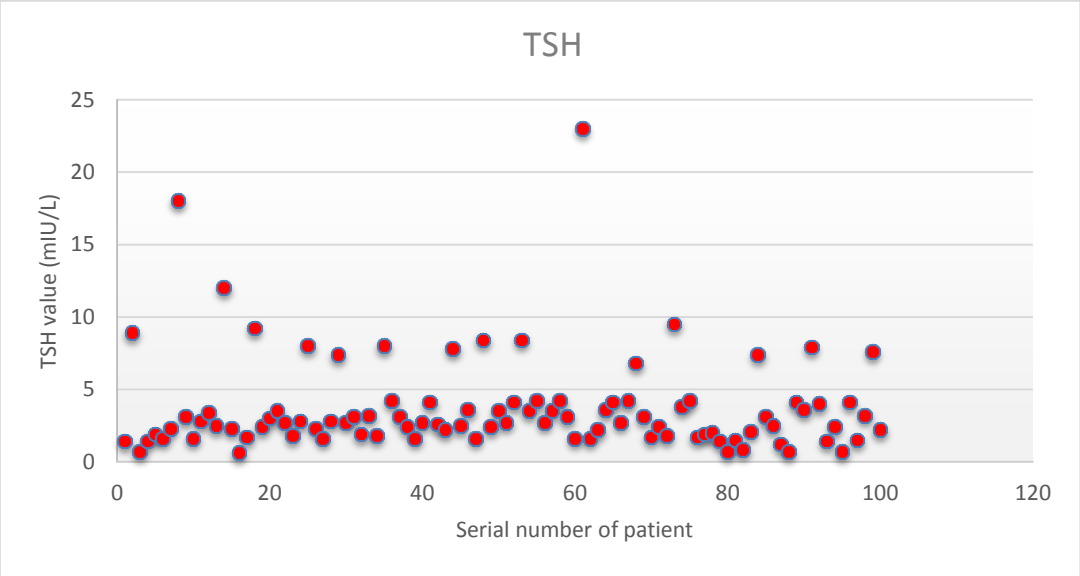


CHART 4: SCATTER PLOT DIAGRAM OF TSH VALUE OF ALL PATIENTS



- Charts 2 shows the scatter plot of T3 values obtained from the study population
- Charts 3 shows the scatter plot of T4 values obtained from the study population
- Charts 4 shows the scatter plot of TSH values obtained from the study population

TABLE 7: AGE DISTRIBUTION OF TYPE 1 DIABETES MELLITUS

AGE GROUP	NUMBER OF PATIENTS
10-15	14
16-20	31
21-25	28
26-30	16
31-35	11
36-40	NIL

Out of 100 patients, majority (31 patients) are in the age group of 16 to 20, followed by 21 to 25 age group (28 patients). None were below 10 years as they are not included in the study and late adulthood are also less.

