CLINICAL STUDY OF HYPOTHYROIDISM IN PATIENTS OF DIABETES MELLITUS

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for the award of

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CERTIFICATE

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INTRODUCTION[1]

Diabetes is the most common endocrine disorder seen in clinical practice. The prevalence of diabetes in West is between 6-7.6 %. India has already become the "diabetes capital" of the world with over 4 crore affected patients. Between 1995 and 2025, there is predicted to be a 35% increase in the worldwide prevalence of diabetes. The rising number of people with diabetes will occur mainly in population of developing countries, leading to more than 300 million people with diabetes globally by 2025. The disease has tremendous impact on the quality of life, and morbidity and mortality occur ue to complications that affect the small vessels resulting in retinopathy, nephropathy, neuropathy and large vessels resulting in ischemic heart disease and stroke.

Various studies done suggest that thyroid disorders are more common in diabetics (both type I and type II) than in the general population, highest in type I diabetic females and lowest in type II diabetic males.

Thyroid dysfunction is more common in older patients.Several alterations in thyroid function are found in DM.The most profound changes occur in patients with IDDM. Plasma T4 is normal but plasma T3 is diminished.Plasma level of T3 is elevated in DKA or in

patients with severely uncontrolled diabetes.Thyroid peroxidase (TPO) antibodies (also called as anti-microsomal antibodies, AMA) is found in large percentage of IDDM with elevated TSH levels and when positive in those with normal TSH levels, indicate future probability of the development of hypothyroidism in a diabetic.Patients with hypothyroidism usually present with vague and subtle symptoms like generalized weakness, lethargy, weight gain and some present with hoarseness of voice to ENT surgeon, decreased urine output (nephritic syndrome) to nephrologist, carpal tunnel syndrome to neurologist, cardiomegaly to cardiologist, irregular and heavy bleeding to gynecologist. Also clinically, it is frequently difficult to differentiate the clinical features of hypothyroidism from that of diabetes mellitus like peripheral neuropathy and autonomic neuropathy.

Thyroid function tests are especially recommended in patients with clinical suspicion and /or unexplained changes in glycemic control or serum cholesterol. The ability to diagnose and treat unsuspected hypothyroidism in these population may greatly enhance the quality of life.

OBJECTIVES

1. To do the clinical study of hypothyroidism in patients of diabetes mellitus, during the study period in Coimbatore Medical College.

2. To study the patients having both endocrine disorders and their thyroid function status, in relation to the age and sex, the type of diabetes , age at detection of either condition, the clinical features, relation to the lipid profile, body mass index and other co-morbid conditions.

REVIEW OF LITERATURE[2,3,4]

HISTORICAL REVIEW

According to Thomson, Greeks referred thyroid gland as bronchocele (hernia or swelling of the windpipe). The Latin term introduced by Pliny and Juvenal, "tumid gutter" (swollen throat) eventually became the French "goitre", and later the English "goitre", and in America, goiter. Wharton in 1956 named the glands glandulae thyroidaeae (thyroid glands) because of their anatomical proximity to the thyroid cartilage. Early belief that it enhanced the beauty of women , are evidenced by the numerous paintings of the old Dutch, German and Italian masters, many of which depict madonnas with an enlarged thyroid.

The relationship between the thyroid gland and the various body functions was studied by experimental thyroidectomy as early as 1827, and the concept of an internal secretory function was formulated by King 9 years later. The injection of a glycerine extract of thyroid to relieve myxedema, and finally the feeding of lightly cooked sheep thyroid with successful relief of disease completed the background for modern knowledge about thyroid function.

Meckel (1806) was probably the first person to describe systematically the physiological enlargements of the thyroid in relation to adolescence, menstruation, defloration and pregnancy. Hippocrates gave practical association of various features of exophthalmic goitre. Juvenal's query "who wonders at a swollen throat in the Alps?" indicates that goitre was endemic in that area in the first century. Sir Robert Mecarrision studied the goitre in the foothills of Himalayas in 1905 for 30 years. Early concepts about the etiology of goiter were thought to be due to drinking water coursing through limestone deposits or drinking snow water.

ANATOMY OF THE THYROID GLAND [5,6]

The thyroid gland consists of two symmetrical lobes united in front of the second, third and fourth tracheal rings by an isthmus of gland tissue.It is enclosed by an envelope of pretracheal fascia. Each lateral lobe is pear shaped with a narrow upper pole and is triangular on cross section with lateral, medial and posterior surfaces. The lateral surface is overlapped by strap muscles.

The medial surface is along the larynx and upper trachea. The posterior surface is in relation to the carotid sheath and parathyroid glands. Pyramidal lobe projecting upwards from the isthmus represents the glandular tissue at the caudal end of the thyroglossal duct. Arterial supply is by superior and inferior thyroid and thyroidea ima arteries and venous drainage is into the jugular venous system by superior, middle and inferior thyroid veins. Lymphatic drainage is into the deep cervical nodes.

DEVELOPMENT OF THE THYROID GLAND[7]

The thyroid gland appears as an epithelial proliferation in the floor of the pharynx between the tuberculum impar and the copula at a point later indicated by foramen caecum. It then descends in front of the pharyngeal gut as a bilobed diverticulum, while remaining connected to the tongue by a narrow canal, the thyroglossal duct, which later disappears, to reach its final position in front of the trachea in the seventh week. The gland begins to function at about the end of the third month of intrauterine life, at which time the first follicles containing colloid become visible. Parafollicular or C cells are derived from the ultimobranchial body. They secrete calcitonin.

SYNTHESIS AND SECRETION OF THYROID HORMONES [8]

Chemistry

The principal hormones secreted by the thyroid are thyroxine (T4) (93%) and tri- iodothyronine (T3) (7%). Both are iodine containing amino acids. Almost all the T4 is eventually converted to T3 in the tissues. T3 is present in blood in much smaller quantities and persists for a much shorter time than does T4.

Physiologic Anatomy

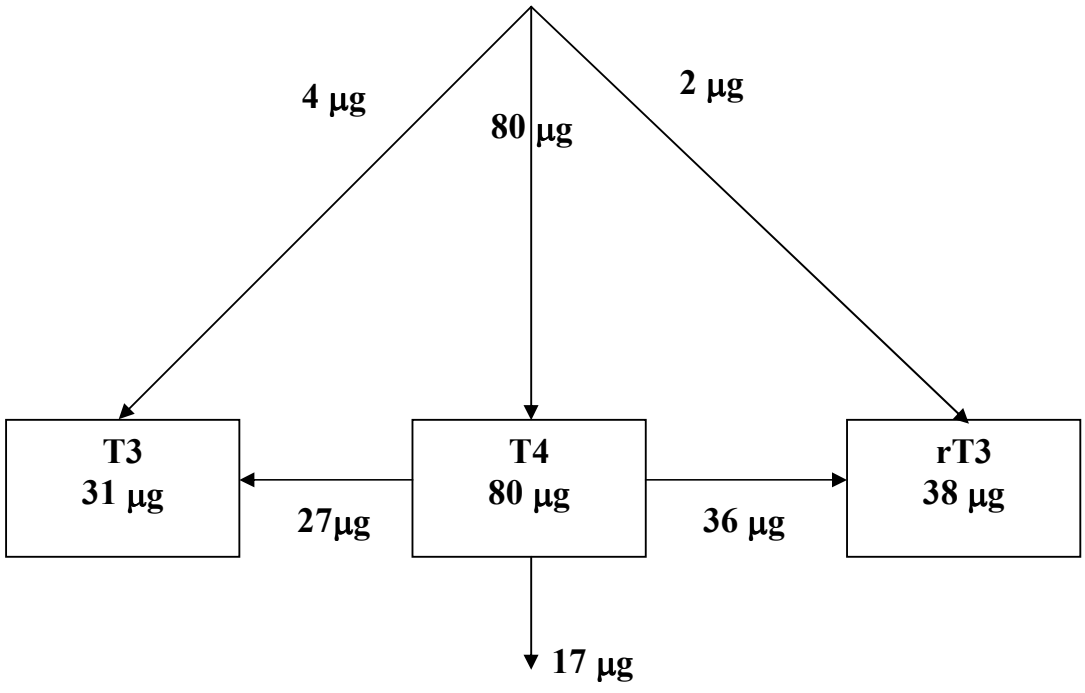
The major constituent of colloid present in the follicles is the glycoprotein, thyroglobulin (Tg) which is bound to thyroid hormones and is synthesised by endoplasmic reticulum and golgi apparatus.Each molecule of thyroglobulin contains about 70 tyrosine amino-acids.When secreted, colloid is ingested by the thyroid cells, the peptide bonds are hydrolysed, and free T4 and T3 are discharged into the capillaries.

Hormone synthesis:

Iodines ingested are absorbed from GIT into the blood. A fifth of it is taken up by the thyroid gland for hormone synthesis.The minimum daily iodine intake that will maintain normal thyroid function is 150 μg in adults.

- Iodine pump (iodine trapping) – Na^{++} & I^- are co-transported into the thyroid cell by secondary active transport.
- Oxidation of I^- to form nascent iodine (I^O) or I_3^- by thyroid peroxidase.
- Organification of Tg – is by binding of oxidised iodine to tyrosine molecule attached to Tg forming mono-iodotyrosine (MIT) and di-iodotyrosine (DIT). T3 is formed by condensation of MIT with DIT. A small amount of rT3 is formed by condensation of DIT with MIT. Two DIT molecules condense to form T4.

Thyroid Gland[9]



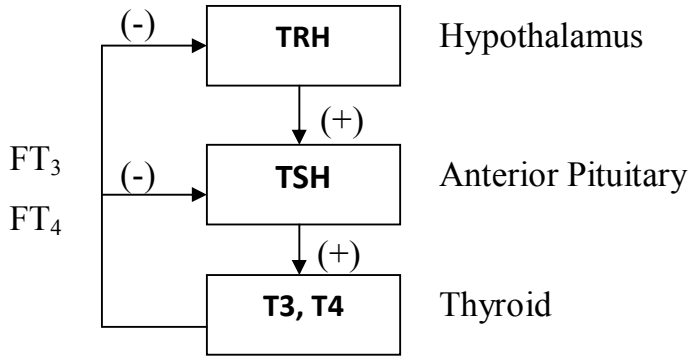
Protein Binding:

Normally, 99.98 % of T4 in plasma is bound, so FT4 is only 2 ng/dl and 99.8% of T3 is protein bound, so FT3 is only 0.3 ng/dl. The lesser binding of T3 correlates with the fact that T3 has a shorter half life than T4 and that its action on the tissues is much more rapid. The major binding protein is TBG (Thyroxine binding globulin); others are TBPA (Thyroxine binding prealbumin or Transthyretin) and Albumin. TBG levels are increased in pregnancy and with drugs-estrogens, methadone, heroin, major tranquilizers and clofibrate; and decreased by glucocorticoids, androgens, danazol and asparagine. But free levels of T3 and T4 are normal so that the patients are euthyroid.

PHYSIOLOGIC FUNCTONS OF THE THYROID HORMONES

1. Increase in the transcription of large numbers of genes by binding of T3, T4 to nuclear receptors.
2. Increase in cellular metabolic activity by increasing the number and activity of mitochondria and increased activity of Na-K-ATPase
3. Skeletal growth and closure of epiphyses, development of brain in fetus and early postnatal life.
4. Specific body mechanisms – Enhanced carbohydrate and fat metabolism, increased BMR, increased cardiac output and heart rate, increased respiration and gastrointestinal motility, excitatory effects on CNS and increase in the rates of secretion of insulin, PTH and glucocorticoid. Also necessary for normal muscle and sexual functions.

REGULATION OF THYROID SECRETION



Human TSH is a glycoprotein consisting of two subunits α and β. TSH-α is identical to the α subunit of LH, FSH and HCG–α and β subunit provides the functional specificity.

INVESTIGATIONS FOR THE ASSESSMENT OF THYROID STATUS [10,11]

The clinical features of hypothyroidism develop insidiously over months or years; and the diagnosis is often delayed. However once diagnosed, the treatment is simple , yet very effective. Further, the late manifestations of hypothyroidism, including cardiac complications are preventable by early detection and institution of early treatment. Hence hypothyroidism should be suspected in any patient with compatible symptoms. A careful history and a high index of suspicion is the key in early diagnosis.

In suspected primary hypothyroidism, the plasma TSH is the best initial diagnostic test. Plasma TSH is the first parameter to rise in primary hypothyroidism. A normal value excludes primary hypothyroidism and a markedly elevated value (more than 15μU/ml) is diagnostic of hypothyroidism. A level between 5-15 μU/ml usually indicates subclinical hypothyroidism. Plasma total T4 (TT4) or free T4 (FT4) is the next parameter to fall below normal level. A combination of a raised TSH concentration and a low T4 concentration has a great diagnostic value for primary hypothyroidism than serum T3 level.

In central hypothyroidism, serum T4 and T3 are low and serum TSH is low or inappropriately normal due to the presence of inactive isomers of TSH in the blood.

TSH assays: Second generation assays, namely immuno-radiometric assays (IRMA) or immuno-enzymometric assays have a sensitivity of 0.1-0.2 μU/ml.Third generation assays, namely immuno-flourometric or immuno-chemiluminometric assays have a sensitivity of 0.01-0.02 μU/ml

Plasma T4: Conventional T4 assays measure total (bound + unbound) hormone, which correlates well with free hormone concentration. However it varies with TBG levels.Hence FT4 (free T4) is the most reliable measure of clinical thyroid status and is especially recommended in

- Monitoring treatment – thyroid replacement or suppression.
- Hospitalized patients showing symptoms of non thyroidal illnesses.
- Pregnant women suffering from thyroid disorders.
- Patients known to take certain drugs which will interfere with total T3 and total T4 results
- When patient's TFTs do not correlate with clinical history.

Free T4 index (FT4I): It is proportional to the actual concentration of FT4 in plasma and hence an indirect measure of FT4. It is the product of total T4 and RT3U (T3 Resin uptake). RT3 U is obtained by an in-vitro uptake test, in which the serum is enriched with labeled T3 and incubated with insoluble resin that binds free hormone. RT3U is the percentage of labeled hormone that is taken up by the resin.

TT3 and FT3: are useful in patients with pituitary disease or after prolonged suppressed thyrotroph function due to prior thyrotoxicosis.

MiscellaneousTests:

1. Thyroid auto-antibodies: Three types are useful. Anti-microsomal antibody (AMA), also called anti-thyroperoxidase antibodies (anti-TPO) are positive in almost all cases of Hashimotto's disease and ~ 80% of Grave's disease. Grave's disease with elevated titers of AMA should direct surgeon to perform a more limited thyroidectomy to avoid future hypothyroidism. TSHRAb (TSH receptor antibody) is a predictor of relapse of hyperthyroidism in Grave's disease.

Table 1: Auto-antibodies in Thyroid Disorders (%)

Group	AMA	TgAb	TSHRAb
General population	8-27	5-20	0
Autoimmune thyroiditis	90-100	80-90	10-20
Grave's disease	50-80	50-70	80-95
Relatives of patients	40-50	40-50	0
IDDM patients	40	40	0
Pregnant women	14	14	0

2. TRH stimulation test : The TSH response to TRH is of less importance in the diagnosis of hypothyroidism, confined only for suspected hypothalamic disease

3. RAIU : Radioactive Iodine Uptake Test uses isotopes I^{123} and Tc^{99} for localizing functional thyroid tissue including ectopic thyroid, diagnosing thyroid agenesis in congenital hypothyroidism, differential diagnosis of hyperthyroidism (high uptake in Grave's and low in thyroiditis), identifying a toxic / cold nodule and postoperative / ablation evaluation of thyroid carcinoma.

