PREVALENCE OF THYROID DISORDERS IN TYPE 2 DIABETIC PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY

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ENDORSEMENT

This is to certify that the dissertation entitled "**PREVALENCE OF THYROID DISORDERS IN TYPE 2 DIABETIC PATIENTS - A ONE YEAR CROSS SECTIONAL STUDY"** is a bonafide research work done by **REG NO. BG0114006.**

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LIST OF ABBREVIATIONS USED

µg/min	-	Micro gram per minute
ACE	-	Angiotensin-converting enzyme
ADA	-	American Diabetes Association
AGEs	-	Advanced glycosylated end products
ARIC	-	Atherosclerosis Risk in Communities
ATP	-	Adenosine triphosphate
BMI	-	Body mass index
BP	-	Blood pressure
CAD	-	Coronary artery disease
cAMP	-	Cyclic adenine monophosphate
DCCT	-	Diabetes Control and Complications Trial
dL	-	Decilitre
DM	-	Diabetes mellitus
DNA	-	Deoxyribonucleic acid
DPN	-	Diabetic peripheral neuropathy
DRI’s	-	Dietary reference intakes
e.g.	-	For example
ECF	-	Extracellular fluid
ESRD	-	End-stage renal disease
FDA	-	Food and Drug Administration
FPG	-	Fasting plasma glucose
FT3	-	Free Triiodothyronine
FT4	-	Free Thyroxine
g	-	Grams

GDM	-	Gestational diabetes mellitus
GLUT 4	-	Glucose Transporter 4
gms	-	Grams
HbA1C	-	Glycosylated haemoglobin
HDL	-	High density lipoprotein
HDL-C	-	High-density lipoprotein-cholesterol
HNF	-	Hepatocyte nuclear transcription factor
HTN	-	Hypertension
Hz	-	Hertz
IDDM	-	Insulin dependent diabetes mellitus
IDF	-	International Diabetes Federation
ie,	-	That is
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
IPF	-	Insulin promoter factor
IRMA	-	Intraretinal microvascular abnormality
kg	-	Kilograms
LDL	-	Low-density lipoprotein
LDL-C	-	Low-density lipoprotein-cholesterol
m	-	Meter
mEq	-	Milliequivalents
mg	-	Milligram
MI	-	Myocardial infarction
mmHg	-	Millimeter of mercury
mmol	-	Millimole

MODY	-	Maturity Onset Diabetes of Young
mol	-	Mole
n	-	Total number
NA	-	Not applicable
Na	-	Sodium
NIDDM	-	Non-insulin dependent diabetes mellitus
NPDR	-	Non Proliferative Diabetic Retinopathy
NVD	-	Neovascularisation disc
NVE	-	Neovascularisation elsewhere
p	-	Probability value
PAD	-	Peripheral arterial disease
PAI-1	-	Type-1 plasminogen activator inhibitor
PDR	-	Proliferative diabetic retinopathy
PKC	-	Protein Kinase C
PTH	-	Parathyroid hormone
RBS	-	Random Blood Sugar
RDA	-	Recommended Dietary Allowances
RNA	-	Ribonucleic acid
RT3	-	Reverse Triiodothyronine
SCH	-	Subclinical Hypothyroidism
SD	-	Standard deviation
T3	-	Triiodothyronine
T4	-	Thyroxine
T2DM	-	Type 2 daibetes mellitus
TGF	-	Transforming growth factor

TRPM6	-	Transient receptor potential channel melastatin 6
TSH	-	Thyroid Stimulating Hormone
UKPDS	-	United Kingdom Prospective Diabetes Study
UTI	-	Urinary Tract Infection
VEGF-A	-	Vascular endothelial growth factor A
vs	-	Versus
WHO	-	World Health Organization
Yrs	-	Years

ABSTRACT

BACKGROUND AND OBJECTIVES

Diabetes is one of the commonest health problem and has become a major health challenge worldwide. Evidence from literature suggests that the intricate bond between Thyroid disorder and diabetes mellitus deceptively contributes to micro and macro-vascular complications. This study is being undertaken to conclusively establish in our population an association between prevalence of thyroid disorders in Type 2 diabetic patients.

METHODOLOGY

The present one year cross-sectional study was done on 100 patients with type 2 diabetes mellitus from January 2015 to December 2015 in the Department of General Medicine at KLES Dr Prabhakar kore Hospital and Medical Research Centre, Belagavi. Patients were subjected to clinical examination, laboratory workup like Thyroid function test, fasting and post prandial blood sugar level, glycosylated haemoglobin, creatinine, urea and presence of Thyroid disorder in these patients was assessed based on the test results.