CHART 5: AGE DISTRIBUTION OF TYPE 1 DIABETES MELLITUS

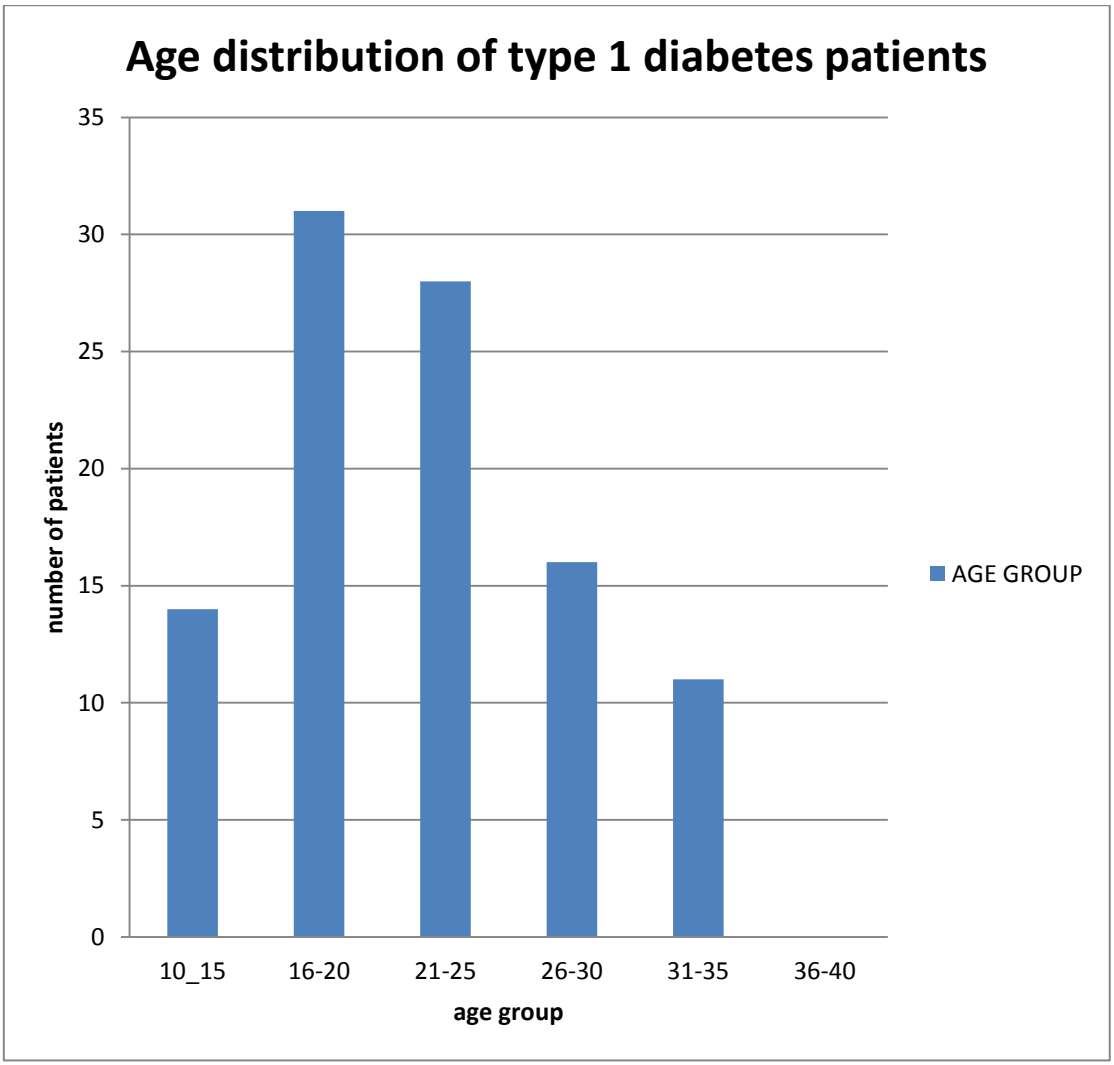


TABLE 8: AGE DISTRIBUTION OF ONSET OF TYPE 1 DIABETES

AGE OF ONSET	NUMBER OF PATIENTS
0-5	6
6-10	20
11-15	51
16-20	16
21-25	7
26-30	NIL

CHART 6: AGE DISTRIBUTION OF ONSET OF TYPE 1 DIABETES

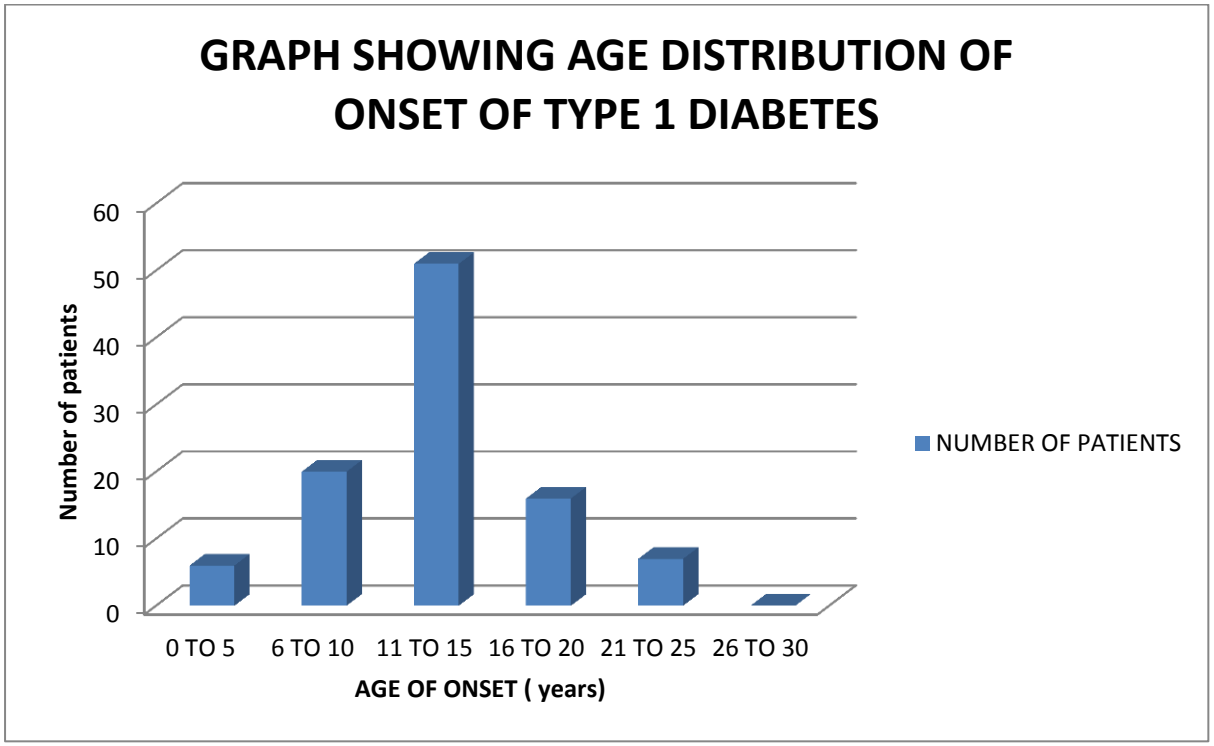


TABLE 9: DISTRIBUTION OF DURATION OF T1DM

DURATION OF DIABETES	NUMBER OF PATIENTS
0-5	6
6-10	20
11-15	51
16-20	16
21-25	7

CHART 7: DISTRIBUTION OF DURATION OF T1DM

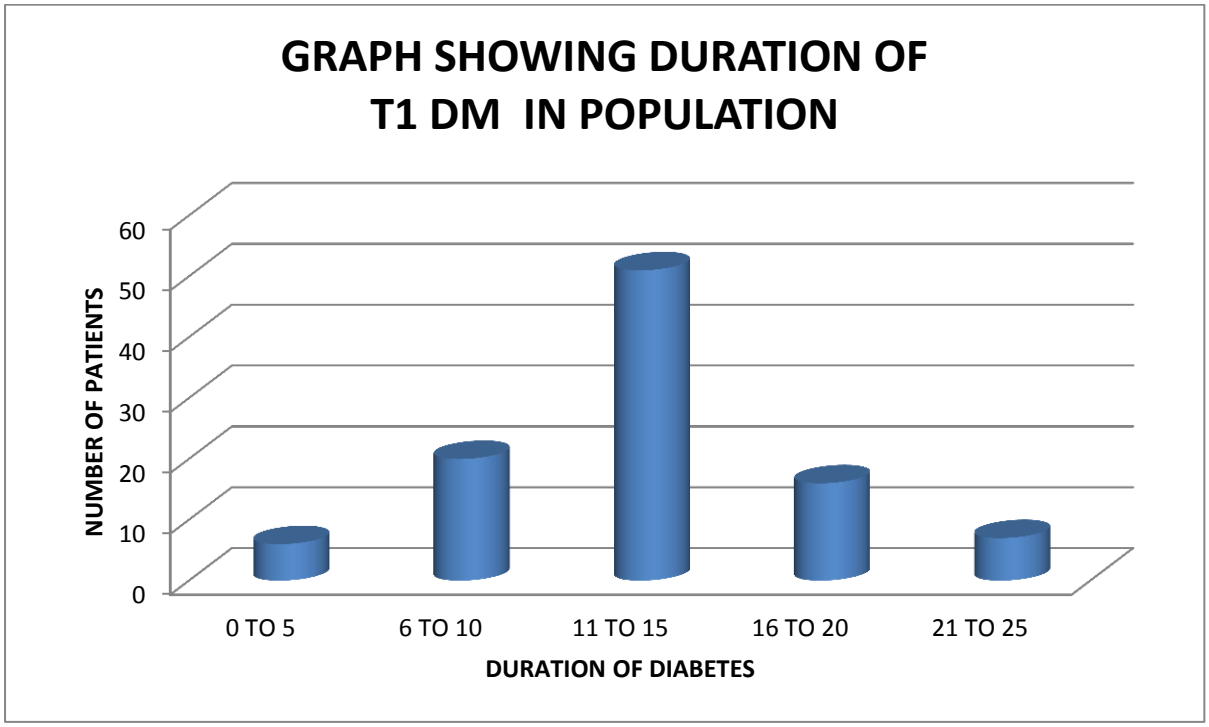


TABLE 10: THYROID AUTOIMMUNE STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS

THYROID AUTOIMMUNITY	GENDER		TOTAL
	MALE	FEMALE	
TPOA NEGATIVE	50	32	82
TPOA POSITIVE	4	14	18

On comparing the female: male ratio by chi square test**,** the p value is 0.006 which is > 0.05 . So, the association between gender and thyroid autoimmunity is very significant indicating that there is significant gender difference among those who are positive for TPOA and those who are negative for the same in type 1 diabetics as per this study.Thus female are more prone to have thyroid autoimmunity than males.

CHART 8: THYROID AUTOIMMUNE STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS

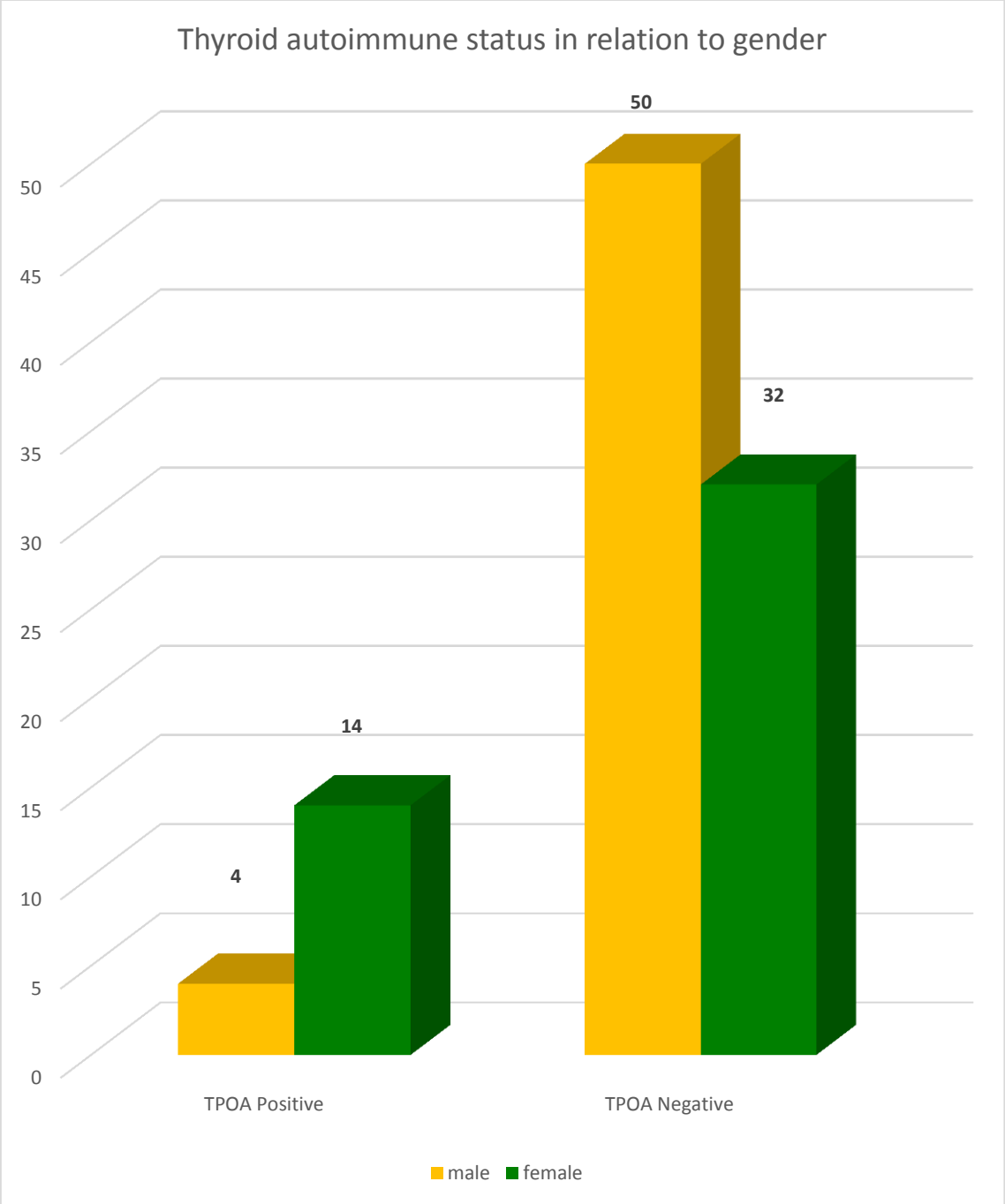


TABLE 11: CORRELATION BETWEEN THYROID FUNCTION AND AUTOIMMUNITY

CATEGORY	HYPOTHYROID	EUTHYROID	TOTAL
TPOA POSITIVE	14	4	18
TPOA NEGATIVE	0	82	82
TOTAL	14	86	100

77% of TPOA positive patients are hypothyroid whereas none of TPOA negative patients are hypothyroid. 100% of hypothyroid patients are TPOA positive whereas none of them are TPOA negative. On comparing these two values by chi square test, the p value is <0.001 which is very statistically significant. So, the association between thyroid autoimmunity and hypothyroidism is very significant indicating that hypothyroidism is more prevalent among TPOA positive individuals than in TPOA negative individuals.