4. Ultrasound scan of thyroid : is done using 10 MHz to detect nodules and cysts more than 3 mm in diameter.Also used to see echogenicity, determination of blood flow and vascularity, guidance in FNAC and for aid in treatment – cyst aspiration, nodule injection etc.

5. MRI, CT and PET scans : are used to assess the size of large goitres those extending into mediastinum, imaging of adjoining structures and impingement of goiter on them, locating areas of abnormal uptake.MRI is preferable when metastasis or vascular invasion is considered and in those allergic to iodine contrast media.

6. FNAC : is used to evaluate both palpable and nonpalpable (under USG guidance) nodules. .But it is of limited utility in differentiating follicular neoplasms. Malignancy is diagnosed based on capsular invasion.

SICK EUTHYROID SYNDROME [12]

Any acute, severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease, making these measurements potentially misleading. The major cause of these hormonal changes is the release of cytokines. The term refers to the global pattern of changes in thyroid physiology that occurs during illness due to suppression of pituitary release of TSH, which is either endogenous, because of loss of hypothalamic input or worsened by some agents, such as dopamine and glucocorticoids, commonly given to such patients. The changes in thyroid function are a continuum, with the abnormalities becoming progressively more severe in accordance with the patients clinical condition.

Table 2: Stages of Sick Euthyroid Syndrome

Severity of Illness	FT4	FT3	r T3	TSH
Stage I (mild)	N	↓ 50%	↑ 2 fold	N
Stage II (moderate)	↑	↓ 90%	↑ Many fold	N
Stage III (Severe)	↓	Almost undetectable	Variable	↓

DRUGS THAT CAUSE DECREASED LEVELS OF T4:

Decreased T4 with elevated TSH (True hypothyroidism):

- Iodine (Amiodarone, radiographic contrast), Lithium

Decreased T4 with normal TSH:

- Androgens – by decreasing TBG levels
- Frusemide (high dose), Salicylates – by inhibition of T4 binding to TBG
- Phenytoin – multiple mechanisms

Decreased T4 with decreased TSH:

- Glucocorticoids, Dopamine – by inhibition of TSH secretion.

Table 3: NORMAL THYROID PROFILE [13]

Analyte	Serum levels in	
	SI units	Conventional units
T3	0.92 – 2.78 n mol/L	60-181 ng/dl
T4	58-140 n mol/L	4.5-10.9 g/dl
TSH	0.5-4.7 mU/L	0.5-4.7 U/ml
FT3	0.22-6.78 p mol/L	1.4-4.4 pg/ml
FT4	10.3-35 p mol/L	0.8-2.7 ng/dl
FT4I	4.2-13	4.2-13

Table 4: Interpretation of Thyroid Function Tests:[14]

TSH normal T3, T4 Normal	TSH high T3, T4 normal	TSH high T3, T4 low or T3 normal T4 low	TSH low T3, T4 low
Euthyroid	**Subclinical Hypothyroidism**	**Primary Hypothyroidism**	**Central Hypothyroidism**

HYPOTHYROIDISM

Hypothyroidism is a clinical state due to the decreased secretion of thyroid hormones namely thyroxine (T4) and triiodothyronine (T3) or very rarely due to the decreased action of these hormones at tissues.

Hypothyroidism can be classified into three main categories :[15]

I Primary Hypothyroidism: Hypothyroidism due to the permanent loss or atrophy of thyroid tissue.

II Goitrous Hypothyroidism: Hypothyroidism with compensatory thyroid enlargement due to transient or progressive impairment of hormone biosynthesis.

III Central hypothyroidism: Hypothyroidism due to the insufficient stimulation of a normal gland. It includes:

a. Secondary Hypothyroidism is due to defect at pituitary level.

b. Tertiary Hypothyroidism is due to defect at hypothalamic level.

PRIMARY ATROPHIC HYPOTHYROIDISM:

1. Primary idiopathic hypothyroidism
2. Post-ablative (iatrogenic): I^{131}, or surgery or therapeutic radiation to non-thyroidal malignancy.
3. Sporadic hypothyroidism (agenesis or dysplasia)
4. Endemic Cretinism (agoitrous form)

GOITROUS HYPOTHYROIDISM

1. Hashimoto's thyroiditis
2. Riedel's struma
3. Endemic Iodine Deficiency
4. Antithyroid agents
5. Inherited defects of hormone synthesis
6. Amyloidosis, Cystinosis, Sarcoidosis, Hemochromatosis, Scleroderma

CENTRAL HYPOTHYROIDISM

1. Secondary hypothyroidism (Pituitary)

a. Panhypopituitarism (Sheehan's syndrome, tumors, infiltrative disorders).
b. Isolated TSH deficiency.

2. Tertiary (hypothalamic) hypothyroidism (idiopathic, traumatic, tumors, infiltrative disorders)

Clinical Manifestations of Thyroid HormoneDeficiency[16,17,18]

The clinical features of hypothyroidism are due to the direct result of under or absent exposure of end organs to the action of thyroid hormones viz., T3 and T4.Almost all the cells in the body have thyroid hormone receptors in their cytosol and respond to thyroid hormones to a greater or lesser degree.

Skin and Appendages: Skin is often dry and coarse due to the reduced secretion of sweat and sebum. In some cases it may resemble icthyosis. It may show faint yellow tint due to hypercarotenaemia. Nails are brittle with vertical and transverse fissures and grow slowly.Hair may be lost from the lateral 1/3 of the eyebrow (madarosis). In severe cases (myxoedema), periorbital puffiness and non-pitting boggy edema is seen; especially in feet and legs and even in hands.These features are due to the

accumulation of mucopolysaccharides hydrophilic hyaluronic acid and chondroitin sulfate, in the ground substance of the dermis and other tissues.

Respiratory System: Pleural effusions are minimal and asymptomatic, and may accompany other serious effusions in myxoedema.Lung volumes are usually normal; but maximal breathing capacity and diffusing capacity are reduced.

Gastrointestinal System: Mucosal oedema of the gastrointestinal tract leads to the poor absorption of nutrients. Appetite is also reduced. But there is modest gain in the weight due to fluid retention. However, true obesity is not a feature of hypothyroidism.

Nervous system: Thyroid hormone is essential for the development of the central nervous system. If the deficiency is not corrected in the early postnatal life, the damage is irreversible.Deficiency of thyroid hormone beginning in adult life causes less severe nervous system manifestations, which usually respond to treatment with thyroid hormone.All intellectual functions, including speech are slowed.Lethargy and somnolence are prominent.

Muscular System: Delayed contraction or relaxation of skeletal muscle is the hallmark of hypothyroidism and is the basis of hung-up tendon jerks.Cretinism in association with these muscle abnormalities is known as Kocher-Debre- Semelaigne syndrome and myxoedema with muscle hypertrophy is known as the Hoffmann syndrome.

Bones & Calcium metabolism: Deficiency of this hormone in the early life leads to abnormal delayed development of ossification centres leading to epiphyseal dysgenesis. Impairment of linear growth leads to dwarfism.

Renal system: Total body water is increased and is responsible for the generalized edema.Renal blood flow, GFR, tubular reabsorption and secretory maxima are reduced. Urinary volume is reduced and is one of the first noticeable parameters to reverse with treatment.

Reproductive System: Infantile hypothyroidism, if untreated, leads to sexual immaturity and juvenile hypothyroidism causes a delay in the onset of puberty, followed by anovulatory cycles.The only significant manifestation in the male is loss of libido and erectile dysfunction.

Table 5: Symptoms of Hypothyroidism[19]

Symptoms	% of cases	Symptoms	% of cases
Weakness	99	Constipation	61
Dry skin	97	Gain in weight	59
Coarse skin	97	Loss of hair	57
Lethargy	91	Pallor of lips	57
Slow speech	91	Dyspnoea	55
Edema of eyelids	90	Peripheral edema	55
Sensation of cold	89	Anorexia	45
Decreased sweating	89	Nervousness	35
Cold skin	83	Menorrhagia	32
Thick tongue	82	Palpitation	31
Edema of face	79	Deafness	30
Coarseness of hair	76	Precordial pain	25
Pallor of skin	67		
Memory impairment	66		

Cardiovascular system : Bradycardia, Diastolic hypertension, Small volume pulse, Pericardial effusion and Cardiomegaly are some of the features. ECG changes : Sinus bradycardia, prolonged PR interval, low amplitude complexes, ECG manifestations of other cardiac diseases like IHD etc.

Table 6: Cutaneous manifestations of Hypothyroidism[20]

Cutaneous manifestations	**Approximate Frequency**
Cold intolerance	50-95
Nail abnormality (thin, brittle)	90
Thickening and dryness of hair and skin	80-90
Edema of hands, face and eyelids	70-85
Change in shape of face	70
Malar flush	50
Non-pitting or dependent edema	30
Alopecia (loss or thinning of hair)	30-40
Pallor	25-30
Yellowish discoloration of skin	25-50
Decrease or loss of sweat secretion	10-70

TREATMENT OF HYPOTHYROIDISM:[22,23]

Historically, hypothyroidism was the first endocrine disorder to be treated by supplementation of the deficient hormone. The most widely used and preferred preparation is synthetic T4 (Thyroxine sodium). Starting dose is 1.6 μg/kg/day (usually100 μg qd), orally, on empty stomach, in the morning. In the elderly and those with cardiovascular disease, starting dose is 12.5 μg to 25μg qd. Plasma TSH should be measured after 3-4 months. Dose is adjusted in 12-15 μg increments at intervals of 6-8 weeks until plasma TSH is normal.Subclinical hypothyroidism is treated if symptoms of hypothyroidism, goitre, hypercholesterolemia or positive AMA are there. Untreated patients should be monitored annually.

Myxoedema coma[24] is life threatening and should be managed with intensive supportive care and thyroid hormone replacement. Management includes respiratory and cardiovascular assistance, correction of hyponatremia and hypoglycemia and treatment of infection and hypothermia.Hydrocortisone 200-400 mg/day is recommended. As IV preparations of thyroid hormones are not marketed in India, give 400-500 μg of thyroxine through Ryle's tube on the first day and 100 μg/day subsequently.

DIABETES MELLITUS[25,26,27,28]

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, even death. Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.The long-term complications of diabetes mellitus include retinopathy with potential blindness,nephropathy that may lead to renal failure,and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic disturbances like sexual dysfunction.People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebro vascular disease.

Several mechanisms are involved in the development of diabetes.These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action.

Table 7: Values for diagnosis of diabetes mellitus and other categories of hyperglycemia[29,30]

	Plasma Venous Glucose concentration, mmol/ l(mg /dl)
Diabetes Mellitus: Fasting Or 2-h post glucose load or both	 ≥7.0 (≥126) ≥11.1 (≥200)
Impaired Glucose Tolerance (IGT): Fasting and 2-h post glucose load	 >6.1(>110) <7.0 (<126) ≥7.8 (≥140) and <11.1 (<200)
Impaired Glucose Glycaemia (IGG) Fasting and 2-h post glucose load	 ≥6.1 (≥110) and <7.0 (<126) <7.8 (<140)

Table 8: CLASSIFICATION OF DIABETES MELLITUS[31,32]

Type 1

(beta cell destruction, usually leading to absolute insulin deficiency)

- Autoimmune
- Idiopathic

Type 2

(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)

Other specific types

- Genetic defects of β-cell function(HNF4alpha MODY1, glucokinase MODY4 etc)
- Genetic defects in insulin action
- Diseases of the exocrine pancreas (Fibrocalculouspancreatopathy,Haemochromatosis)
- Endocrinopathies (Cushing'sSyndrome,Acromegaly,Phaeochromocytoma Glucagonoma ,Hyperthyroidism, Somatostatinoma)
- Drug or chemical induced
- Infections (Congenital rubella ,Cytomegalovirus)
- Uncommon forms of immune-mediated diabetes

Treatment of Diabetes mellitus

Table 9: Oral Antihyperglycemic Agents[33,34]

Drug class	Agents	Reduction in HbA1c (%)	Patients best suited For treatment
Sulfonylureas	Glyburide Glipizide Glimepiride Glibenclamide Gliclazide	0.8 to 2.0	Patients with recently diagnosed type 2 diabetes
Meglitinides	Repaglinide Nateglinide	0.5 to 2.0	Patients with recently diagnosed type 2 DM who have high postprandial glucose levels
Biguanides	Metformin	1.5 to 2.0	Obese patients with recently diagnosed type 2 diabetes
Thiazolidinediones	Pioglitazone Rosiglitazone	0.5 to 1.5	Patients who are obese or Insulin resistant
Alpha glucosidase inhibitors	Acarbose Miglitol	0.7 to 1.0	Patients with high postprandial glucose levels

Table 10: Types of insulin[35,36]

INSULIN TYPE	INSULIN	ONSET (hours)	PEAK (hours)	DURATION (hours)
Rapid acting analogue (clear)	Lispro Aspart	**0.25**	**0.5-1.5**	**2-5**
Fast acting (clear)	Regular	**0.5-0.7**	**1.5-4.0**	**5-8**
Intermediate-acting (cloudy)	NPH Lente	**1-2**	**6-12**	**18-24**
Long-acting (cloudy)	Ultralente	**4-6**	**16-18**	**20-36**
Extended long-acting analogue	Glargine Detemir	**2-5**	**5-24**	**18-24**
Premixed (cloudy) A single vial contains a fixed ratio of insulin (% rapid or fast acting to % intermediate acting insulin)	30/70, 50/50, etc.	–	–	–

<u>Complications of Diabetes mellitus:</u>

Short term Complications:
Hypoglycemia, Diabetic ketoacidosis,
Hyperglycemic hyperosmolar syndrome.

Long-Term Complications

Dyslipidemia,Hypertension ,Cardiovascular Disease ,Vascular Complications, Diabetic Retinopathy, Renal Complications etc.

HYPOTHYROIDISM AND DIABETES MELLITUS[37]

Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population.

Thyroid Disease in Diabetics:

Overall prevalence: 10.8–13.4%

Subclinical Hypothyroidism:5-9%

Clinical Hypothyroidism: 1 – 2%

The overall prevalence of hypothyroidism in women with diabetes was 8.8% with 5% in those <60 years and 21% in ≥60 years[38].The prevalence of hypothyroidism among people with diabetes ranges from 0.2 to 6 % depending on age and sex[39]. Ganz and Kozak, at Joslin's clinic, reviewed the records of 60,703 patients with diabetes from 1957 to 1972 and reported 114 (0.19%) cases of hypothyroidism[40].Among these, from October 1957 to September 1965, an additional 52 cases of primary hypothyroidism (0.24%) were diagnosed among 21,500 new diabetic patients[41]. Hecht and Gerschberg reported 9 hypothyroid patients(1.7%) out of 530 patients with diabetes who attended their metabolism clinic[42]. Perros reported a prevalence rate of 13.4% for all types of thyroid disease among a population with diabetes receiving annual thyroid screening[43]. Smithson noted that 65 of the women with diabetes also had hypothyroidism on screening of 197 patients[44].