RESULTS

In the present study the mean age of the study group was 60.03 years. Males (55%) out numbered females in the study and male to female ratio was 3:2. The duration of diabetes in 51% of the patients was between 11 to 20 years.The prevalence of Thyroid disorder in our study was 35% of which Subclinical hypothyroidism was 16%, followed by subclinical hyperthyroidism in 10%, primary hyperthyroidism in 6% and primary hypothyroidism in 3% of the total diabetics. Subclinical hypothyroidism was the most prevalent (16%) among the thyroid

disorders in the diabetic patients in our study. Also non proliferative diabetic retinopathy was associated with subclinical hypothyroidism (p=0.034). An association was also found with duration of diabetes and Thyroid disorder (p=0.0240)

CONCLUSION

Thyroid dysfunction is widely prevalent in patients with type 2 diabetes in our study, hence it is prudent to screen for or to ask for Thyroid panel in Diabetics which will help in improving the quality of life and reduce the mortality rate.

KEYWORDS

Thyroid Disorder; Type 2 Diabetes Mellitus; TSH; NPDR.

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INTRODUCTION

Diabetes mellitus is a clinical syndrome characterised by hyperglycaemia caused by absolute or relative deficiency of insulin.[1] The metabolism of carbohydrate, protein and fat is affected by lack of insulin and can cause significant disturbance of water and electrolyte homeostasis; death may result from acute metabolic complications.[1]

The worldwide prevalence of DM has raised over the past two decades, from an estimated 30 million cases in 1985 to 382 million in 2013.[2] Based on current trends, International Diabetes Federation projects that 592 million individuals will have diabetes by the year 2035.[2] Diabetes is a major cause of mortality, but several studies indicate diabetes is likely under reported as a cause of death.[2]

The thyroid gland produces two hormones, thyroxine (T4) and triiodothyronine (T3), acting through the thyroid hormone receptors α and β, these hormones play a major role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in adults.[1]

Thyroid disorders are widely common with variable prevalence among the different populations. Several reports documented a higher than normal prevalence of thyroid dysfunction in the diabetic population.[3]

Hypothyroidism and hyperthyroidism are the two entities with vast difference in pathophysiology as well as clinical picture. Thyroid hormones affect glucose metabolism via several mechanisms in diabetes, is a matter of investigation. [4]

A systematic approach to thyroid testing in diabetic subjects is favourable as various studies have reported different prevalence rates of the two associated

disorders ranging with a wide difference from 12.5% to 13.2%. However, no definitive guidelines exist regarding screening for thyroid dysfunction in diabetic patients.[5]

Evidence from literature suggests that the intricate bond between subclinical hypothyroidism and diabetes mellitus deceptively contributes to the major complications such as retinopathy and neuropathy. Cardiovascular events and micro or macro-angiopathies are the counter reflection of resurgence of heavily disturbed lipid metabolism due to thyroid dyscrasias.[4]

The identification of new cases of thyroid dysfunction and early intervention, the possible aggravation of risk factors such as hypertension and dyslipidemia, arising from an undiagnosed thyroid dysfunction may significantly reduce.[6]

This study is being undertaken to conclusively establish in our population an association between prevalence of thyroid disorders in Type 2 diabetic patients.

OBJECTIVE OF THE STUDY

The objective of the present study is:

- To study the prevalence of thyroid disorders in Type 2 Diabetics.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is defined as a group of common metabolic disorders that share the phenotype of hyperglycemia. Many types of diabetes mellitus are present and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology, the factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems which imposes tremendous burden on the individual with diabetes and on the health care system.[2]

Diabetes mellitus is the leading cause of end-stage renal disease, nontraumatic lower extremity amputations and adult blindness and it also predisposes to cardiovascular diseases. As diabetes mellitus is an increasing incidence worldwide, it will likely be a leading cause of morbidity and mortality in the future.[2]

Epidemiology and Global Consideration

Worldwide

In all age-groups worldwide the prevalence of diabetes was estimated to be 2.8% in 2000 and 4.4% in 2030. In the whole world there are 382 million people living with diabetes. The estimated worldwide prevalence of diabetes in adults (aged 20-79 years) was calculated to be 135, 285 million in 1995 and 2010 respectively and is expected to be 300 million in 2025 and 439 million in 2030.[7-14]

Indian scenario

The International Diabetes Federation (IDF) estimated that, there will be increase in the people living with diabetes in India up to 87.0 million by 2030 from 50.8 million (2010), making it the 'Diabetes Capital' of the world.[15-17] The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemicalabnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease.[18]

Sex predilection

It has been observed that the prevalence of diabetes is higher in men than women.[8-14]