CHART 9: THYROID STATUS OF TPOA POSITIVE PATIENTS

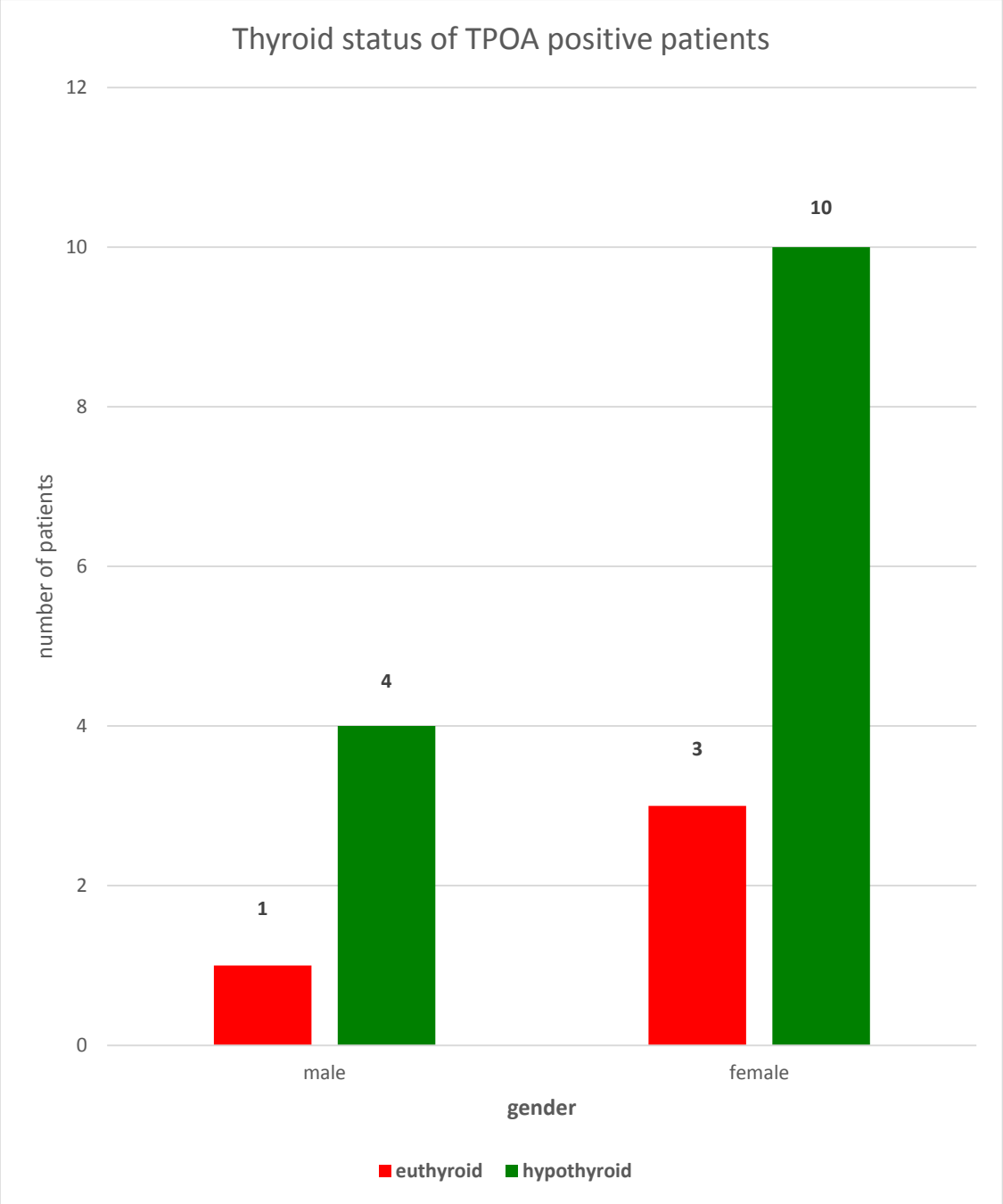


CHART 10: THYROID ANTIBODY STATUS IN STUDY POPULATION

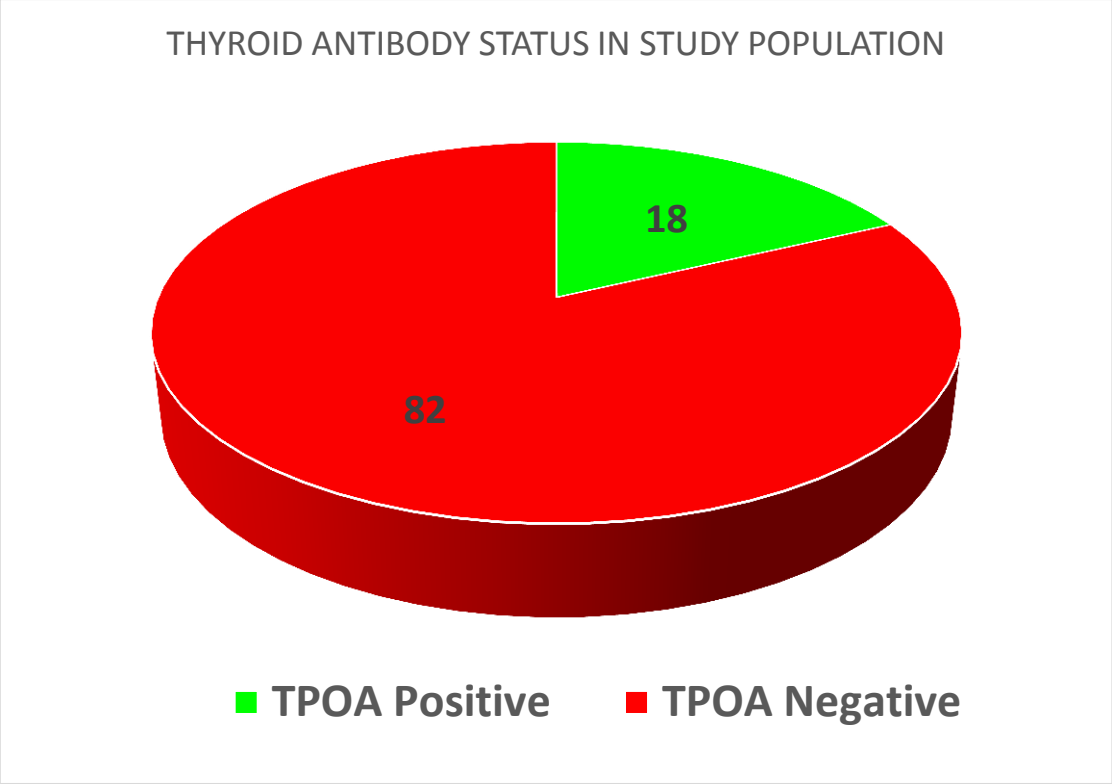


CHART 11: STATUS OF TPOA POSITIVE HYPOTHYROID PATIENTS

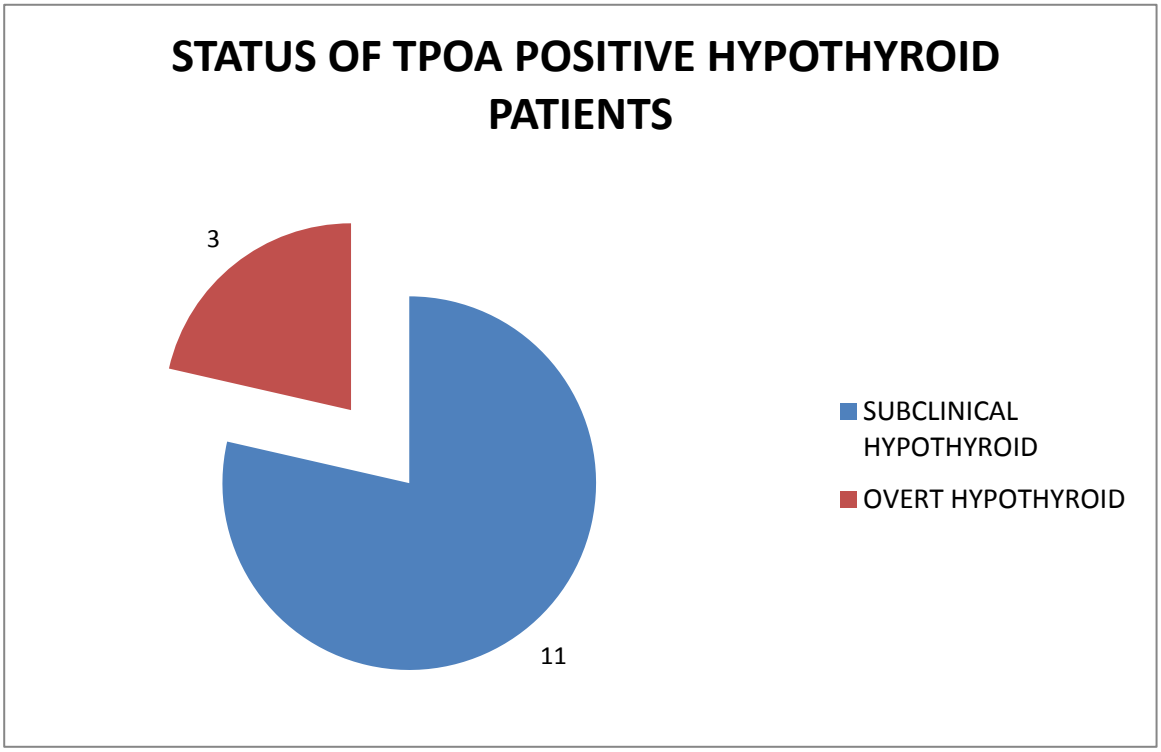


TABLE 12: THYROID AUTOIMMUNITY IN RELATION TO DURATION OF DIABETES

AUTOIMMUNE STATUS	MEAN DURATION OF DIABETES IN YEARS ± SD
TPOA POSITIVE	13.17± 4.5
TPOA NEGATIVE	8.23± 4

On comparing the two means by student t test, the p value is 0.0002 which is < 0.05. So, the association between thyroid autoimmunity and duration of diabetes is very significant indicating that prevalence AITD is related to duration of diabetes as per this study

TABLE 13: THYROID AUTOIMMUNITY IN RELATION TO AGE

THYROID AUTOIMMUNITY	MEAN AGE IN YEARS ±SD
TPOA POSITIVE	25.6± 6.3
TPOA NEGATIVE	20.9± 5

On comparing the two means by student t test**,** the p value is 0.002. So, the association between prevalence of thyroid autoimmunity and age of diabetics is significant, indicating that prevalence of AITD is related to age of the patients as per this study

INTERPRETATION OF RESULTS

- ✓ Most of the TPOA positive individuals have abnormal thyroid function.
- ✓ Abnormal thyroid function is mainly in the form of subclinical.
- ✓ Hyperthyroidism is seldom seen.
- ✓ Hypothyroidism is more common among those who are positive for TPOA

.

DISCUSSION

The study showed the high prevalence of a second organ-specific autoimmune manifestation in individuals with type 1 diabetes. By cross sectional analysis, the prevalence of thyroid autoimmunity in our study population is 18% (18 out of 100). This is in concordance with many other similar studies from various parts of the world.

Most of the studies state the prevalence to be between 15 to 30%.

Roldán MB et al[30]-17.6%;

Prázný M[31]- 22%,

McCanlies E[32]-26.6% ,

Maugendre D et al[33]- 9-17%.

Initial screening of type 1 diabetic patients at the time of diagnosis, for the presence of thyroid antibodies was done by Gemma et al[34] in march 2007 and O Kordonouriet al[35] in 2005 and they found out TPOA positivity in 14.2% and 15.4% respectively.

Study by Aaron Hanukoglu et al[36] is a multicenter cross sectional study which included both newly diagnosed as well as previously diagnosed patients.They give the prevalence as 27%.

Same study says the prevalence in first degree relatives as 25%. Similar single time measurement of antibodies was done by Jennifer M. Barker etal[37] which showed the prevalence as 29%.