Feely and Isles reported a 4% prevalence of clinical hypothyroidism in diabetics. They also noted an increased prevalence (5%) in women with diabetes who were older than 60 years[45].Cross sectional studies have reported a prevalence of hypothyroidism in 12-24 % of female and 6% of male patients with IDDM as well as in 3-6% of NIDDM patients[46,47,48,49]

TYPE I DIABETES MELLITUS AND AUTOIMMUNITY[50,51]

The basis of increased thyroid dysfunction in type I diabetes is autoimmunity. Primary hypothyroidism in most instances is probably due to thyroid atrophy resulting from end-stage chronic lymphocytic thyroiditis.The prevalence of autoantibodies in juvenile diabetics has been reported by different authors to be around 22%, 17% and 8% respectively[52,53,54].The study by Riley et al.,showed 17% of IDDM to be positive for AMA, of which 38% were hypothyroid (including subclinical and 1/3rdof which were undiagnosed) and another 5% (total 43%) of IDDM with AMA positive became clinically and /or biochemically hypothyroid.

In a study of 278 patients with diabetes mellitus, the incidence of goiter was 31.8% and was higher in females than in males; and the incidence of AMA and T_g-Ab was 18.5% and 1.8% respectively.

In the study by Umpierrez[55], 33% patients of type I Diabetes had positive TPO Ab. Hypothyroidism was most common in female subjects with positive (83%) as compared with negative (12%) TPO. Similarly, the rate of hypothyroidism was higher in male subjects with positive (51%) than with negative (3%) TPO antibodies. 17/18 0f TPO positive at the beginning of the study remained positive throughout the study period.The mean age of onset of hypothyroidism was earlier in those TPO positive and also of onset of diabetes when compared to TPO negative subjects.

Patients who were TPO positive were 17.91 times more likely to develop hypothyroidism.Also, long term follow up is necessary because the onset of diabetes usually precedes the diagnosis of thyroid dysfunction by about one decade.The prevalence of hyperthyroidism (including subclinical) was 1.7% and 0.3% in type I and type II diabetics respectively.Screening for AMA in IMD (Immune Mediated Type I Diabetes) is strongly advised, and if negative every 2-3 years until adulthood.Those positive for AMA should have TFTs done annually.

Other observations that support the possibility of autoimmune process in diabetes mellitus are as follows:

1. The demonstration of islet-cell antibodies in diabetics
2. Both thyroiditis and IDDM show a stronger association with HLA-B8 when they accompany other autoimmune disorders, including Addison's disease and pernicious anemia, and with HLA-DR3 and DR4. The adult form of polyglandular autoimmune syndrome (type2) is associated with disorders of the thyroid, adrenal and pancreas (IDDM).In a study in southern India, autoimmune diseases were diagnosed in 1.68% of persons with diabetes mellitus (147/15,523). Diabetes mellitus was diagnosed in 2.3% of persons with hypothyroidism (33/1435) and in 4.35% with thyrotoxicosis (15/345)[56].
3. Insulitis or lymphocytic infiltration of the pancreas islets has been found in Type 1 DM
4. Autoantibodies to endogeneous insulin were found by some Investigators

The study by Gray R.S, Herd R and Clarke B.F[57] was done on diabetics with coexisting Grave's disease or primary hypothyroidism.Those with Grave's disease developed thyroid dysfunction and diabetes at an earlier age, than patients with primary hypothyroidism.87% of diabetics with thyroid disease were female, 56% required insulin treatment and those requiring insulin, the median age at diagnosis of diabetes was 36 years (older than the general diabetic population). Whilst diabetes precedes thyroid disease in juvenile onset diabetes, the order is reversed in late onset diabetes. Hypothyroidism was diagnosed later (6.7 $\pm$ 1.2 years) than hyperthyroidism 2.4 $\pm$ 1.2 years) the diagnosis of diabetes, probably explained by the extended natural history of asymptomatic autoimmune thyroiditis.Similar correlation was also seen with NIDDM who presumably share the same etiology. Absence of any seasonal variations suggest that the pathological processes responsible for the development of diabetes and autoimmune thyroid disease in the same subject are initiated simultaneously and independently of acute environmental influences.

In the follow-up study done on 109 young adults with type 1 diabetes by Vondra in Prague[58], cumulative incidence of antibodies (AMA and Tg-Ab) was 51% with predominance of women over men (65% versus 38%). Subgroup I (25%) had both AMA and Tg-Ab positive (women predominantly); 30% of these had TSH > 4.5 mIU/L and subclinical hypothyroidism developed in all patients within 4 years. Subgroup II (26%) had only AMA positive (men and women equally); 7% only had TSH > 4.5 mIU/L and subclinical hypothyroidism developed in only 11% within 4 years.USG pattern of hypoechoic gland was seen in 59% and 25 % respectively in 2 subgroups.

Among a diabetic clinic population of 5000, there were 113 patients (2.26%) with concurrent clinical thyroid dysfunction (56 hyperthyroid, 57 hypothyroid – 1.1 % each).71 (62.8%) of these were IDDM and diabetes preceded thyroid disease in 85 (75.2%). 96 (85%) of these were females – 87.7 % in hypothyroid and 82.1 % in hyperthyroid group. Percentage of patients on insulin was more in hypothyroid group than in hyperthyroid group (77.2 % Vs 48.2 %). Diabetes was diagnosed first in 89% of hypothyroid Vs only 64.3% of hyperthyroid patients. Mean age at diagnosis of hypothyroidism was later than of hyperthyroidism (54 years Vs 32 years)[59].

STUDIES DONE ON TYPE II DIABETICS

Thyroid function done in 298 type 2 diabetics showed 38 (12.7%) suffered from thyroid dysfunction – 10.7% had hypothyroidism (>2/3rd sub clinical) and 2% had hyperthyroidism. In 31 cases (10.4%) the diagnosis was performed 'de novo'.Thyroid disease was more prevalent among females and elderly[60].

In a study done on 908 T2DM and 304 non-diabetics at Amman, Jordan, the overall prevalence of thyroid disease in diabetics was found to be 12.5% of which 5.9% were known to have thyroid disease and rest (6.6%) were newly diagnosed cases as a direct result of screening. The most common was subclinical hypothyroidism (4.1%). The prevalence of thyroid disease was 6.6% in the control group[61].

The Indian study done at GND hospital[62], Amritsar, of 184 cases of T2DM showed thyroid disease (TD) present in 78 (40.4%) cases (50 males, 28 females), but autoimmune thyroiditis (AT) was present in 32 (17.4%) cases (8 males, 24 females). There was positive correlation with age of patient in TD group but no correlation was found with complication of diabetes.There was no correlation of age, severity or complications in AT group but this finding was significantly more in female cases.

In the study sample of 100 patients with T2DM at Chennai[63], the prevalence of TD was 15%subclinical hypothyroidism 11%, hypothyroidism 1%, subclinical hyperthyroidism 2% and hyperthyroidism 1%.The prevalence is higher than in the general population and in females.

In the study of 120 T2DM patients at Hyderabad[64] , hypothyroidism was seen in 32 (27%, 10% being subclinical), of which 80% were females. 70% of patients with hypothyroidism were between 40-60 years age. Only in 1%, hypothyroidism preceded T2DM. Only 2% of hypothyroid patients had significant AMA titres. Goiter was noted in 2% of patient.

POSTPARTUM THYROID DYSFUNCTION IN TYPE I DIABETICS[65]

Transient thyroid dysfunction is common in the postpartum period in women with T1DM and warrants routine screening with TSH 6-8 weeks after delivery. Glucose control may fluctuate during the transient hyperthyroidism followed by hypothyroidism, typical of postpartum thyroiditis. It is important to monitor TFTs in these women since approximately 30% will not recover from the hypothyroid state and will require thyroxine replacement. Recurrent thyroiditis with subsequent pregnancies is also common.

In a study by Hertzel C Gerstein, PPTD (postpartum thyroid dysfunction) occurred in 10/40 (25%) – postpartum thyroiditis in 9 and postpartum Grave's in 1, during the first 6 months after delivery. PPTD occurs in about 5% of women within 1 year of delivery. Risk factors for PPTD are family history of thyroid disease/autoimmunity, past history of thyroid disease, female child, goiter, subclinical hypothyroidism, positive AMA at term or before delivery and the presence of the HLA marker DR4. Thus patients with T1DM may benefit from routine screening for thyroid dysfunction at postpartum visits and from regular follow-up of any abnormal results.

INTERACTION BETWEEN THYROID ABNORMALITIES AND DIABETES MELLITUS

Thyroid hormone enhances the absorption, production and utilization of glucose. Often latent diabetes may be unmasked by hyperthyroidism, while hypoglycemia is sometimes a manifestation of hypothyroidism.Diabetes mellitus appears to influence thyroid function at several sites, from hypothalamic control of TSH, release of T3,production from T4 in the target tissue etc. The best studied effect is the lowering of circulating T3 in diabetics.

1) Thyroid function in diabetes mellitus

Thyroid hormone metabolism is altered in diabetes and other acute and chronic illnesses. Low T3 is always present in diabetic ketoacidosis. There is a lowered T3:T4 ratio in the diabetic group. Further, serum T3:T4 ratio shows an inverse correlation with both, fasting blood glucose level and HbA1c.Uncontrolled hyperglycemia with ketosis lowers T4 and T3 levels and rT3 is elevated. No change is observed in plasma TSH and FT4I is normal.

2. Hyperthyroidism and diabetes:[66,67]

IGT was found in 57% of a group of hyperthyroid patients and the proportion dropped to 30% when these patients were rendered euthyroid. There is

- Increased intestinal glucose absorption
- Glucose induced insulin release is altered (AMP mediated)
- Marked elevation of fasting plasma glucagon in 30% with blunting of arginine induced and protein meal induced glucagon responses.
- Increased activity of gluconeogenic enzymes in liver and kidneys.
- Role of catecholamines due to hyperadrenergic state
- Resistance to the peripheral action of insulin.

3. Hypothyroidism and Diabetes[66,67]

The mechanisms of carbohydrate derangements in hypothyroidism are unclear. GIT absorption of glucose slows down,contributing to the amelioration of hyperglycemia. Glucose turnover is decreased probably due to generalised slowing of the metabolic rate. Hypothyroidism may lead to decrease in insulin requirements in diabetic patients. Possibility of hypoadrenalism is considered in hypothyroid patients with hypoglycemia. Long standing diabetic patients complicated with nephropathy may appear pseudomyxedematous with pallor and facial puffiness suggestive of hypothyroidism. Derangements of lipid metabolism in the hypothyroid state can give rise to hypercholesterolemia, a well known risk factor for cardiovascular morbidity, especially when it is associated with hypertension by aggravating the macro and micro-angiopathic complications of long standing diabetes mellitus.

4.Hypothalamic-pituitary-thyroid axis in DM

Diabetic subjects have reduced TRH as well as a blunted pituitary TSH response to TRH. Diabetes mellitus and stress of ketoacidosis have an inhibitory effect on the pituitary itself

STUDIES DONE TO SHOW THYROID FUNCTION IN DIABETICS:[68]

- Plasma T4 is normal whereas plasma T3 is diminished and plasma level of rT3 is elevated in DKA or in patients with severely uncontrolled diabetes.
- A negative linear correlation was found between T3 and glycosylated Hb, and a positive correlation between rT3/T3 and HbA1c.
- In a study of 112 IDDM Patients, T4, T3, rT3 and TBG were lower han in control whereas FT4 and FT3 were normal. T3/rT3 ratios were stable indicating that peripheral deiodination of T4 is preferentially oriented to production of rT3 only during ketoacidosis.
- Before insulin treatment, T3 and FT3 were lower and rT3 slightly increased. With good metabolic control following insulin treatment, T3 and FT3 were slightly increased, whereas rT3 slightly decreased. Basal and were not influenced by insulin therapy.
- T3 level was signifigantly reduced in diabetic patients with vascular disease and in female diabetics.

- Glucose intolerance was seen in 7/9 patients with subacute thyroiditis, which returned to normal after the recovery except 2 cases with family histories of DM. The results indicated the importance of follow-up study of glucose tolerance in subacute thyroiditis.
- In a study of 290 T2DM, abnormal TSH levels were detected in Patients (31.4%). TSH was repeated in these patients after two months of adequate treatment of diabetes with OAD or insulin. TSH concentrations decreased in all but one patient with initial subclinical hypothyroidism and ncreased in all patients with initial subclinical hyperthyroidism.These changes were coupled with a significant fall of HbA1c levels.In view of the transient changes in TSH secretion, it is suggested that the diagnosis of thyroid dysfunction in T2DM should be delayed until improvement of the metabolic status.

- 59 patients with both clinical evidence of TD and DM were investigated.With development of hyperthyroidism,deterioration was seen 63% of insulin treated patients with a 82% increase in insulin dosage in 53%.Following treatment of hyperthyroidism, control improved in 63% with 44% decrease in insulin dosage in 59% of them, and insulin was withdrawn in one of them. When

hypothyroidism developed,73% of them had their insulin dosage reduced with a high frequency of hypoglycemic disorders, repeated malaise in 55% and coma in 27%.

HYPOTHYROIDISM AND DIABETIC NEPHROPATHY

DM with nephropathy and nephritic syndrome may clinically appear myxedematous and pose a differential diagnostic problem. In addition to becoming more insulin sensitive and requiring less insulin, the diabetic patient who develops Kimmelstiel-Wilson (KW) disease can have physical findings similar to those of myxoedema – a slowed down appearance, facial puffiness, pallor, and pasty countenance. In addition, kidney dysfunction with proteinuria tends to affect the results of TFTs to the extent that some of them may be misleading or contradictory. The serum T4 and protein- bound iodine levels are low in patients with myxedema and may possibly be low in patients with protein-losing diabetic nephropathy. Proteinuria results in loss of serum proteins, including TBG. In patients with myxedema, the resin T3 uptake is low, whereas in patients with KW disease, it can be high.

HYPOTHYROIDISM IN DIABETICS TREATED WITH SULFONYLUREAS

It has been postulated that patients treated with sulfonylureas have a higher frequency of hypothyroidism than those treated with insulin or diet alone. The incidence of hypothyroidism was shown to increase with the duration of sulfonylurea therapy

These results have been questioned by Burdick and Brice, who in their study showed that treatment with sulfonylureas lowers the PBI significantly as compared to a matched group treated with diet and insulin or diet alone. This affect is most pronounced with carbutamide, but is not seen with tolbutamide in which the amino group is replaced by a methyl group. Furthermore, the doses of sulfonylureas used in the treatment of diabetes are too low to have significant anti-thyroid effects.

In the study by Portioli and Rocchi in 200 patients treated with tolbutamide and followed for upto 7 years, TFT suggested hypothyroidism in 3%, although clinically none of the patients were hypothyroid.

At the Joslin clinic, a survey revealed that among 9000 diabetic patients who had ever received “first generation” sulfonylureas, very few only 14 (0.15%) had developed hypothyroidism.

METHODOLOGY

Study Subjects:

This study was conducted at Coimbatore Medical college Hospital,Coimbatore from March 2009 to August 2010. Outpatients attending to the outpatient department and inpatients admitted to the wards who were either previously or newly diagnosed diabetic were included in the study.

Inclusion Criteria:

Patients of diabetes mellitus either previously or newly diagnosed aged more than19 years were included in the study.

Exclusion Criteria:

1. All patients less than or equal to 19 years of age.
2. Hypothyroidism arising as a result of thyroid surgery or radiotherapy.

Study Design:

1. Randomly selected diabetic patients were subjected to evaluation for thyroid function clinically and biochemically.

2. Diagnosis of Diabetes mellitus was done as per WHO guidelines.

a. Fasting venous plasma glucose > 126 mg/dl (7.0 mmol/L)

b.Two hour venous plasma glucose (post 75 gm glucose) > 200 mg/dl (11.1 mmol/L)

3. Diagnosis of hypothyroidism was based on values given in table 3 on page 16.

4. Patients already known to have both diabetes mellitus and hypothyroidism were also included.

5. The patients having both the conditions included in the study, underwent other relevant investigations at first visit and on follow-up.

6. All data regarding patients included was documented as per proforma enclosed in the annexure.

7. Ethical clearance was taken from the institution prior to the commencement of the study.

8. Interpretation of data was done by various statistical methods.

Investigations:

Routine:

1. Hb%, TC, DC, ESR
2. Urine – Albumin, Sugar and Microscopy
3. Serum urea and creatinine levels
4. ECG
5. Chest X-Ray
6. Complete Hemogram
7. Lipid Profile

Diabetes Related:

1. Fasting and two hour postprandial venous plasma glucose levels were done by glucose oxidase method.

Thyroid Related:

1. Serum TSH, T3, T4: by chemiluminescence immunoassay (CLIA) method.

RESULTS

One hundred twenty two known or newly detected cases of diabetes mellitus aged more than 19 years were selected randomly from the outpatients attending to the outpatient department and from the inpatients admitted to the wards in Coimbatore Medical college Hospital during the study period.

Table 11: Distribution of Subjects according to the type of Diabetes

Type of Diabetes	Male	Female	Total
Type 2	59	32	91
Type 1	19	12	31
Total	**78**	**44**	**122**

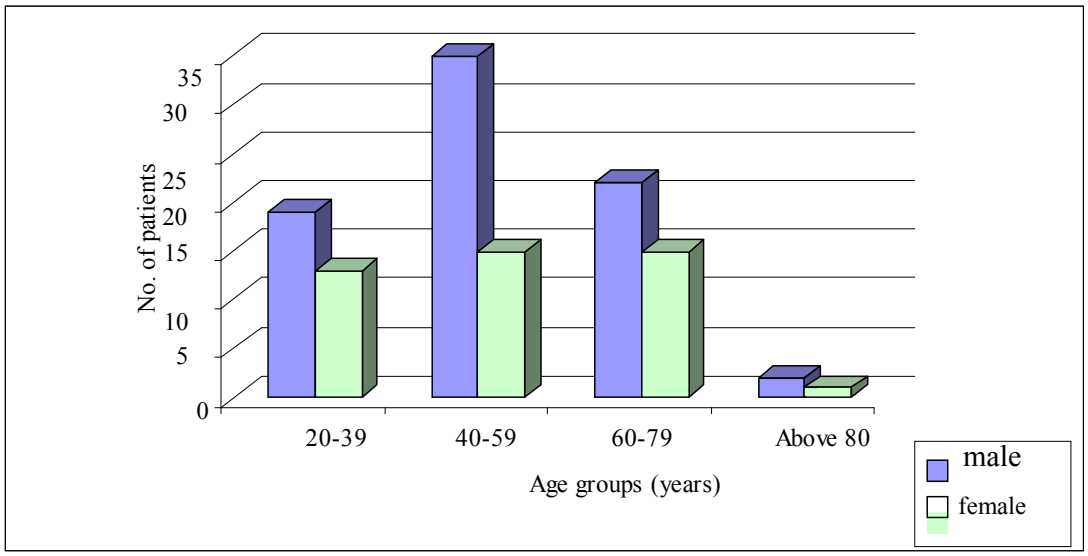
Thus of 122 subjects, 91 were type 2 diabetics (59 males, 32 females) and 31 were type 1 diabetics (19 males and 12 females).

Table 12: Distribution of Subjects as per Age and Sex

Age group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
20-39	19	15.6	13	10.6	32	26.2
40-59	35	28.7	15	12.3	50	41.0
60-79	22	18.0	15	12.3	37	30.3
Above 80	2	1.6	1	0.9	3	2.5
Total	**78**	**63.9**	**44**	**36.1**	**122**	**100**

CC = 0.064, p = 0.909 (NS)

Figure 1: Distribution of subjects as per age and sex



Among 122 subjects, 78 (64%) were males and 44 (36%) were females; and 50 (41%) patients were in the age group of 40-59 years, 37 (30.3%) in 60-79 age group, 32 (26.2%) in 20-39 age group, and 3(2.5%) in above 80 age-group.

Hypothyroidism in Diabetics:

Table 13: Known and Newly Detected cases of Hypothyroidism In Diabetics

Group	Hypothyroid Patients			Total	%
	Known	Newly Detected			
		At First Visit	On Follow up		
Diabetes First	3	12	1	16	13.1
Hypothyroidism First	2	0	0	2	10.5
Both simultaneously	1	0	0	1	5.2
Total	**6**	**12**	**1**	**19**	**15.6**

F = 1.727; p = 0.182 (NS)

Out of 122 subjects, hypothyroidism and diabetes were observed to occur together in 19 patients, of which 8 were clinically hypothyroid. All the cases were of primary hypothyroidism. One patient was found to have subclinical hyperthyroidism. Thus, the prevalence of hypothyroidism (clinical and subclinical) in diabetics was 15.6 %(19/122).Of 19 hypothyroid patients, 6 were known to be hypothyroid (5 clinical and 1 subclinical), 12 were newly detected and 1 patient was found to become hypothyroid on follow-up.

Table 14 Newly Detected cases of Clinical and Subclinical Hypothyroidism in 116 diabetics not known to have hypothyroidism prior to inclusion into the study

Newly Detected cases of	Number	Percentage
Clinical hypothyroidism In Diabetics	**2**	**1.7**
Subclinical Hypothyroidism In Diabetics	**11**	**9.5**
Total	**13**	**11.2**

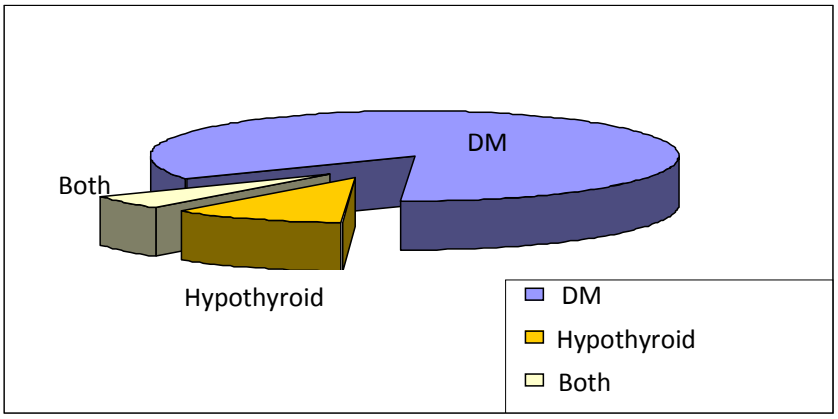
Thus, totally 2 new cases of clinical hypothyroidism and 11 new cases of subclinical hypothyroidism were detected on screening 116 diabetics not known to have hypothyroidism prior to inclusion into the study. The two cases of clinical hypothyroidism were detected on follow up of 12 months and 16 months respectively.

Table 15: First Detected condition in patients having both Hypothyroidism (clinical and subclinical) and Diabetes mellitus

First Detected	No.	%
Diabetes Mellitus	16	84.2
Hypothyroidism	2	10.5
Both	1	5.3
Total	**19**	**100**

Chi-Square = 267.791; p = 0.000 (S)

Figure 2: First Detected condition in patients having both Hypothyroidism (clinical and subclinical) and Diabetes mellitus

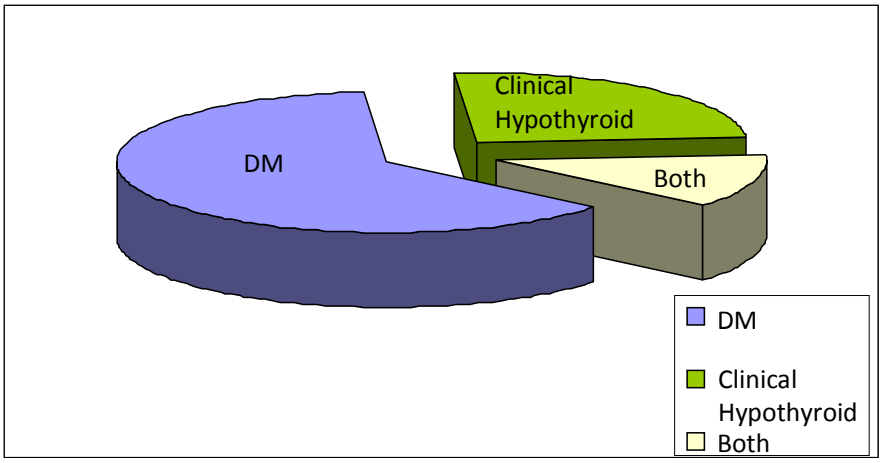


Hence, among the group of subjects having both the conditions, diabetes mellitus was detected first in 84.2%, hypothyroidism in 10.5% and both conditions were detected simultaneously in 5.3%

Table 16: First Detected condition and Gap between the two conditions in patients having both Clinical Hypothyroidism and Diabetes mellitus

First Detected	Type of Diabetes	No	%	Gap (years)		
				Mean	Min.	Max.
Diabetes mellitus	T1DM	1	–	9.00	–	–
	T2DM	4	–	9.62	0.83	22.00
	Total	**5**	**62.5**	**9.50**	**0.83**	**22.00**
Clinical Hypothyroidism	T1DM	1	–	19.50	–	–
	T2DM	1	–	2.20	–	–
	Total	**2**	**25.0**	**10.85**	**2.20**	**19.50**
Both simultaneously	T1DM	0	–	–	–	–
	T2DM	1	–	0.00	–	–
	Total	**1**	**12.5**	**0.00**	–	–
Total		**8**	**100**	–	**0.83**	**22.00**

Figure 3: First detected condition in patients having both clinical hypothyroidism and diabetes mellitus



Thus, clinical hypothyroidism was seen in 6.5 % (8/122) of diabetics. Diabetes was detected first in 5 (62.5%), clinical hypothyroidism in 2 (25%), and both simultaneously in 1 (12.5%) patients having both conditions

Oral Antidiabetic Drugs and Hypothyroidism

Table 17: Use of Oral antidiabetic drugs in Type 2 diabetes with different thyroid status

Oral Antidiabetic Drugs	Thyroid Status			Total
	Normal	Subclinical Hypothyroid	Clinical Hypothyroid	
Used (%)	73 (93.6)	7 (100)	6 (100)	86 (94.5)
No. of type 2 diabetics	**78**	**7**	**6**	**91**

CC = 0.098; p = 0.643 (NS)

Thus, 94.5% of type 2 diabetics were on oral antidiabetics.

Table 18: Duration of use of oral antidiabetic drugs in different thyroid status groups

Thyroid Status	Mean (years)	No.
Normal	7.6281	78
Subclinical Hypothyroidism	13.7500	7
Clinical Hypothyroidism	6.8080	6
Total	**8.1212**	**91**

F = 1.727; p = 0.182 (NS)

Thus, the difference in the duration of use of oral antidiabetic drugs in different thyroid status was not statistically significant.

Analysis of Hypothyroid Patients

Table 19: Distribution of diabetics with coexisting hypothyroidism as per age-group

Age-group (years)	Type 1 Diabetics				Total	Type 2 Diabetics				Total	Grand Total
	CH		SH			CH		SH			
	M	F	M	F		M	F	M	F		
20-39	1	1	2	2	6	0	0	0	0	0	6
40-59	0	0	0	0	0	2	2	2	0	6	6
> 60	0	0	0	0	0	0	2	2	3	7	7
Total	**1**	**1**	**2**	**2**	**6**	**2**	**4**	**4**	**3**	**13**	**19**

CC = 0.378 (M), 0.480 (F)
p = 0.361 (M), 0.147 (F) (NS)

Figure 4: Distribution of type 1 diabetics with coexisting hypothyroidism as per age- group

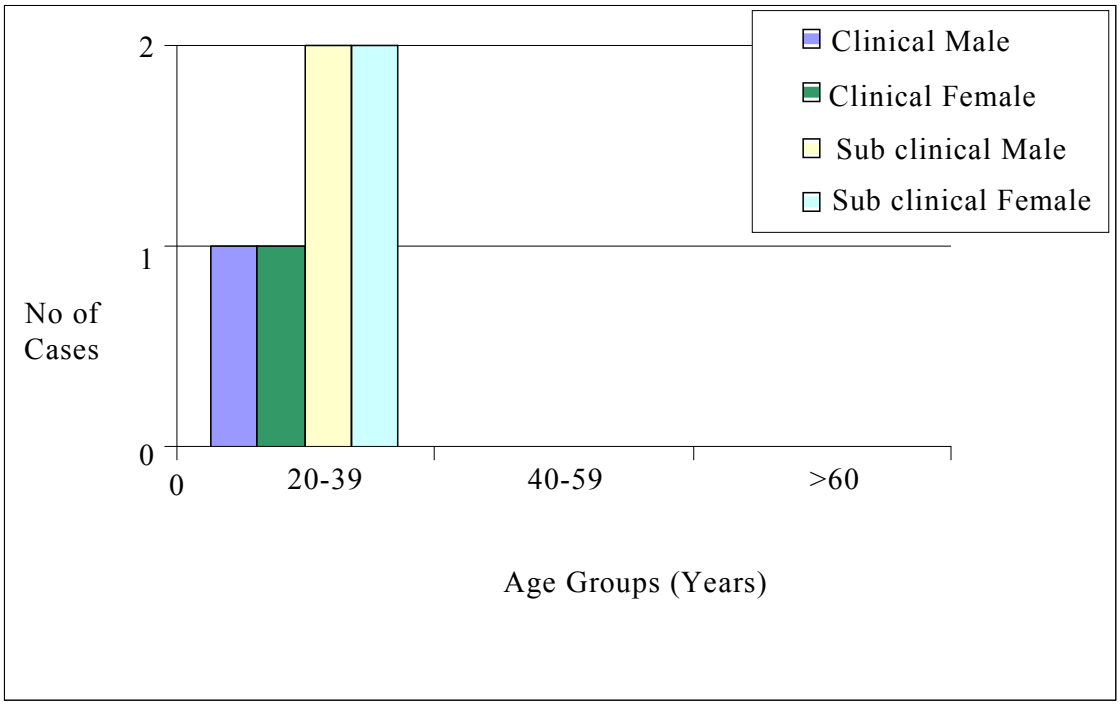
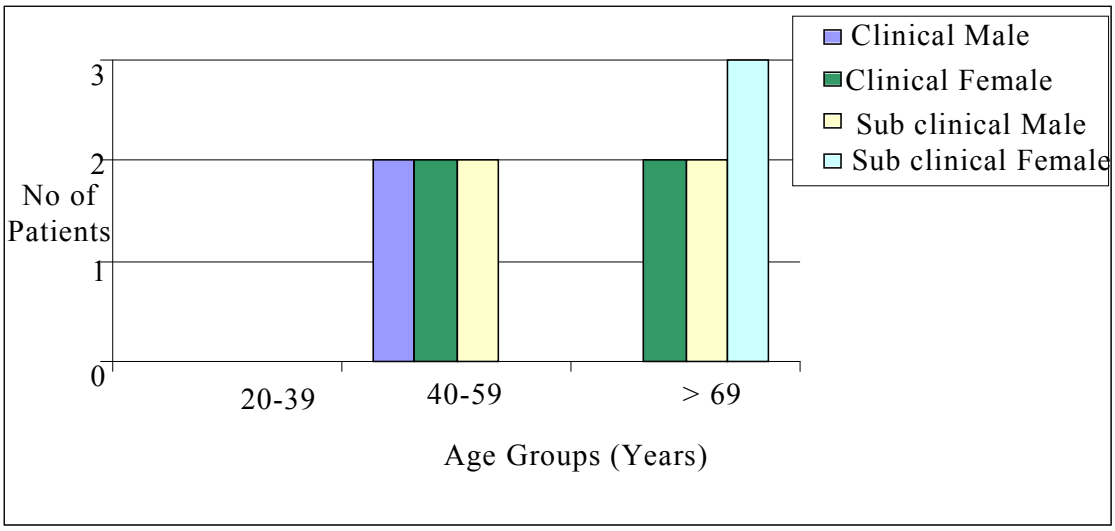


Figure 5: Distribution of type 2 diabetics with coexisting hypothyroidism as per age- group



Thus, all type 1 diabetics with hypothyroidism were in 20-39 years age-group, whereas type 2 diabetics with hypothyroidism were older, maximum in the age-group above 60 years.