Many longitudinal studies have shown a still higher prevalence due to late appearance of thyroid peroxidase antibodies. Adriana Franzese et el[38] diagnosed 50% of AITD patients at initial screening, remaining 50% on follow up. Longitudinal study by Guillermo E. Umpierrezet al[39] has shown it to be 33% but most of tested positive in the beginning itself.

A study by Menon et al[40], conducted in Department of Pediatrics, All India Institute of Medical Sciences, New Delhi in 2001, is the only Indian study available in this context. According to this study TPO prevalence is 54.3%. This is a higher value when compared to our study as well as many other studies. But the limitation of this study is that, only 35 patients were included.

Sarah J. Glastras et al[41] and D Hansen et al[42] give relatively lower values of 7.8% and 12.9% respectively.

While most of the studies included patients of any age, the one by Miguel Fernandez-castaneret al[43] is similar to ours. They included only adult population of age > 14 years and found out the prevalence to be 27.9%

Thus, our study on type 1 diabetes supports previous studies in terms of AITD prevalence.

PREVALENCE OF THYROID DYSFUNCTION IN TYPE1 DIABETES

The reported prevalence of thyroid dysfunction in diabetic population varies widely between studies. But, thyroid dysfunction is seen particularly in those who are positive for thyroid autoimmunity and so the presence of thyroid

autoimmunity is considered to predict the future development of thyroid dysfunction.

O Kordonouri et el[35] performed a long term, large scale study, which included 659 T1D patients. The cumulative incidence of hypothyroidism at 10 years of observation time was 0.69 (0.08) in positive anti- TPO compared with 0.12 (0.05) in 539 patients with negative anti-TPO measurements ($p < 0.001$)

Guillermo E. Umpierrez et al[40] showed a prevalence of thyroid dysfunction to be 33%. All patients had hypothyroidism mostly subclinical. None had hyperthyroidism. 80% of them were positive for TPOA antibodies. Among the TPOA positive individuals, 83% of females and 51% of males developed hypothyroidism on follow up. In their study, TPOA positivity as a predictor for development of thyroid dysfunction was assessed and they found out 67% positive predictive value and a 90% negative predictive value. As per their study, patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54).

Miguel Fernandez-castaner[43] investigated 111 adult T1D patients and found 15.3% thyroid dysfunction, and all of them were positive for thyroid antibodies. None of the TPOA negative individuals developed thyroid function abnormality.

Similarly in the report by Maugendre D et al[33], 24% had abnormal thyroid function among anti-TPO positive patients, while none among those who were negative for the antibody. Gemma C et al is in favour with this.

Similar to the report by Guillermo E. Umpierrez et al[39], all our patients with thyroid dysfunction had only hypothyroidism. Most of them were subclinical. While we didn't find any hyperthyroid patients, hyperthyroidism has been reported as a presentation of thyroid autoimmunity in T1D in several studies.

In the study by Gemma C et al[34], 72% of patients with thyroid autoimmunity developed thyroid dysfunction. 68% hypothyroidism, 4% hyperthyroidism. Roldán MB et al[30] found 11% subclinical hypothyroidism, 3% overt hypothyroidism, 3% subclinical hyperthyroidism and 6% overt hyperthyroidism among those who were positive for AITD.

Adriana Franzese et al[38] investigated 37 DM1 patients with TPO-AB, the prevalence of hypothyroidism was 16% and that of hyperthyroidism was 4% among them. On the whole, in agreement with many similar reports, we observed a higher prevalence of thyroid dysfunction mostly as subclinical hypothyroidism in type 1 diabetes than in the general population, especiallyin patients with positive TPO antibodies.

THYROID AUTOIMMUNITY IN RELATION TO GENDER

Generally thyroid autoimmunity is more common in females than in males, this holds good for T1DM also as per many cross-sectional as well as prospective studies. In our study also, there is preponderance for female to develop thyroid autoimmunity.

Gemma C et al[34] reported female preponderance. 18.3% females had AITD whereas it was 7% in males. Olga Kordonouriet al[35] showed a similar female preponderance and they had 63% of AITD patients as females. Reports by Holl RW et al[46], O Kordonouri et al[35], Adriana Franzese et al[38], Jennifer M. Barker et al[37]support this gender difference.

Miguel Fernandez-castaner et al[43] investigated 814 T1D patients and found a female predominance among TPOA positive patients but not among Tg -Ab positive patients.

Guillermo E. Umpierrez et al[44]found a higher incidence of hypothyroidism in TPO positive females than in antibody positive males, but reported the prevalence of thyroid autoimmunity as equal in both the sex.

Menon PS et al[40] showed that sex doesn't influence the development of thyroid autoimmunity among Indian paediatric population.

Sarah J. Glastras et al[41], D Hansen, FN Bennedbaek et al[47], D Hansen Penny R et al[48] Aaron Hanukoglu et al[36] , Maugendre D et al[33] are in agreement with equal prevalence in both the sex.

As in general population, thyroid autoimmunity is expected to be more common in female.

THYROID AUTOIMMUNITY IN RELATION TO AGE

Many studies have shown that the prevalence of thyroid autoimmunity is high among older patients than younger patients. In our study we find a significant association between increasing age group and thyroid antibodies Olga Kordonouri et al states that the prevalence of significant thyroid antibody titers increases with increasing age of patients and reached its maximum in the 15- to 20year age group. Holl RW et al[46] found the prevalence of AITD to increase dramatically with age. O Kordonouri R, Hartmann et al[35] reports the prevalence to be high in > 12 years age group.

Jennifer M. Barker et al[37], Czerniawska E et al[49] agree the higher prevalence in older age. In the study by Gemma C et al, there is a significant age difference between those who develop thyroid dysfunction and those who remain euthyroid among the TPOA positive subjects. Thyroid function abnormality being more common among those who were older at the onset of diabetes. But age of onset does not influence the positivity for the antibodies. Guillermo E. Umpierrez et al[39], Sarah J. Glastras et al[41], D Hansen et al[47], Maugendre D et al[33] observed no significant age difference. Gregory Goodwin et al[50] is totally against other reports by stating that the risk of thyroid autoimmunity is more in sibling pairs with younger age of onset of diabetes.

The influence of age of onset of diabetes or age of the patient on development of AITD may or may not be there depending on the population.

THYROID AUTOIMMUNITY IN RELATION TO DURATION OF DIABETES

According to many prospective studies incidence of thyroid autoimmunity increases as years pass by since the diagnosis of diabetes. The net result would be a higher prevalence of AITD among patients with longer duration of diabetes than the newly diagnosed cases. In our study there is significant association between duration of diabetes and development of TPOA positive persons.

According to Olga Kordonouri et al prevalence increases with increasing duration. O Kordonouri, R Hartmann et al and Jennifer M. Barker et al favour the same. Adriana Franzese et al found a higher prevalence in those with longer duration particularly when they are in peripubertal age group.

D Hansen et al, Maugendre D et al showed that the duration of diabetes doesn't influence development of AITD. The Indian study by Menon PS et al also observed that the thyroid autoimmunity did not change with duration.

In the report by Guillermo E. Umpierrez et al most subjects with positive TPO antibodies (17 of 18) tested positive at the beginning of the study and remained positive throughout the study period. Only one patient with an initial negative TPO titer developed low-TPO titer after 12 years of follow-up.

In the prospective study by Gemma C et al, TPOA was measured only at the onset of diabetes. Future conversion to positivity was not assessed. But only

one of the initial TPOA negative individuals developed hypothyroidism who later turned out to be positive for antibody.