Table 20: Distribution of hypothyroid patients according to the type of diabetes mellitus, sex and clinical / subclinical hypothyroidism

Diabetic Patients			Hypothyroid Patients							
Type of Diabetes	No.		Male				Female			
	Male	Female	SH	%	CH	%	SH	%	CH	%
T1DM	19	12	2	10.5	1	5.3	2	16.7	1	8.3
T2DM	59	32	4	6.8	2	3.4	3	9.4	4	12.5
Total	78	44	6	7.7	3	3.8	5	11.4	5	11.4

CC = 0.444 (M), 0.626 (F)
p = 0.001 (M), 0.000 (F) (S)
(CH= Clinical Hypothyroidism, SH=Subclinical Hypothyroidism)

Thus, clinical as well as subclinical hypothyroidism was more common in females (11.4% Vs 3.8%, and 11.4% Vs 7.7% respectively).

Table21:Mean age at Detection of Diabetes mellitus and of Clinical Hypothyroidism in patients having both or either of the two conditions

Mean age (in years) At Detection of	Patients of DM with Clinical Hypothyroidism	Patients of DM with Normal Thyroid Function
Diabetes Mellitus	40.20	43.18
Type 1 Diabetes	21.56	21.75
Type 2 Diabetes	46.36	50.14
ClinicalHypothyroidism	43.46	--

Thus, the mean age at detection of diabetes mellitus in patients having both conditions was 40.2 years which was earlier, compared to patients having diabetes mellitus with normal thyroid function where it was 43.18 years (21.56 Vs. 21.75 and 46.36 Vs. 50.14 years among type 1 and type 2 diabetics respectively

Table 22:Age at detection of Diabetes mellitus and Clinical Hypothyroidism in patients having both conditions

Sl. No.	Age(in years) at Onset of		Gap Between Two (in years)
	Diabetes mellitus	Clinical Hypothyroidism	
1	49.1	50	0.83
2	50	63	13
3	23	32	9
4	39	41.6	2.66
5	50	72	22
6	42	40	-2
7	20.5	1	-19.5
8	48	48	0

Thus, the gap between the onset of two conditions varied from 0.83 to 22 years in those where diabetes was first to be detected.

Clinical Symptoms and Signs of Hypothyroidism seen in Clinically Hypothyroid Patients (n = 8)

Table 23: Symptoms of Hypothyroidism

Sl. No.	Symptoms	Present in	Percentage
1.	Gen. Weakness & lethargy	8	100
2.	Dryness of skin	6	75
3.	Cold intolerance	5	62.5
4.	Decreased sweating	4	50
5.	Weight gain	4	50
6.	Paraesthesia	4	50
7.	Constipation	3	37.5
8.	Hoarseness of voice	2	25
9.	Anorexia	2	25
10.	Decreased hearing	1	12.5
11.	Menorrhagia	1	12.5
12.	Palpitations	1	12.5

Thus, generalized weakness and lethargy was the most common symptom of hypothyroidism seen in all patients, followed by dryness of skin and cold intolerance.

Table 24: Signs of Hypothyroidism

Sl. No.	Signs	Present in	Percentage
1	Delayed relaxation of ankle jerk	6	75
2	Coarse skin	5	62.5
3	Periorbital puffiness	5	62.5
4	Slow speech	5	62.5
5	Cold skin	4	50
6	Bradycardia	3	37.5
7	Slowness of movements	2	25
8	Facial puffiness	2	25
9	Goitre	2	25
10	Thick tongue	1	12.5
11	Hair loss	1	12.5
12	Limb edema	1	12.5

Thus, delayed relaxation of ankle jerk was the most common clinical sign seen in 6 patients, followed by coarse skin and periorbital puffiness seen in 5 patients.

GOITRE AND THYROID STATUS

Table 25: Presence of goitre in different thyroid status groups

Thyroid Status	Total no.	Goitre present	%
Normothyroid	102	1	0.98
Subclinical Hypothyroidism	11	2	18.18
Clinical Hypothyroidism	8	2	25
Subclinical Hyperthyroidism	1	0	0
Total	**122**	**5**	**4.09**

CC= 0.388; p =0.000 (S)

Thus, goitre was seen in 4.09% of cases. All the patients with goitre had diffusely enlarged thyroid gland. It was seen more common in those hypothyroid (25% of clinical,18.18% of subclinical), than normothyroid patients (0.98%).

Diabetic Complications and Hypothyroidism

Table 26: Frequency of various diabetic complications in relation to thyroid status

Type of Diabetes	Thyroid Status	Complications (%)								
		Hypo	**DKA**	**HHS**	**Neur**	**Nep**	**DR**	**CVA**	**IHD**	**PVD**
Type 1	N	33.3	20.8	8.3	62.5	16.7	50.0	0	16.7	0
	SH	25.0	50.0	50.0	50.0	25.0	50.0	0	25.0	0
	CH	0	50.0	0	50.0	0	50.0	0	0	0
Type 2	N	6.4	3.8	6.4	69.2	21.8	47.4	5.1	67.9	2.6
	SH	12.5	12.5	0	100	87.5	87.5	0	100	0
	CH	20.0	0	0	60.0	0	40.0	0	60.0	0
Contingency Coefficient	T1DM	0.213	0.273	0.397	0.230	0.160	0.174	-	0.160	-
	T2DM	0.128	0.129	0.098	0.198	0.407	0.226	0.087	0.201	0.06
p value	T1DM	0.688	0.477	0.122	0.628	0.846	0.809	-	0.846	-
	T2DM	0.471	0.464	0.643	0.157	0.000	0.087	0.706	0.146	0.84

(CH= Clinical Hypothyroidism, SH=Subclinical Hypothyroidism)

Thus, there was no significant correlation between the thyroid status in diabetics and various complications of diabetes mellitus.

Table 27: Body Mass Index (BMI), Mean Triglyceride and Cholesterol levels in various groups of diabetic patients

Groups	BMI (kg/m^2)	Triglycerides (mg/dl)	Cholesterol (mg/dl)
T1DM with SH	19.36	195	186
T1DM with CH	19.96	225	198
T1DM with N	19.09	192	166
T2DM with SH	25.87	176	226
T2DM with CH	26.30	235	288
T2D with N	23.05	174	198
F	0.973	0.985	0.292
p (NS)	0.408	0.402	0.831

(CH= Clinical Hypothyroidism, SH=Subclinical Hypothyroidism, N=Normal Thyroid Status)

Thus, BMI, mean triglyceride and cholesterol levels were more in those diabetic patients having coexisting hypothyroidism, than those diabetic patients having normal thyroid status. But all three were statistically not significant.

DISCUSSION

Numerous studies on the prevalence of hypothyroidism (clinical and subclinical) in diabetics and relation between them regarding various parameters have been done.

Table 28: Subject groups, Parameters studied and Number of subjects in various studies

Study	Subject Group	Parameters Studied	Subject No.		
			M	F	T
Present study	DM	All	78	44	122
Michalek AM et al	DM	Prevalence CH	54	102	156
Hecht A et al	DM	Prevalence CH	-	-	530
Perros P et al	DM	First Detected	-	-	1310
Smithson MJ et al	DM	New Cases	122	84	206
Feely J et al	DM	Prevalence CH	98	157	255
Umpierrez GE et al	T1 DM	Detection Gap	26	32	58
Gray RS, Herd R et al	DM with HT	Detection Gap	9	89	98
Gray RS, Borsey DQ et al	T1 DM	Prevalence HT	294	311	605
Nobre EL et al	T2 DM	Prevalence HT	-	-	77
Rajan SK et al	T2 DM	Prevalence HT	-	-	100
RamaSwamy M et al	T2 DM	First Detected	24	96	120
Zulewski H et al	HT	Signs and Symptoms of Hypothyroidism	-	50	50
Tachman ML et al	HT		13	64	77
Murray IP et al	HT		22	78	100
Oddie TH et al	HT		12	38	50

(DM=Diabetes mellitus; HT=Hypothyroids; CH=Clinical Hypothyroidism, SH=Subclinical Hypothyroidism)

Table 29: Prevalence of hypothyroidism (clinical and subclinical in %) in different diabetic groups

Diabetic Groups	Present study	Gray R S ,Borsey et al	Nobre E L et al	Rajan S K et al
Type 1 Diabetics	19.3	11.7	-	-
Type 2 Diabetics	14.3	-	10.7	12
Type1DM Females	25	17	-	-
Type 1DM Males	15.8	6.1	-	-
Type2 DM Females	21.8	-	-	-
Type 2DM Males	10.2	-	-	-

Prevalence of hypothyroidism (clinical and subclinical) was 15.6% in present study, compared to 13.4 % in study by Perros P et al. Prevalence of hypothyroidism in type 1 diabetics was 19.3% in the present study compared to 11.7% in the study by Gray R S,Borsey DQ et al. Hypothyroidism was most common in type 1 diabetic females.

Table 30: Prevalence of Clinical Hypothyroidism in Diabetics (%)

Clinical Hypothyroidism in Diabetics	Total
Present study	6.5
Michalek A M et al	6.4
Hecht A et al	1.7
Feely J et al	4.0
Clinical Hypothyroidism in Type2 DM	**Total**
Present study	6.6
Nobre E L et al	7.2
Rajan S K et al	1.0

Thus, the prevalence of clinical hypothyroidism in diabetics was 6.5% in present study, and ranged from 1.7% to 6.4% in other studies. In type 2 diabetics, the prevalence of clinical hypothyroidism was 6.6% in present study, and 7.2% and 1.0% in other studies.

Table 31: First Detected Condition among those with both diabetes mellitus and hypothyroidism (clinical and subclinical)

First Detected	Present study	Ramaswamy et al
Diabetes mellitus	78.9	99
Hypothyroidism	15.8	1
Both	5.3	-

Thus, in both the studies, diabetes mellitus was detected first in most patients with both conditions.

Table 32: First detected condition in patients having both Diabetes Mellitus and Clinical Hypothyroidism

First detected	Present study	Perros Petal
Diabetes mellitus	62.5	89.0
Clinical Hypothyroidism	25.0	8.8
Both	12.5	5.2

Thus, diabetes mellitus was detected first in most patients having both the conditions, whereas both were detected simultaneously in 12.5% of cases in the present study.

Table 33: Gap between Detection of type 1 Diabetes and Clinical Hypothyroidism

Mean Gap (in years)		
Present study	**Umpierrez GE et al**	**Gray RS, Herd R et al**
9.00	8.0	6.7

Thus, in type 1 diabetics the gap between the detection of two was 9 years in present study, was 8 years and 6.7 years, in studies by Umpierrez G E et al and Gray RS, Herd R et al respectively.

Table 34: Percentage of New Cases of Hypothyroidism detected among Diabetics not known to be hypothyroid prior to inclusion into the study

% New cases of	Present study	Perros P et al	Smithson MJ et al	Feely J et al
Subclinical hypothyroidism in diabetics	9.5	4.8	2.24	30.1
Clinical hypothyroidism in Diabetics	1.7	0.9	1.79	2.7

Thus, new cases of subclinical hypothyroidism detected as a result of present study was 9.5%, whereas it was 4.8%, 2.24% and 30.1% in other studies. New cases of clinical hypothyroidism detected as a result of present study was 1.7%, whereas it was 0.9%, 1.79% and 2.7% in other studies. The high rates of detection of new cases of subclinical hypothyroidism in the study by Feely J et al was probably due to biochemical reassessment of thyroid function tests in those having normal and borderline TSH levels. The higher prevalence of subclinical hypothyroidism than clinical hypothyroidism in some of the studies may be due to the use of sulfonylureas.

Table 35: Frequency of Symptoms of Hypothyroidism (%)

Sl. No.	Symptoms	Present Study	Zulewski et al	Tachman et al	Murray et al	Oddie et al
1	Gen. Weakness & lethargy	100	100	99	98	90
2	Dryness of skin	75	76	97	95	79
3	Cold intolerance	62.5	64	89	84	78
4	Decreased sweating	50	54	89	68	68
5	Weight gain	50	54	59	76	63
6	Paraesthesia	50	52	60	56	50
7	Constipation	37.5	48	61	54	47
8	Hoarseness of voice	25	34	52	74	66
9	Anorexia	25	22	45	40	24
10	Decreased hearing	12.5	22	30	40	17
11	Menorrhagia	12.5	12	32	33	15
12	Palpitation	12.5	10	31	23	13

Thus, generalized weakness and lethargy was the most common symptom of hypothyroidism seen in all patients, followed by dryness of skin and cold intolerance, seen in majority of cases.

Table 36: Frequency of Signs of Hypothyroidism (%)

Sl. No.	Signs	Present Study	Zulewski et al	Tachman et al	Murray et al	Oddie et al
1	Delayed relaxation of ankle jerk	75	77	82	81	84
2	Coarse skin	62.5	60	80	70	69
3	Periorbital puffiness	62.5	60	79	70	59
4	Slow speech	62.5	60	62	65	65
5	Cold skin	50	50	60	58	55
6	Bradycardia	37.5	46	40	48	50
7	Slowness of movements	25	36	40	40	34
8	Facial puffiness	25	25	30	32	32
9	Goiter	25	26	28	24	28
10	Thick tongue	12.5	13	15	18	16
11	Hair loss	12.5	10	14	18	13
12	Limb edema	12.5	10	12	14	10

Thus, delayed relaxation of ankle jerk was the most common clinical sign seen in more than 75% of patients, followed by coarse skin.

CONCLUSION

- The coexistence of diabetes mellitus with hypothyroidism is a known clinical observation. Various meta-analyses done show the prevalence of hypothyroidism in general population to be about 1%. Routine screening of thyroid function in diabetics gives a greater yield - 5 to 15 times than that found in the general population.
- Hypothyroidism in these diabetics may cause subtle symptoms especially weight gain and tiredness, also commonly seen in diabetic patients, and difficult to control hyperglycemic state and dyslipidemia.
- In patients having both clinical hypothyroidism and diabetes mellitus, diabetes is detected earlier in most patients.
- Increased prevalence of hypothyroidism is seen in female sex, type 1 diabetics and in elderly type 2 diabetics.
- The ability to diagnose and treat unsuspected hypothyroidism in diabetic populations may result in better control of the diabetic as well as of the dyslipidemic states, thereby greatly enhancing the quality of life by preventing premature atheroscelerosis and Coronary artery dieses.
- This study justifies the view that all diabetic patients should be screened for hypothyroidism.

BIBLIOGRAPHY

1. Clinical diabetes journal vol.1.18 no.1, winter 2000
2. Werner Sidney .C. Editor The Thyroid 5th edition Berlin: Springer 1986 p.3-5
3. Spear Dorothy B, Mc Gavack Thomas Hodge. History of the Thyroid Gland. In: McGavack T H, editor. The Thyroid. New York: McGraw Hill; 1951. p. 17-21.
4. Hall R, Maurice F S. Hypothyroidism: Clinical features and Complications. Clinics in Endocrinology and Metabolism. 1979 Mar 8; (1) : 29-38
5. Gray's Textbook of Anatomy 39th, Edition,Section 3, Chapter 31
6. Keith L.Moores Textbook of Anatomy p.1083-1085
7. Langmans Medical Embryology 9th Edition p.384-385
8. Ganong Textbook of Physiology 23rd Chapter 20
9. Ganong Textbook of Physiology Chapter 20, Table 7
10. Larsen P R, Davies T F, Schlumberger M J, Hay I D. Thyroid. In : Larsen P R, Kronenberg H M, Melmed Shlomo, Polonsky K S, editors. William's Textbook of Endocrinology. 10th ed. Philadelphia: Saunders; 2003. p. 331-490.
11. Hypothyroidism. In : Green G B, Harris I S, Lin G A, Moylan

K C, Schaiff R editors. The Washington Manual of Medical Therapeutics.31st ed. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 490-1.

12. Greenspan's Basic and Clinical Endocrinology, 8th Edition- Chapter 8
13. Harrison's Principles of Internal Medicine, 17th Edition, Appendix-Table 2
14. William Petit's Encyclopedia of Endocrine Diseases p.221-222
15. Conn's Current Therapy Chapter161, 2008 ,60th Edition by Rakel and Bope
16. Greenspan's Basic and Clinical Endocrinology 8th Edition, Chapter 8
17. Current Medical Diagnosis ant Treatment 2009, Chapter 26, p.393-395
18. NMS Medicine by Wolfsthal Chapter 15, p.312
19. William's Text book of Endocrinology Section 3, Chapter 12
20. Shah N.F.Tests of Thyroid function, JAPI 2008;48.Suppl. 1:15-8
21. Souhami's Textbook of Medicine p.915-917
22. Kumar and Clark'sTextbook of Medicine ,7th Edition Chapter 18
23. Harrison's Principles of Internal Medicine, 17th Edition, Chapter 335
24. ACP Book of Medicine,2007 Edition, Part3,Chapter 1

25. Joslin's Book of Diabetes,14 Edition,Section 3

26. New Concepts in Diabetes and Treatment by Karges

27. Edwards C R W,Toft AD, Walker B.R. Endocrine Diseases

28. Goldstein DE, Drash A.Gibbs.DiabetesMellitus

29. Harrison's Principles of Internal Medicine, 17th Edition, Table 338-2

30. ADA-Diabetic Care, volume 31,Jan 1,2008

31. Joslin's Diabetes, 14th Edition,Section 3

32. Harrison's Principles of Internal Medicine 17th Edition, Table 338-1

33. Goodman and Gilman's The Pharmacologic Basis of Therepeutics-11th Edition,Table 60-6

34. Katzung's Basic and Clinical Pharmacology,11th Edition, Section 8, Chapter 41, Table 41-6

35. Goodman and Gilman's The Pharmacologic Basis of Therepeutics-11th Edition,Table 60-3

36. Katzung's Basic and Clinical Pharmacology,11th Edition, Section 8, Chapter 41,Table 41-4

37. Patricia Wu.Thyroid Diseases and Diabetes:Practical Pointers Clinical Diabetes2000, Winter 18-1: 10-12

38. Michaelek,Mahoney,Carebaugh - Hypothyroidism and Diabetes Mellitus in an American Indian Population, Journal of family practice 2000,July;49:633-7
39. US Preventive Sciences Task Force- Guide to Clinical Preventive Services- 2nd Edition,1986
40. Ganz k. Kozak, Diabetes and Primary Hypothyroidism- Archives of Internal Medicine 134,1974;430-8
41. Kozak, Cooppan Ramachandran associated endocrine disorders in Joslin's Diabetes,796-8
42. Hecht a.Gershbert H.Diabetes and Primary Hypothyroidism- Metabolism- 968;17;108-13
43. Perros,Macrimmon,Shaw-Frequency of Thyroid dysfunction in Diabetes Mellitus- Diabetic Medicine 1995;22:622-7
44. Smithson- Screening 0f Thyroid dysfunction in community population of Diabetic patients- Diabetic Medicine-1998; 14:148-50
45. Feely.J, Isles TE- Screening of Thyroid Dysfunction in Diabetis Mellitus_British Medical Journal;1979:1:1678
46. Duckworth,Badlissi,Kitabchi-Thyroid function in Diabetes Mellitus-In Vanmidddlewor Editor-Thr Thyroid Gland, Chicago;Year Book Medical; 1986;p.247-6

47. Petitt,Landing,Grest-Journal of clinical endocrinology and metabolism 1963;21:119-120
48. Nakazonu,Kudo,Baba,Kikuchi Takebe-Thyroid abnormalties in Diabetes-tokuhu Journal of Exp.Medicine, 1986 Dec,141:Suppl.275-81
49. Maugendre, Guilhem, Lorcy, Legurrier-Annals of Endocinology(paris) dec.2000;524-30
50. Whitigham,Mathew,Mckay-Diabetes mellitus, Autoimmunity and ageing- Lancet1971;763-66
51. Riley,Lesothe,Spillar,Rosenblom- Thyroid Autoimmunity and IDDM-Journal of Pediatrics 1987;99:350-4
52. Landing- Chronic Thyroiditisin Diabetes-Journal of clinical endocrinology- 1961;29:119-20
53. Mclaren,Riley-Thyroid,Gastric and Adrenal antibodies associated with IDDM- Diabetic care,1985:8:34
54. Riley.W.J.Autoimmune Polyglandular syndromes 1992;38:1
55. Umpierrez.G.E, Latif,Murphy-Thyroid dysfunction in patients with IDDM-A Longitudinal study-Diabetic care,2003;April,26:1181-85
56. Sridhar,Nagamani-Clinical association of Autoimmune disease with Diabetes Mellitus- Analysis fom South India,2002, April;958:190-2

57. Gray,Herd and Clarke- Clinical features of Diabetes with coexisting autoimmune Thyroid Disease- Diabetologia-1981,20:602-6
58. Vondro,Vrbikova,Sterzl,Zamrazil-Thyroid Antibodies and their clinical relevance in young adults with IDDM during first 12 years of Diabetes onset-Journal of Endocrinological Investigations,2004,Sep.27-728-32
59. Surgue,Mcenvoy-Thyroid diseases in Diabetes,Post graduate medical journal 1982 Nov:680-4
60. Nobre,Jorge and Pratas-Profile of thyroid function in a population of type 2 DM- Endocrine Abstracts 3:290
61. Radieh, Nusier,Amari,Naser-Thyroid dysfunction in Type 2 DM in Jordan-Saudi Medical Journal 2001Aug.,25:1046-50
62. Bal, Kaur and Gurpal singh-Prospective analysis of Thyroid abnormalties in cases of Type 2 DM-JAPI 2003,Dec:51:1165-6
63. Rajan, Ezilarasi,Sasidharan and Madhu-Thyroid dysfunction in patients of Type 2 DM- JAPI 2003 Dec:51;1229
64. Ramasamy,Balaraj,ramarao Chandar and Mohan Rao-Hypothyroidism in Type 2 DM-JAPI 2003 Dec,51:1100
65. Gallos,Stolk,Endes and Weirsinga-Thyroid dysfunction during pregnancy and first year postpartum in IDDM-Eoropean Journal of Endocrinology 2002,Oct;147:443-457

66. Greenspan's book of clinical Endocrinology-8th edition, chapter 8
67. Williams text book of Endocrinology-11th edition,section 3
Chapter 12
68. Contemporary Endocrinology-Terry.F.Davies-Chapter7,Page242-4
69. Williams textbook of Endocrinology 11th edition, chapter12,
section 3

PROFORMA

Clinical Study of Hypothyroidism in Patients of

Diabetes Mellitus at CMCH, Coimbatore

Case No.	:	OP/IP No.	:
Name	: Mr. / Mrs.	Unit	:
Age	: years	DOA	:
Sex	: M/F	DOD	:
Address	:	Occupation	:
		Income	:

Presenting Complaints and History Of Presenting Complaints:

Hypothyroidism Related	Diabetes Related
General Gen. Weakness & lethargy Somnolence Cold intolerance Gen. Edema , Wt.gain Periorbital puffiness Hoarseness of voice slowness of speech Swelling in thyroidregion **Dermatological** Dryness of skin Decreased sweating Lower limb skin changes & swelling Hair loss (head/eyebrow) Brittle nails Yellowish discoloration of skin	**General** Polyuria Polydipsia Polyphagia Weight loss **ShortTerm Complications** Poor healing of wounds Abscess / Carbuncle Burning micturition Fever (with description) Cough Nausea , vomiting Pain abdomen **Microvascular Complications** Visual blurring/diplopia/Tingling / Numbness/Neuropathic pain

Gastrointestinal Constipation Abd.Distension **Cardiorespiratory** Dyspnea Palpitations **Neuromuscular** Paresthesia Aches & pains Muscle & joint stiffness Muscular Cramps Physical and/or mental slowness Depression Ataxia (cerebellar) **Reproductive** Menorrhagia Infertility Galactorrhoea Impotence	**Miscellaneous** Giddiness on standing Dependant edema (Lower limbs/sacral area) Abd. bloating/nocturnal diarrhea Gustatory sweating Impotence Puffiness of face Swelling of feet / whole body Decreased urine output Freq. /day; amt. ml/day **Macrovascular complications** Ulceration of skin (non-healing) Claudication pain : duration progression Gangrene of limb(s) Chestpain / other IHD features **Others**

Past History: If already a known

Diabetic	Hypothyroid
• duration • how detected • type I / II • treatment (with duration) OAD, Insulin • degree of control • h/o complications	Type-Pri. / Sec. treatment (withduration)

- h/o pulmonary tuberculosis
- h/o thyroid surgery / radio abalation of thyroid
- h/o drug intake :
  Antithyroiddrugs/Amiodarone/Sertraline/Chloroquine or drugs causing inadequate control (Phenobarbitone/Phenytoin/Rmp)
- Which was diagnosed earlier :

  DM/Hypothyroidism/Simultaneously

  : Gap between the two.

Personal History:

Diet – Pred. veg/Pred. non-veg-

Fiber content of diet: good/low

Appetite:normal / decreased /increased;

Sleep : normal / disturbed (cause)

Bowel Habits: normal / altered;

Bladder Habits: normal / altered

Smoking: Beedis / Cigarrettes;

No. / Day; since years

Alcohol: CAGE Questionnaire Score: < 2 / > 2 (total 4)

Menstrual History:

Cycles: reg/irregular; duration of cycle days; flow for days;

amt. ml/ flow; clots + / -; pain assoc.; recent change

Obstetric History:

H/O infertility + / -;

Last childbirth (time since)

No. of pregnancies & outcome

Family History

(Diabetes,Hypothyroidism)

Other significant ; Pedigree Analysis

General Physical Examination

1. Appearance : young/middle aged/elderly; slowness of movements
2. Built & Nourishment :
3. Wt. _ Kg; Ht. cm; BMI = kg/sqm ;US/LS; Hip/Waist Ratio
4. Hair : Texture – normal/coarse/dry; Hair loss (scalp/outer eyebrow)
5. Skin : dry & coarse/cold skin/xanthelesma/acanthosis nigrans
   : dilated veins over neck/upper thorax
6. Eyes : Pallor / icterus / periorbital edema
7. Oral cavity : Tongue; teeth ; mucosa
   : Hoarseness of voice
8. Cyanosis / Clubbing (grade) - / nails (Platynychia / Koilonychia/brittle/pallor)
9. Lymphadenopathy (description) :
10. Oedema : Face/UL/Body/LL/Anasarca; Pitting/non-pitting

Vital Signs:

Pulse: rate ___/ min; rhythm; Volume;

Character: radio-radial / radio-femoral delay

other pulses felt

BP: _____mm Hg in _____limb in _____position

DiastolicHTN

Orthostatic Hypotension (> 20/10 fall on standing for 3 min.)

Sustained Handgrip (increased DBP by < 10 mm Hg after 5 min.)

Respiration: rate _/ min;

abdominal/thoracic/abdominothoracic.

Body temperature (Axillary):

JVP: normal / increased (description)

Local Examination (Thyroid Region)

Goitre: Present / absent

If present: Grade I / II / III (in neutral position of neck)

: Movement with deglutition

: Tender / non-tender; local temp. Normal/increased

: Shape & size

: Surface – smooth/nodular

: Consistency – soft / firm / hard

: Mobility ; bruit

: Carotid pulsations felt / not felt.

Systemic Examination

Cardiovascular System:

Apical Impulse: Localization &
character

LPH/Epigastric / other pulsation(s)

Cardiac borders:

pericardialeffusion:

Auscultation:

Respiratory System:

Droop of shoulders

Tracheal position

Chest movements

Percussion: evidence of pleural effusion

Auscultation:

Per Abdomen:

Hepatomegaly / Splenomegaly

Evidence of ascites

Bowel sounds: normal / sluggish / absent

Central Nervous System:

Higher Mental Functions:

Level of consciousness

Orientation

Memory / Speech & Language / Intelligence

Cranial Nerves:

Optic Fundi

III, IV

Deafness: if present type ; other cranial N.