CONCLUSION

- There is higher prevalence of thyroid autoimmunity in type 1 diabetes mellitus
- Most of the patients develop subclinical form of disease
- Gender, age, and duration of diabetes have a significant association with autoimmune thyroid disease
- Hypothyroidism is much more common than hyperthyroidism in autoimmune thyroid disease associated with type 1 diabetes

SUMMARY

Our study confirms the association between T1DM and autoimmune thyroid disease and suggests all Type 1 Diabetes Mellitus individuals should be screened for autoimmune thyroid disease at the time of diagnosis soon after metabolic control of glucose and to be followed up with annual TSH measurement in case of autoimmune positive individuals.

BIBLIOGRAPHY

1. Jung, EuiSeok, Dong Kyun Han, EunMi Yang, Min Sun Kim, Dae-Yeol Lee, and Chan Jong Kim. "Thyroid autoimmunity in children and adolescents with newly diagnosed type 1 diabetes mellitus", Annals of Pediatric Endocrinology & Metabolism, 2014.
2. Type 1 Diabetes-Associated Autoimmunity: Natural History, Genetic Associations, and Screening. Jennifer M. Barker, The Journal of Clinical Endocrinology & Metabolism 2006 91:4, 1210-1217.
3. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2009; 32(Suppl 1):S62-S67. doi:10.2337/dc09-S062.
4. MirellaHage, Mira S. Zantout, and Sami T. Azar Journal of Thyroid Research Volume 2011, Article ID 439463, 7 pages doi:10.4061/2011/439463
5. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979; 28:1039–57.
6. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2008; 31(Suppl 1):S55–S60.

7. Dabelea D, Pihoker C, Talton JW, et al. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 2011; 34:1628.
8. Opie EL. On the Relation of chronic interstitial pancreatitis to the islands of Langerhans and to diabetes melutus. J Exp Med 1901; 5: 397–428. doi: 10.1084/jem.5.4.397
9. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes 1965; 14: 619–33.
10. Nerup J, Andersen OO, Bendixen G, Egeberg J, Poulsen JE. Anti-pancreatic cellular hypersensitivity in diabetes mellitus. Diabetes 1971; 20: 424–7.
11. Kawasaki E, Gill RG, Eisenbarth GS. Type 1 diabetes mellitus. In: Eisenbarth GS, ed. Molecular mechanisms of endocrine and organ specific autoimmunity. Austin, Texas: R.G. Landes Company; 1999:149-82.
12. Kota SK, Meher LK, Jammula S, Kota SK, Modi KD. Clinical profile of coexisting conditions in type 1 diabetes mellitus patients. Diabetes MetabSyndr 2012; 6: 70–6. doi: 10.1016/j.dsx.2012.08.006
13. Kordonouri O, Klinghammer A, Lang EB, Grüters-Kieslich A, Grabert M, Holl RW.. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002; 25: 1346–50. doi: 10.2337/diacare.25.8.1346

14. Glastras SJ, Craig ME, Verge CF, Chan AK, Cusumano JM, Donaghue KC. The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications. Diabetes Care 2005; 28: 2170–5. doi:10.2337/diacare.28.9.2170
15. Horie I, Kawasaki E, Ando T, Kuwahara H, Abiru N, Usa T, et al. . Clinical and genetic characteristics of autoimmune polyglandular syndrome type 3 variant in the Japanese population. J ClinEndocrinol Metab2012; 97: E1043–50. doi: 10.1210/jc.2011-3109
16. Kawasaki E, Matsuura N, Eguchi K. Type 1 diabetes in Japan. Diabetologia 2006; 49: 828–36. doi: 10.1007/s00125-006-0213-8
17. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974;2: 1279–83. doi:10.1016/S0146736(74)90140-8
18. MacCuish AC, Irvine WJ, Barnes EW, Duncan LJP. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. Lancet 1974;2: 1529–31. doi: 10.1016/S0140-6736(74)90281-5
19. Baekkeskov S, Aanstoot HJ, Christgau S, Reetz A, Solimena M, Cascalho M, et al. . Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature 1990; 347: 151–6. doi: 10.1038/347151a0

20. Lan MS, Lu J, Goto Y, Notkins AL. Molecular cloning and identification of a receptor-type protein tyrosine phosphatase, IA-2, from human insulinoma. DNA Cell Biol 1994; 13: 505–14. doi:10.1089/dna.1994.13.505

21. Wenzlau JM, Juhl K, Yu L, Moua O, Sarkar SA, Gottlieb P, et al. . The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. ProcNatlAcadSci USA 2007;104: 17040–5. doi: 10.1073/pnas.0705894104

22. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, et al. . Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies.Diabetes 1996; 45: 926–33. doi:10.2337/diab.45.7.926

23. Kawasaki E, Nakamura K, Kuriya G, Satoh T, Kobayashi M, Kuwahara H, et al. . Differences in the humoralautoreactivity to zinc transporter 8 between childhood- and adult-onset type 1 diabetes in Japanese patients. ClinImmunol 2011; 138: 146–53. doi:10.1016/j.clim.2010.10.007

24. Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, et al. . Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 1988; 318: 1012–20. doi: 10.1056/NEJM198804213181602

25. Kawasaki E, Takino H, Yano M, Uotani S, Matsumoto K, Takao Y, et al. Autoantibodies to glutamic acid decarboxylase in patients with

IDDM and autoimmune thyroid disease. Diabetes 1994;43:80–6.doi: 10.2337/diab.43.1.80

26. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447: 661–78. doi: 10.1038/nature05911

27. Gabriela Brenta. A View of Diabetes from thyroid corner. Thyroid International. 2011; 3: 2-15

28. MirellaHage, Mira S. Zantout, Sami T. Azar. Thyroid disorders and diabetes mellitus. Journal of Thyroid Research. 2011;1-7

29. Feng X, Jiang Y, Meltzer P, Yen PM. Thyroid hormone regulation of hepatic genes in vivo detected by complementary DNA microarray. Mol. Endocrinol. 2000; 14(7):947-955.

30. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with Type 1 diabetes mellitus: Diabetes Nutr Metabolism 1999 Feb;12(1):27-31.

31. Prázný M, Skrha J, Límanová Z, Vanícková Z, Hilgertová J, Prázná J,Jaresová M, Stríz I. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control: Physiological Research.2005;54(1):41-8.

32. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, Libman A, Swan JS. Hashimoto's thyroiditis and insulin-dependent diabetes mellitus:

differences among individuals with and without abnormal thyroid function: Journal of ClinEndocrinol Metabolism 1998 May; 83(5):1548-51

33. Maugendre D, Guilhem I, Karacatsanis C, Poirier JY, Leguerrier AM, Lorcy Y, Derrien C, Sonnet. Anti-TPO antibodies and screening of thyroiddysfunction in type 1 diabetic patients: Ann Endocrinol (Paris). 2000 Dec;61(6):524-530.

34. Gemma C. González, Ismael Capel, José Rodríguez-Espinosa, Didac Mauricio, Alberto de Leiva,Antonio Pérez. Thyroid Autoimmunity at Onset of Type 1 Diabetes as a Predictor of Thyroid Dysfunction: Diabetes Care 2007; 30:1611-1612

35. O Kordonouri, R Hartmann, D Deiss, M Wilms , A Grüters-Kieslich**.** Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty: Archives of Disease in Childhood 2005; 90:411-41

36. Aaron Hanukoglu, AvraamMizrachi,IlanDalall. Extrapancreatic Autoimmune Manifestations in Type 1 Diabetes Patients and Their First-Degree Relatives: Diabetes Care 2003; 26:1235-1240

37. Jennifer M. Barker, Jeesuk Yu, Liping Yu, Jian Wang, Dongmei Miao FeiBao, Edward Hoffenberg, Jerald C. Nelson, Peter A. Gottlieb. Autoantibody "Subspecificity" in Type 1 Diabetes: Diabetes Care2005; 28:850-855.