Motor System:

Bulk; Tone

Power

Reflexes – Delayed relaxation of Ankle Jerk ;

Any wasting / motor weakness of Quadriceps

Sensory System:

Peripheral neuropathy (vibration/joint position sense/touch/pain)

Others:

Gait:

Coordination: normal/RUL/RLL/LUL/LLL

Cerebellar function:

Meningeal irritation signs

Involuntary movements:

INVESTIGATIONS;

Routine:

Hb ___g/dl; TC ____/cu-mm; DC :N _% L ___%, M ____% E ____%,
B ___%,

ESR ___mm/1st hr; Urine: Alb _____, Sug __, Microscopy

Blood Urea __mg/dl; Serum creatinine __mg/dl;

Peripheral Smear:

CXR

ECG:

Diabetes Related:

FPG ____mg/dl; PPG _____mg/dl; HbA1C (if done) ___%;

Lipid Profile (mg/dl): TGs _____; HDL ___;LDL _____;

VLDL __ X-ray Abdomen (evidence of FCPD):

Hypothyroidism Related:

Thyroid Profile: TSH ___, TT3 ____, TT4 ____

Serum Cholesterol:

Neck X-ray:

Thyroid Ultrasound(if done)

Others:

- Echocardiography / LFTs / X-ray of involved bones & joints
- Others needed in relation to complication (s) present

Final diagnosis:

I .Treatment

Drugs	Dose	Duration

II Dietary Advice:

III Problem related to management of either condition in relation to the other

IV Follow Up (when done):

SUMMARY OF THE CASE:

Sl No	Name	Age	Sex	FD	Gap	Thyroid Related														Rx			Symptoms of Hypothyroidism											
						TY	D	FPG	PPG	Complications										OAD	INS	Reg	10	11	12	13	14	15	16	17	18	19	20	21
										1	2	3	4	5	6	7	8	9																
1.	Dovaki	70	F	DM	19.66	2	20	166	255				+	+	+		+		+	-	IR	+						+				+	
2.	Ramesh	24	M		.	1	1	90	108										-	+	R			+						+			
3.	Shanti	40	F	DM	2.66	2	1	102	128										+	-	R	+	+	+	+	+	+	+	-	-	-	+	-
4.	Sushila	54	F	T	2	2	12	139	164				+		+		+		+	-	R	+	+	+	-	-	-	-	+	+	-	-	-
5.	Shivraju	21	M	T	19.5	1	0.5	80	140										-	+	R	+	-	-	-	-	-	-	-	-	-	-	-
6.	Devarajan	48	M	DT	0	2	2	235	273										+	-	IR	+	+	+	+	+	+	-	-	-	-	-	-
7.	Govindammal	70	F		.	2	14	80	110				+	+	+		+		+	+	IR			+									
8.	Kandasamy	50	M	DM	0.83	2	0.83	142	230				+				+		+	-	IR	+	+	+	+	-	-	+	-	-	-	-	-
9.	Anandhi	24	F		.	1	3	104	136										-	+	R												
10.	Annapoorani	49	F		.	2	6	235	281				+		+				+	+	IR												
11.	Parvathy	55	F		.	2	3	160	230	+			+		+		+		+	-	IR			+									
12.	Begum Jaan	70	F		.	2	15	185	211	+			+		+		+		+	+	IR												
13.	Parthasarthy	75	M		.	2	0.5	130	170				+		+		+		+	+	IR	+					+						
14.	Rangammal	75	F		.	2	4	134	160				+	+	+	+			+	-	IR												
15.	Vincent	59	M		.	2	4	111	266				+		+				+	+	IR												
16.	Vijaya	28	F		.	1	6	100	149	+			+	+	+		+		-	+	IR												
17.	Pechiyammal	85	F		.	2	0	176	233										-	-	.												
18.	Kuppayee	75	F		.	2	20	98	132				+		+				+	+	R			+									
19.	Madammal	60	F		.	2	20	234	273	+			+		+				+	-	IR												
20.	Lakshmiammal	70	F		.	2	15	354	412				+	+	+		+		+	-	IR												
21.	Abida Banu	52	F		.	2	0	199	247					+					-	+	.			+									
22.	Shakuntala	75	F	DM	20	2	20	140	188	+			+	+	+		+		+	+	IR		+					+					
23.	Mylathal	60	F	DM	9	2	9	160	210				+	+	+		+		+	+	IR												
24.	Nazeema	20	F	DM	2	1	2	190	260		+								-	+	IR				+			+				+	
25.	Mangalam	34	F		.	1	10	170	230	+			+		+				-	+	IR												
26.	Somashekar	30	M		.	1	8	180	232				+		+				-	+	IR												
27.	Gurumurthy	36	M		.	1	12	380	490				+		+				-	+	IR												
28.	Amnadurai	70	M		.	2	4.5	180	240				+				+		+	-	IR												
29.	Devaraj	50	M		.	2	0.5	160	237								+		+	-	IR			+						+			
30.	Mahadevan	60	M		.	2	2	172	289										+	-	IR												
31.	Mahadevaraj	54	M		.	2	1	180	255										+	-	IR												
32.	Nanjaiah	54	M		.	2	10	190	252				+	+	+				+	+	IR												
33.	Alexander	70	M		.	2	4	230	280		+		+		+		+		+	-	IR												
34.	Nagaraj	46	M		.	2	2	170	210								+		+	-	IR							+					
35.	Thangamani	78	M		.	2	5	160	190				+		+	+	+	+	+	-	IR												
36.	Srinivas	43	M		.	2	0.16	180	212			+					+		+	-	IR												
37.	Rajammal	50	F		.	2	0.83	180	238										+	-	IR												
38.	Madammal	60	F		.	2	1	168	207								+		+	-	IR												
39.	Uma Devi	55	F		.	2	0.5	134	181										+	-	R							+					
40.	Mariyathal	56	F		.	2	0.5	200	270										+	-	IR												
41.	Fatima	58	F		.	2	13	170	198				+	+	+		+		+	+	IR			+									
42.	Mary	79	F		.	2	30	210	270		+		+	+	+		+		+	+	IR												
43.	Gulab Jaan	60	F		.	2	15	170	213				+	+	+		+		+	+	IR							+					

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Sl No	Htn	FH	BMI	Other Systemic S/S					Tg	Ch	Fu																				
	Signs of Hypothyroidism																TFTs														
	22	23	24	25	26	27	28	29	30	31	32	33	Stat	KNFU	D	Goit	T3	T4	TSH	DOC				CVS	RS	PA	CNS			
1.									-				SH	n	0	-	75	5	10	P	+	2	27.81					177	289	+
2.									-				N	.		-	120	7	1.2	.	-		17.3					122	154	-
3.	+	-	-	-	-	-	-	-	-	-	-	-	CH	fu	2.66	-	186	12.8	1.4	.	+	2	35.6					120	143	+
4.	-	+	+	+	-	-	-	-	+	-	-	-	CH	k	14	+	106	12.4	1.29	G	-		26.17					159	195	+
5.	+	-	-	-	-	-	-	-	-	+	-	-	CH	k	20	-	42	2.35	104.6	P	-		21.35		PlE	A	MR	200	204	+
6.	-	+	+	+	+	+	-	+	-	-	-	-	CH	k	2	-	53	2.1	34.18	P	-		21.8					188	160	+
7.									-				N	.	.	-	54	6	2.55	.	+		25.15					160	125	-
8.	+	+	+	+	+	+	-	-	-	-	+	-	CH	n	0	-	50	3.2	31.7	P	+		22.95					184	237	-
9.									-				iS	n	0	-	118	8.3	0.21	.	-		21.33					140	169	-
10.									+				N	.	.	+	161	10.17	0.7	.	+		27.73					143	190	-
11.									-				N	.	.	-	160	9	1.4	.	+		24.98					180	220	-
12.									-				N	.	.	-	76	7	1.54	.	+	2	21.34					176	250	-
13.				+				+	-				N	.	.	-	87	5.66	5.66	.	-		23					130	170	-
14.									-		+		N	.	.	-	118	6.08	0.5	.	+		30.47	LS3	BC			140	180	-
15.									-				N	.	.	-	145	5.21	6.16	.	+	2	19.47					109	177	+
16.		+						+	-				N	.	.	-	143	5.2	1.93	.	+		19.95					178	150	-
17.									-				N	.	.	-	177	5.51	1.02	.	-	2	20.5					180	191	+
18.									-				N	.	.	-	64	5.2	1.52	.	-		24					124	170	-
19.									-				N	.	.	-	82	6.89	1.13	.	-	2	12.14					108	120	+
20.		+				+			-			+	N	.	.	-	86	10.82	0.77	.	+		30					117	150	-
21.									-				N	.	.	-	20	8.65	2.72	.	-		23			HMA		140	154	-
22.									-	+			SH	n	0	-	73	7.11	8.14	.	-	2	27.14	LV3	BC			170	220	+
23.					+				-	+			SH	n	0	-	78	8.2	9	.	+		27					168	207	+
24.			+				+		-			+	SH	n	0	-	62	6.24	8.8	.	-		22.4					202	180	-
25.									-				N	.	.	-	70	4.6	0.8	.	-		16.84					160	150	-
26.									-				N	.	.	-	121	7.21	1.53	.	-		17.23					162	138	+
27.									-				N	.	.	-	64	4.5	3.42	.	-	1	18.2					148	140	-
28.		+	+						-				N	.	.	-	133	8.14	3.17	.	-		24.03					150	210	-
29.									-		+		N	.	.	-	162	8.2	3.2	.	-		24					172	216	-
30.									-				N	.	.	-	97	4.53	3	.	-		25.23					140	182	+
31.									-				N	.	.	-	103	7.12	1.62	.	-		23.2					131	184	-
32.									-				N	.	.	-	65	4.81	2.74	.	-	2	22.24					172	210	-
33.			+				+		-				N	.	.	-	131	7.93	2.7	.	-		27.09					170	176	-
34.									-				N	.	.	-	150	9.21	12.91	.	-		20.05	LV3	BC	HMA		133	230	-
35.									-				N	.	.	-	68	4.73	4	.	+		26.23					147	245	-
36.									-			+	N	.	.	-	77	5.23	3.88	.	-		25.29					143	288	-
37.									-				N	.	.	-	140	7.32	4.1	.	-		22.01					149	180	+
38.				+					-				N	.	.	-	143	7	2.88	.	-		24.06					150	173	-
39.									-				N	.	.	-	92	6.3	3	.	-		27	LV3				140	253	-
40.									-				N	.	.	-	117	6.72	1.98	.	+		22.34					191	200	-
41.									-				N	.	.	-	113	6.8	3.42	.	-		21.29	LV3				190	192	+
42.									-				N	.	.	-	89	7.68	2.16	.	-	2	17.05			A		138	262	-
43.									-				N	.	.	-	95	6.17	2.34	.	-	2	23.07					131	206	+

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44.	Kuruvammal	68	F	DM	13	2	18	147	184	+			+		+		+		+	+	IR	+	+	-	-	-	-	-	-	-	-	-	-	-
45.	Gafoor	60	M	DM	7	2	7	150	210				+	+	+		+		+	-	IR			+				+						
46.	Siddayan	75	M	DM	20	2	20	180	230		+		+	+	+		+		+	+	IR												
47.	Madayan	50	M	DM	5	2	5	138	160								+		+	-	R												
48.	Kumarswamy	48	M		.	2	4	142	180			+	+	+	+		+		+	-	IR												
49.	Laxmi	38	F		.	1	16	180	250				+						-	+	IR												
50.	Papammal	22	M	DM	3	1	3	130	190										-	+	R												
51.	Krishnaraj	58	M		.	2	10	160	230				+		+		+		+	+	IR												
52.	Nagaraj	43	M		.	2	3	170	230				+						+	+	IR												
53.	Sankaran	40	M		.	2	2	110	170										+	-	R												
54.	Gurumurthy	20	M		.	1	1	140	190										-	+	IR												
55.	Dhandapani	45	M		.	2	5	136	164										+	-	R												
56.	Krishna	42	M		.	2	2	160	198				+				+		+	-	IR												
57.	Lawrence	30	M	DM	8	1	8	130	180	+	+	+	+	+	+				-	+	R	+						+	+					
58.	Sivaraj	55	M		.	2	10	190	240				+		+		+		+	+	IR	+	+			+								
59.	Sivaraman	55	M	DM	9	2	9	188	230				+	+	+		+		+	-	IR	+											
60.	Hanif	49	M		.	2	7	210	270				+				+		-	-	IR												
61.	Rajashekar	40	M		.	2	2	138	174										-	-	R												
62.	Mutaiah	60	M		.	2	12	130	250			+	+		+		+		+	+	IR												
63.	Narayan	60	M		.	2	16	132	250				+		+		+		+	+	IR												
64.	Raju	30	M		.	1	10	270	350	+	+	+	+	+	+				-	+	IR												
65.	Madhu	49	M		.	2	2	180	230								+		+	-	IR	+	+					+						+
66.	Govinda	68	M		.	2	17	140	182			+	+	+	+		+		+	-	R												
67.	Krishna	63	M		.	2	10	150	230				+				+		+	+	IR												
68.	Raja	30	M		.	1	12	140	190	+	+				+				-	+	R												
69.	Mohan	55	M		.	2	8	117	264				+				+		+	-	R												
70.	Krishna	82	M		.	2	3	104	150	+			+				+		+	-	R												
71.	Ameer	60	M		.	2	6	190	230				+	+	+		+		+	+	IR												
72.	Nanjappan	50	M		.	2	7	210	290				+	+	+	+			+	-	IR												
73.	Veerasamy	70	M		.	2	15	210	230				+				+		+	+	IR					+					+		+
74.	Shahabudeen	42	M		.	2	4	146	184										+	-	R												
75.	Manoharan	70	M		.	2	13	140	180				+				+		+	+	R												
76.	Satish	34	M		.	1	10	190	240				+		+		+		-	+	IR	+											
77.	Rajgopal	66	M		.	2	12	116	173				+	+	+		+		+	+	R	+											
78.	Venkatesh	50	M		.	2	8	180	210				+		+		+		+	-	IR	+						+					
79.	Senniyappan	52	M		.	2	6	130	170				+				+		+	-	IR												
80.	Rangasamy	62	M		.	2	10	110	130				+				+		+	+	R												
81.	Raju	20	M		.	1	0.5	128	142										-	+	R												
82.	Surendran	50	M		.	2	4	139	179		+		+	+	+		+		+	-	IR												
83.	Subbaiah	60	M		.	2	11	130	148				+				+		+	-	R												
84.	Mahalingam	68	M		.	2	14	160	204				+				+		+	+	IR			+							+		
85.	Lingaraju	26	M		.	1	2	190	210										-	+	R												
86.	Krishna	38	M		.	1	16	250	270		+		+	+	+		+		-	+	IR												
87.	Ayyadurai	79	M		.	2	23	132	178				+				+	+	+	+	R												
88.	Venkatesh	50	M		.	2	7	154	209			+	+		+		+		-	-	IR												
89.	Aziz Khan	70	M		.	2	15	136	172				+		+		+		+	-	R					+							
90.	Selvaraju	50	M		.	2	8	170	230				+	+	+		+		+	+	IR												
91.	Muniyandi	50	M		.	2	10	130	180										+	-	R												