38. Adriana Franzese, PietroBuono,MassimoMascolo,AnnaLusia Leo. Thyroid Autoimmunity Starting During the Course of Type 1 Diabetes Denotes a Subgroup of Children With More Severe Diabetes: Diabetes care 2000; 23, No. 8: 1201-2.
39. Guillermo E. Umpierrez, Kashif A. Latif, Mary Beth Murphy, Helen C.Lambeth, Frankie Stentz, Andrew Bush. Thyroid Dysfunction I Patients With Type 1 Diabetes: Diabetes Care 2003;26:1181-118.
40. Menon PS, Vaidyanathan B, Kaur M. Autoimmune thyroid disease in Indian children with type 1 diabetes mellitus.J PediatrEndocrinolMetab. 2001 Mar;14(3):279-86.
41. Sarah J. Glastras, Maria E. Craig, Charles F. Verge, Albert K. Chan, Janine M. Cusumano,and Kim C. Donaghue. The Role of Autoimmunity at Diagnosis of Type 1 Diabetes in the Development of Thyroid and Celiac Disease and Microvascular Complications: Diabetes Care 2005;28:2170-2175.
42. Bilimoria KY, Pescovitz OH, DiMeglio LA. Autoimmune thyroid dysfunction in children with type 1 diabetes mellitus: screening guidelines based on a retrospective analysis. J PediatrEndocrinolMetab. 2003 Oct-Nov;16(8):1111-7.
43. MiguelFernandez-castaner, AnaMolina, Luzlopez-Jimenez JoseM.Gomez, Juanseler. Clinical Presentation and Early course of Type 1 Diabetes in

Patients With and Without Thyroid Autoimmunity: Diabetes Care 1999;22:377–381.

44. Guillermo E. Umpierrez, Kashif A. Latif, Mary Beth Murphy, Helen C.Lambeth, Frankie Stentz, Andrew Bush. Thyroid Dysfunction in Patients With Type 1 Diabetes: Diabetes Care 2003;26:1181-1185.
45. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, LibmanA,Swan JS. Hashimoto's thyroiditis and insulin-dependent diabetes mellitus: differences among individuals with and without abnormal thyroid function: Journal of ClinEndocrinol Metabolism 1998 May;83(5):1548-51
46. Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: Effect of age, gender and HLA type: Hormone Research 1999;52(3):113-8.
47. D Hansen, FN Bennedbaek, M Hoier-Madsen, L Hegedus, and BB Jacobsen . A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes: European Journal of Endocrinology 2003; Vol 148, Issue 2: 245-251.
48. D Hansen, Penny R, Snyder R, Goldstein I, Graves D. Antithyroid in Hispanic patients with type I diabetes mellitus. Prevalence and significance: Am J Dis Children 1986 Dec;140(12):1278-80.
49. Czerniawska E, Szalecki M, Piatkowska E, Młynarski W, Bodalski J, Lewiński A. Prevalence of thyroid antibodies (TPO and ATG) at the onset of

type 1 diabetes mellitus in children treated in two diabetes centres in Łódź and Kielce: Med WiekuRozwoj. 2003 Apr -Jun; (2):223-8

50. Gregory Goodwin, Lisa K. Volkening, d Lori M.B. Laffel. Younger Age at Onset of Type 1 Diabetes in Concordant Sibling Pairs Is Associated With Increased Risk for Autoimmune Thyroid Disease: Diabetes Care 2006; 29:1397-1398.

ABBREVIATIONS

AD	-	Addison disease
AITD	-	Auto Immune Thyroid Disease
APS	-	Autoimmune Polyglandular Syndrome
CD	-	Coeliac disease
GADA	-	Glutamic Acid Decarboxylase Antibodies
GDM	-	Gestational Diabestes Mellitus
GLUT4	-	Glucose transporter type 4
IAA	-	Insulin autoantibodies
ICA	-	Islet Cell antibodies
IDDM	-	Insulin Dependent Diabetes Mellitus
MC4R	-	Melanocortin 4 receptor
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
PEPCK	-	PhosphoenolpyruvateCarboxykinase
T1DM	-	Type1 Diabetes Mellitus
T3	-	Tri iodothyronine
T4	-	Thyroxine
TA Ab	-	Thyroid autoantibodies
TG Ab	-	Thyroglobulin antibody

Tm Ab	-	Thyroid microsomal antibody
TPO	-	Thyroid Peroxidase
TRH	-	Thyrotropin Releasing Hormone
TSH	-	Thyroid Stimulating Hormone

Ref no 4531/ME I/P.G/2014 Office of the dean
Government Mohan Kumaramangalam
Medical college, Salem 30

Ethical committee Meeting held on 30.07.2014 at 12 noon in the Dean's Chamber, Government Mohan kumaramangalam Medical College Hospital, Salem 01, The following members attended the meeting.

MEMBERS.

1. Dr.N. MOHAN MS., FICS., FAIS., FMMC.,Dean, Member secretary ECIRB
2. Dr. A.P.RAMASAMY, MD., Chairman, ECIRB.External Clinician
3. Dr. V.DHANDAPANI, M.D., Deputy Chairman,External Social Scientist, Salem
4. Dr. S.MOHAMED MUSTHAFA, M.D, Professor Pharmacology,GMKMC, Salem
5. Dr. S.R.SUBRAMANIAN, M.D, Professor & HOD of Medicine GMKMCH,Salem, Internal Clinician.
6. Dr. SINDHUJA, M.D., Professor of OG, GMKMCH,Salem, Internal Clinician.
7. Mr.S.SHANMUGAM, B.Sc.,B.L., Advocate, External Legal Expert.
8. Mr.S.SUBRAMANIAM, B.Sc.,C.A., Chartered accountant, External Lay person.

S.NO	NAME OF THE PRESENTOR WITH ADDRESS	TOPIC	NAME OF THE GUIDE WITH ADDRESS	WHETHER IT IS APPROVED OR NOT
10.	Dr.Prasannakumar P Second year MD(GM) Post Graduate student GMKMC Salem 30	Prevalence study of thyroid disorders in type 1 diabetes mellitus	Dr.Thangaraju, MD., Professor of General Medicine	**Approved**

The Ethical Committee examined the studies in detail and is pleased to accord Ethical Committee approval for the above Post Graduate of this college to carry out the studies with the following conditions.

1. He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or government.
2. He should inform the institutional Ethical committee in case of any change of study or procedure site.
3. He should not deviate from the area of the work for which Ethical clearance applied. He should inform the IEC immediately in case of any adverse events or serious

adverse reactions.

4. He should abide to the rules and regulations of the Institution.
5. He should complete the work within the specific period and apply for if any Extension of time is required she should apply for permission again and do the work.
6. He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. He should not claim any funds from the institution while doing the work or on completion.
8. He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN

21/02/14

PROFORMA

- NAME :
- SEX :
- AGE :
- AGE OF ONSET OF DISEASE :
- DURATION OF DIABETES :
- SYMPTOMS / SIGNS

  OF HYPOTHYROIDISM :
- SYMPTOMS / SIGNS

  OF HYPERTHYROIDISM :
- CO EXISTING MEDICAL

  ILLNESS :
- THYROID PROFILE

➢ TOTAL T3 :

➢ TOTAL T4 :

➢ TSH :

➢ TPO ANTIBODY :