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44.	+	+	+	+	+	+	+	-	+	-	-	-	CH	k	5	+	30	3.01	25	P	+	2	25					174	238	+
45.							+		-				SH	n	0	-	64	5	8	.	+		25					138	220	+
46.									-				SH	n	0	-	70	6	7.04	.	-		24.8					148	210	+
47.	-	-	-	-	-	-	-	-	+	-	-	-	SH	n	0	+	80	7.04	7.62	.	-		23.2					158	208	+
48.								+	-				N	.	.	-	92	9	2.06	.	-		21					170	204	-
49.									-				N	.	.	-	98	6	2.5	.	+		23					200	234	-
50.									-				SH	n	0	-	40	3.8	6.8	.	-		19					210	230	+
51.									-				N	.	.	-	.	.	3.02	.	+		24					204	219	+
52.									-				N	.	.	-	102	7	1.5	.	+	2	23.28					230	202	+
53.		+							-				N	.	.	-	.	.	2	.	-		23			A		190	170	+
54.						+			-		+		N	.	.	-	.	.	3.07	.	-		21					207	140	-
55.									-				N	.	.	-	.	.	2.81	.	-		22.04					170	168	-
56.									-				N	.	.	-	78	5.6	2.19	.	-	2	22.24			HMA		209	170	+
57.				+			+		-				SH	n	0	-	70	5	7.48	.	-		19.06		PT			180	184	+
58.									-				N	.	.	-	.	.	3	.	-		24.12					230	210	-
59.				+					-				SH	n	0	-	78	6.02	9.02	.	+		28					270	220	+
60.						+			-				N	.	.	-	90	5	2.07	.	+	2	19.24					320	182	+
61.									-				N	.	.	-	.	.	0.9	.	-		21.32					174	185	-
62.									-				N	.	.	-	.	.	0.8	.	-		23.23					176	209	-
63.									-	+			N	.	.	-	100	6	1.28	.	+		21.47					202	168	-
64.			+						-				N	.	.	-	87	5.98	1.88	.	-		19.24					260	170	+
65.									-				N	.	.	-	.	.	1.5	.	-		22					210	209	-
66.									-				N	.	.	-	.	.	1	.	-	2	24.1					194	170	-
67.									-			+	N	.	.	-	.	.	2.5	.	-		23					200	202	-
68.									-				N	.	.	-	104	6	2.54	.	-		19					210	140	+
69.									-				N	.	.	-	.	.	1	.	-		21.19	PE				170	172	+
70.				+				+	-				N	.	.	-	.	.	1.76	.	-		22					220	230	-
71.									-				N	.	.	-	.	.	1.25	.	-		23.07					119	210	-
72.									-				N	.	.	-	.	.	3.2	.	+		25.19					232	260	+
73.									-				N	.	.	-	103	5.15	3	.	-		24.2					194	263	-
74.									-				N	.	.	-	.	.	1.43	.	+	2	22.1					170	194	+
75.									-				N	.	.	-	.	.	1.24	.	-		23.15					170	200	-
76.		+				+			-		+		N	.	.	-	.	.	1.93	.	-		18.74					194	153	-
77.									-				N	.	.	-	109	6.1	3	.	-		24.2					160	172	-
78.									-				N	.	.	-	.	.	1.28	.	+		22.02					184	179	-
79.									-				N	.	.	-	.	.	2.51	.	-		23.23					220	241	-
80.									-				N	.	.	-	.	.	3.5	.	+		23					230	231	-
81.		+						+	-				N	.	.	-	.	.	4	.	-	1	20.3					241	239	-
82.									-			+	N	.	.	-	85	7.23	1.07	.	-		27					300	210	+
83.									-				N	.	.	-	.	.	1.46	.	-	2	24.2					170	190	-
84.									-				N	.	.	-	.	.	3.04	.	+		23.09					232	210	+
85.								+	-				N	.	.	-	.	.	1.29	.	-		19.11					190	150	-
86.			+		+				-				N	.	.	-	.	.	2.23	.	-		20.04					270	178	+
87.									-				N	.	.	-	.	.	2.47	.	-		24.6					199	110	-
88.			+			+			-				N	.	.	-	.	.	2.9	.	-		22.04					210	170	-
89.									-				N	.	.	-	.	.	1.9	.	-		21		LA			160	210	+
90.									-				N	.	.	-	.	.	2.05	.	+		23.97					140	202	+
91.									-				N	.	.	-	112	5.7	4.5	.	+		25.83					158	178	-

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92.	Rangan	65	M		.	2	17	116	150				+		+		+		+	-	R														
93.	Cheran	25	M		.	1	7	140	190	+									-	+	R			+				+							
94.	Rallikumar	36	M		.	1	13	180	243				+	+	+		+		-	+	IR														
95.	Prakash	50	M		.	2	7	140	162								+		+	-	R														
96.	Iqbal	58	M		.	2	8	150	199				+	+	+		+		+	-	IR	+													
97.	Chennaiah	25	M		.	1	7	130	171										-	+	R														
98.	Narayana	43	M		.	2	2	130	164										+	-	R														
99.	Shankar	30	M		.	1	10	170	238				+		+				-	+	IR	+						+							
100.	Kemagaraj	55	M		.	2	4	118	169				+						+	-	R														
101.	Sidayan	78	M		.	2	18	139	163				+	+	+		+		+	+	R														
102.	Madan	35	M		.	1	14	174	221	+	+		+	+	+				-	+	IR														
103.	Nageraj	20	M		.	1	2	190	220	+									-	+	R														
104.	Gurumurthy	56	M		.	2	1	188	213				+		+		+		+	-	IR					+									
105.	Siddique	80	M		.	2	23	144	180				+		+		+		+	+	R														
106.	Rehmat	55	M		.	2	1	149	169								+		+	-	R														
107.	Veppammal	55	F		.	2	10	150	202				+				+		+	+	IR														
108.	Puttammal	50	F		.	2	0.5	116	140						+		+		+	-	R														
109.	Saroja	56	F		.	2	3	163	238				+						+	-	IR					+							+		
110.	Gayathri	44	F		.	2	2	190	232				+	+		+	+		+	+	IR														
111.	Jaleena B	36	F		.	2	1	140	170										+	-	R														
112.	Salima B	65	F		.	2	15	178	213	+			+	+	+		+		+	+	IR														
113.	Sadayammal	70	F	DM	22	2	20	180	220				+	+	+		+		+	+	IR	+	+	+	-	+	+	+	+	+	+	+	+	-	-
114.	Bharathi	23	F		.	1	7	190	290		+		+						-	+	IR														
115.	Kumari	35	F	DM	10	1	10	250	370			+	+		+				-	+	IR	+	+					+				+			
116.	Meenaxi	20	F		.	1	1	170	200										-	+	R														
117.	Parvathy	50	F		.	2	2	138	268								+		+	-	R														
118.	Roopa	26	F		.	1	4	160	220	+			+						-	+	IR			+								+			
119.	Kamagammal	58	F		.	2	3	180	240				+						+	-	IR														
120.	Farida	34	F	DM	9	1	11	350	470		+		+		+				-	+	IR	+	-	-	+	+	+	-	-	-	-	-	+		
121.	Ayesha	22	F		.	1	4	330	500			+	+		+				-	+	IR														
122.	Savitri	23	F		.	1	3	138	180										-	+	R														

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92.									-				N	.	.	-	.	.	1.13	.	-		22.38					170	200	-
93.						+			-				N	.	.	-	.	.	1.75	.	-	1	20.22					120	128	-
94.				+					-				N	.	.	-	107	4.87	4.07	.	+		24.9					190	230	+
95.									-		+		N	.	.	-	.	.	1.07	.	-		22					180	154	-
96.									-				N	.	.	-	.	.	3.2	.	-		19.87					152	180	-
97.									-				N	.	.	-	120	5	2.3	.	-		19.01					198	176	+
98.									-		+		N	.	.	-	.	.	3.17	.	+		27					153	150	-
99.		+						+	-				N	.	.	-	.	.	1.23	.	-		18.43					179	188	-
100.									-				N	.	.	-	.	.	3.21	.	-		21.05					169	220	-
101.									-				N	.	.	-	.	.	1.32	.	+	2	24					250	110	-
102.									-				N	.	.	-	92	5.07	1.92	.	-		17.05		PT			117	163	+
103.				+				+	-				N	.	.	-	.	.	3.1	.	-		17.64					230	184	-
104.									-				N	.	.	-	132	5.23	2.12	.	-		23.02					167	189	+
105.									-			+	N	.	.	-	.	.	1.99	.	-	2	19.98					119	220	-
106.									-				N	.	.	-	.	.	2.04	.	+		22.84					123	168	-
107.			+						-				N	.	.	-	109	7.03	5.01	.	-		22.74					180	250	+
108.									-		+		N	.	.	-	.	.	4.22	.	-		23					118	241	-
109.			+				+		-				N	.	.	-	.	.	1.47	.	.	2	21.22					176	200	+
110.									-		+		N	.	.	-	160	7	2.19	.	.		22.43					177	270	+
111.									-				N	.	.	-	.	.	3.51	.	+		23					177	238	-
112.									-				N	.	.	-	.	.	1.42	.	-		21.74					174	198	+
113.	+	+	+	+	+	+	-	+	-	-	-	+	CH	fu	2	-	60	4.8	6.01	P	-		24					180	234	+
114.									-				N	.	.	-	.	.	0.54	.	-		18					142	170	+
115.		+			+		+		-				SH	n	0	-	88	7	6.42	.	-		16.99					188	152	+
116.									-		+		N	.	.	-	.	.	1	.	-		17.53					190	150	+
117.							+		-				N	.	.	-	106	5.4	0.69	.	-		23.2					163	230	-
118.									-			+	N	.	.	-	.	.	1.52	.	-	1	19.04					220	162	+
119.									-				N	.	.	-	95	5.65	0.87	.	+		24					290	250	-
120.	+	-	-	-	-	-	-	-	-	-	-	-	CH	k	2	-	30	2.1	15.88	G	-		18.58					250	142	+
121.									-				N	.	.	-	.	.	1.72	.	-		18.94					190	170	-
122.			+						-				N	.	.	-	.	.	1.68	.	-		17.5					290	138	-

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KEY TO THE MASTER CHART

H.No. = Hospital in/out-patient Number

M = Male

F = Female

FD = First Detected of Diabetes and Hypothyroidism

DM = Diabetes mellitus

T = Thyroid Dysfunction

Gap = Gap between detection of Diabetes and Hypothyroidism

TY = Type of Diabetes mellitus (1 = type 1 / 2 = type 2)

D = Duration

FPG = Fasting Plasma Glucose (mg/dl)

PPG = Postprandial Plasma Glucose (mg/dl)

A1c = Glycated Hemoglobin (%)

1 = Hypoglycemia

2 = Diabetic Ketoacidosis

3 = Hyperglycemic Hyperosmolar State

4 = Neuropathy

5 = Nephropathy

6 = Diabetic Retinopathy

7 = Cerebrovascular Accident

8 = Ischemic Heart Disease

9 = Peripheral Vascular Disease

Rx = Treatment

OAD = Oral Antidiabetics

INS = Insulin

Reg = Regularity of Treatment (IR = Irregular / R = Regular)

10=Generalised Weakness & lethargy

11=Dryness of skin

12= Cold intolerance

13 =Decreased sweating

14 =Weight gain

15 =Paraesthesia

16 =Constipation

17 =Hoarseness of voice

18 =Anorexia

19 =Decreased hearing

20 =Menorrhagia

21 =Palpitations

22 =Delayed relaxation of ankle jerk

23 =Coarse skin

24 =Periorbital puffiness

25 =Slow speech

26 =Cold skin

27 =Bradycardia

28 =Slowness of movements

29= Facial puffiness

30 =Goiter

31 =Thick tongue

32 =Hair loss

33 =Limb edema

Stat = Status

SH = Subclinical Hypothyroidism

CH = Clinical Hypothyroidism

iS = Subclinical Hyperthyroidism

N = Normal

KNFU = Known (k) / Newly Detected (n) / Follow up (fu)

TFTs = Thyroid Function Tests

T3 = Triiodothyronine

T4 = Thyroxine

TSH = Thyroid Stimulating Hormone

AMA = Anti-Microsomal Antibody

FNAC = Fine Needle Aspiration Cytology

CONSENT FORM

Yourself Mr/Mrs/Ms _____ are being asked to be a participant in the study titled – "Clinical study of Hypothyroidism in patients of Diabetes Mellitus" in CMC Hospital, conducted by Dr.T.A.Naufal Rizwan, Post Graduate student, Department of General Medicine,Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any questions before agreeing to participate.

Purpose of the research

To do the clinical study of Hypothyroidism in patients of Diabetes Mellitus and to study the patients having both endocrine disorders and their thyroid function status, in relation to the age and sex, the type of diabetes , age at detection of either condition and the clinical features.

Procedures involved

This research is intended to do a study of hypothyroidism , by means of thyroid function tests, in patients of diabetes mellitus, either previously or newly diagnosed, and aged more than 19 years.

Decline from participation

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

Privacy and confidentiality

Privacy of the individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization publish results

Results of the study may be published for scientific purposes and / or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me and I may ask questions at any time.

_____ _____

Signature of Left Hand thumb Impression Date

(Volunteer Subject)

_____ _____

Signature (Witness) Date

LIST OF ABBREVIATIONS USED

AMA= Anti-Microsomal Antibody

ASH= Asymmetrical Septal Hypertrophy

AT =Autoimmune Thyroiditis

BMI = Body Mass Index (kg/m^2)

BP= Blood Pressure

CABG=Coronary Artery Bypass Graft

CAD= Coronary Artery Disease

CCF=Congestive Cardiac Failure

CH= Clinical Hypothyroidism

CLIA= Chemiluminescence Immunoassay

DBP=Diastolic Blood Pressure

DIT= Di-iodotyrosine

DKA= Diabetic Ketoacidosis

DM=Diabetes Mellitus

DR= Diabetic Retinopathy

DUB=Dysfunctional Uterine Bleeding

EIA= Enzyme Iimmunoassay

FCPD=Fibrocalcific Pancretic Disease

FPG = Fasting Plasma Glucose (mg/dl)

F= Female

FNAC= Fine Needle Aspiration Cytology

FT3=Free triiodothyronine

FT4 =Free Thyroxine

FT4I= Free Thyroxine Index

GCT=Glucose Challenge Test

HbA1c= Glycated

Haemoglobin

HHS= Hyperglycemic Hyperosmolar State

HTN=Hypertension

IDDM=Insulin Dependent Diabetes Mellitus

IFG=Impaired Fasting Glycaemia

IGT=Impaired Glucose Tolerance

IHD= Ischemic Heart Disease

LDL=Low Density Lipoprotein

LPH=Left Parasternal Heave

M=Male

MIT= Mono-iodotyrosine

MODY=Maturity Onset Diabetes of Young

NIDDM=Non- Insulin Dependent Diabetes Mellitus

NS=Not Significant

OAD=Oral antidiabetic drugs

PPG = Postprandial Plasma Glucose (mg/dl)

rT3=reverse Triiodothyronine

RAIU= Radioactive Iodine Uptake

RT3U=T3 Resin uptake

SH=Subclinical Hypothyroidism

S=Significant

T3= Triiodothyronine

T4 =Thyroxine

TBG= Thyroxine Binding Globulin

TBPA= Thyroxine Binding Prealbumin or Transthyretin

TD= Thyroid Disease

TFT= Thyroid Function Tests

Tg = Thyroglobulin

TGs=Triglycerides

TPO= Thyroid peroxidase

TRH=Thyrotropin

TSH=Thyroid Stimulating Hormone

TSHRAb= TSH receptor antibody