MASTER CHART

s.no	SEX	AGE	AGE OF ONSET	DURATION	T3	T4	TSH	TPO	THYROID STATUS
1	M	23	11	12	86	6.8	1.4	N	EUTHYROID
2	M	32	15	17	98	7.4	8.9	P	SUBHYPOTHYROID
3	F	21	8	13	91	11.2	0.7	N	EUTHYROID
4	M	23	18	13	89	6.9	1.4	N	EUTHYROID
5	M	27	21	6	104	8.4	1.9	N	EUTHYROID
6	M	21	15	6	126	8.9	1.6	N	EUTHYROID
7	F	32	22	10	79	7.5	2.3	N	EUTHYROID
8	F	34	17	17	24	3.1	18	P	HYPOTHYROID
9	M	28	21	7	92	5.8	3.1	N	EUTHYROID
10	F	31	17	14	78	6.4	1.6	N	EUTHYROID
11	F	24	14	10	82	8.8	2.8	N	EUTHYROID
12	M	30	17	13	94	6.9	3.4	N	EUTHYROID
13	F	22	9	13	109	9.4	2.5	N	EUTHYROID
14	F	25	7	18	46	2.3	12	P	HYPOTHYROID
15	F	16	6	10	134	7.4	2.3	N	EUTHYROID
16	M	21	10	11	143	6.3	0.6	N	EUTHYROID
17	M	15	9	6	86	8.6	1.7	N	EUTHYROID
18	F	27	12	15	80	6.5	9.2	P	SUBHYPOTHYROID
19	M	19	11	8	95	10.7	2.4	N	EUTHYROID
20	M	29	15	14	88	9.5	3	N	EUTHYROID
21	M	21	13	8	125	6.7	3.5	N	EUTHYROID
22	F	27	12	15	128	5.8	2.7	P	EUTHYROID
23	M	31	17	14	112	6.1	1.8	N	EUTHYROID
24	F	21	15	6	92	11.4	2.8	N	EUTHYROID
25	F	35	21	14	86	9.4	8	P	SUBHYPOTHYROID
26	M	31	21	10	82	6.4	2.3	N	EUTHYROID
27	F	31	11	20	77	9.3	1.6	N	EUTHYROID
28	M	27	16	11	104	10.1	2.8	N	EUTHYROID
29	M	24	13	11	93	8.2	7.4	P	SUBHYPOTHYROID
30	F	29	15	14	89	6.4	2.7	N	EUTHYROID
31	F	25	10	15	132	8.4	3.1	N	EUTHYROID
32	F	19	12	7	118	9.6	1.9	N	EUTHYROID
33	M	16	8	8	112	10.4	3.2	N	EUTHYROID
34	F	19	7	12	79	5.9	1.8	N	EUTHYROID
35	M	26	5	21	86	8.2	8	P	SUBHYPOTHYROID
36	F	14	5	9	112	6.8	4.2	N	EUTHYROID
37	F	27	12	15	96	9.4	3.1	N	EUTHYROID
38	M	17	14	3	128	7.9	2.4	N	EUTHYROID
39	M	18	11	7	134	9.8	1.6	N	EUTHYROID
40	M	22	7	15	108	10.6	2.7	N	EUTHYROID
41	F	15	4	11	89	5.5	4.1	N	EUTHYROID
42	M	16	5	11	84	5.9	2.6	N	EUTHYROID
43	F	18	6	12	112	6.4	2.2	N	EUTHYROID
44	F	32	16	16	135	5.6	7.8	P	SUBHYPOTHYROID
45	M	26	21	5	107	6.7	2.5	N	EUTHYROID
46	M	32	21	11	97	7.5	3.6	N	EUTHYROID
47	F	31	14	17	78	5.5	1.6	P	TPO EUTHYROID
48	F	26	11	15	69	5.9	8.4	N	EUTHYROID
49	F	16	5	11	79	6.2	2.4	N	EUTHYROID
50	M	21	12	9	90	5.8	3.5	N	EUTHYROID

s.no	SEX	AGE	AGE OF ONSET	DURATION	T3	T4	TSH	TPO	THYROID STATUS
51	M	17	11	6	102	7.1	2.7	N	EUTHYROID
52	M	17	9	8	116	5.7	4.1	N	EUTHYROID
53	F	19	7	12	93	5.6	8.4	P	SUBHYPOTHYROID
54	F	23	11	12	79	5.9	3.5	N	EUTHYROID
55	M	16	12	4	88	7.3	4.2	N	EUTHYROID
56	M	21	15	14	97	5.7	2.7	N	EUTHYROID
57	M	17	14	3	115	6.7	3.5	N	EUTHYROID
58	F	14	12	2	152	7.3	4.2	N	EUTHYROID
59	F	16	13	3	95	6.8	3.1	N	EUTHYROID
60	M	18	15	3	80	5.7	1.6	N	EUTHYROID
61	F	17	13	4	31	2.1	23	P	HYPOTHYROID
62	M	19	14	5	110	5.9	1.6	N	EUTHYROID
63	M	23	17	6	118	6.4	2.2	N	EUTHYROID
64	M	21	18	3	96	8.1	3.6	N	EUTHYROID
65	F	15	9	6	79	6.2	4.1	N	EUTHYROID
66	F	19	11	8	89	5.7	2.7	N	EUTHYROID
67	F	20	14	6	84	6.7	4.2	N	EUTHYROID
68	F	21	9	12	123	5.9	6.8	P	SUBHYPOTHYROID
69	M	22	8	14	115	6.2	3.1	N	EUTHYROID
70	F	24	15	9	97	5.8	1.7	P	TPO EUTHYROID
71	M	17	7	10	78	6.7	2.4	N	EUTHYROID
72	F	15	8	7	94	5.8	1.8	N	EUTHYROID
73	F	15	5	10	150	7.4	9.5	P	TPO EUTHYROID
74	M	14	11	3	132	7.1	3.8	N	EUTHYROID
75	M	17	13	4	105	6.2	4.2	N	EUTHYROID
76	M	14	11	3	91	5.5	1.7	N	EUTHYROID
77	M	18	15	3	82	6.2	1.9	N	EUTHYROID
78	M	15	13	2	94	8.1	2	N	EUTHYROID
79	F	17	11	6	87	7.4	1.4	N	EUTHYROID
80	F	19	14	5	112	6.3	0.7	N	EUTHYROID
81	M	16	14	2	135	5.9	1.5	N	EUTHYROID
82	M	19	12	7	127	6.3	0.8	N	EUTHYROID
83	M	21	16	5	109	8.2	2.1	N	EUTHYROID
84	F	26	19	7	93	5.6	7.4	P	SUBHYPOTHYROID
85	F	15	11	4	91	5.9	3.1	N	EUTHYROID
86	M	19	14	5	84	6.4	2.5	N	EUTHYROID
87	M	25	17	8	127	5.7	1.2	N	EUTHYROID
88	M	26	15	11	104	7.8	0.7	N	EUTHYROID
89	M	21	17	4	97	6.9	4.1	N	EUTHYROID
90	F	17	12	5	81	6.1	3.6	N	EUTHYROID
91	F	15	8	7	78	5.7	7.9	P	SUBHYPOTHYROID
92	M	19	12	7	84	6.2	4	N	EUTHYROID
93	M	22	16	6	132	6.7	1.4	N	EUTHYROID
94	F	21	14	7	127	7.4	2.4	N	EUTHYROID
95	F	17	12	5	108	7.8	0.7	N	EUTHYROID
96	M	19	14	5	79	5.7	4.1	N	EUTHYROID
97	M	25	18	7	89	6.4	1.5	N	EUTHYROID
98	M	27	13	14	92	7.2	3.2	N	EUTHYROID
99	M	30	15	15	96	6	7.6	P	TPO EUTHYROID
100	F	23	17	6	124	6.6	2.2	N	EUTHYROID

KEY TO MASTER CHART

M	–	Male
F	–	Female
T3	–	Triiodothyronine
T4	–	Tetraiodothyronine
Subhypothyroid	–	Subclinical hypothyroidism
TPOA euthyroid	–	TPOA positive euthyroidism
P	–	Positive
N	–	Negative