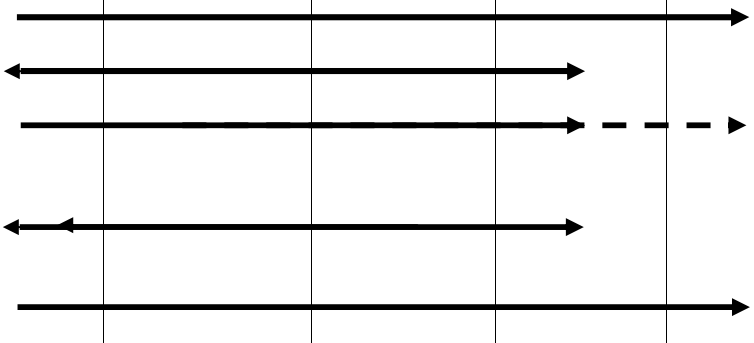
Mortality

The observation shows that 1.5 million deaths have occurred in 2012 worldwide making it the 8th leading cause of death and more than 80% of diabetic deaths occurring in low and middle-income countries. Due to diabetes during pregnancy more than 21 million live births were affected and > 79,000 children developed type 1 diabetes in 2013.[8-14]

CLASSIFICATION OF DIABETES AND SPECTRUM OF GLUCOSE HOMEOSTASIS

Diabetes mellitus is classified on the basis of the pathogenic process which leads to hyperglycemia.[2]

Spectrum of glucose homeostasis and diabetes mellitus[1]

Type of diabetes	Normal glucose tolerance	Hyperglycemia			
		Impaired fasting glucose or impaired glucose tolerance	Diabetes mellitus		
			Not insulin required	Insulin required for control	Insulin required for survival
Type 1 **Type 2** **Other Specific types** **Gestational diabetes** **Time (years)**					
FPG (mg/dL)	< 100	100-125	≥ 126		
2-h pg (mg/dL)	< 140	140 – 199	≥ 200		
HbA1C (%)	< 5.6	5.7 – 6.4	≥ 6.5		

There are two broad categories of diabetes mellitus: Type 1 and Type 2.

Type 1 diabetes mellitus is the result of complete or near-total insulin deficiency due to autoimmune beta cell destruction. Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. In type 2 diabetes mellitus distinct genetic and metabolic defects in insulin action and/or secretion give rise to common phenotype of hyperglycemia.[2]

There are two features of the current classification of diabetes mellitus that differ from previous classifications. First, the terms insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) are obsolete. As many of the individuals with type 2 diabetes mellitus eventually require insulin treatment for control of glycemia, the term NIDDM is not used. A second difference is that age is not a criteria for diagnosis in the classification .[2]

Although type 1 diabetes mellitus most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. It is estimated that individuals who develop diabetes mellitus after age 30 years have type 1 diabetes mellitus are between 5 and 10% . Even though type 2 diabetes mellitus more typically develops with increasing age, it is now being diagnosed more frequently in children and young adults, particularly in obese adolescents.[2]

TYPE 2 DIABETES MELLITUS

Type 2 Diabetes Mellitus is the most common form accounting upto 80% to 95% of all Diabetes and encompasses those individuals with insulin resistance and thus have relative insulin deficiency.[19]

The factors responsible for type 2 Diabetes Mellitus are many and specific etiologies are not known. Obesity is seen in many of the patients with type 2 diabetes mellitus and insulin resistance to some extent is caused by obesity itself. As hyperglycemia develops gradually, this form of diabetes many a times goes undiagnosed. Such patients are at more risk of developing macrovascular and microvascular complications. As the age increases with obesity alongside and lack of physical activity, the risk of developing type 2 diabetes increases. The individuals with hypertension or dyslipidemia and women with Gestational diabetes mellitus,[20]

type 2 diabetes occurs more frequently. Often type 2 diabetes is associated with a strong genetic predisposition, more so than type 1 diabetes mellitus.[21]

Following are the risk factors for Type 2 Diabetes Mellitus[15]

1. Family history of diabetes (i.e. sibling or parent with type 2 diabetes)
2. Obesity (BMI≥25 kg/m2)
3. Physical inactivity
4. Ethnicity/Race (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
5. Identified previously as IFG or IGT
6. History of GDM or delivery of baby > 4kg (>9 Ib)
7. Hypertension (blood pressure ≥ 140/90 mHg)
8. HDL cholesterol level ≤ 35mg/dL (0.90mmol/L) and / or a triglyceride level ≥ 250mg/dL (2.82 mol/L)
9. Polycystic ovary disease or acanthosis nigricans.
10. History of vascular disease.

Symptoms of T_2 Diabetes Mellitus

Symptoms seen in both types of diabetes are similar but vary in their intensity. Development of symptoms are more rapid in type 1 then Type 2 diabetes.

1. Thirst, Dry mouth
2. Polyuria,
3. Nocturia
4. Polydipsia,
5. Polyphagia,
6. Weight loss, fatigue

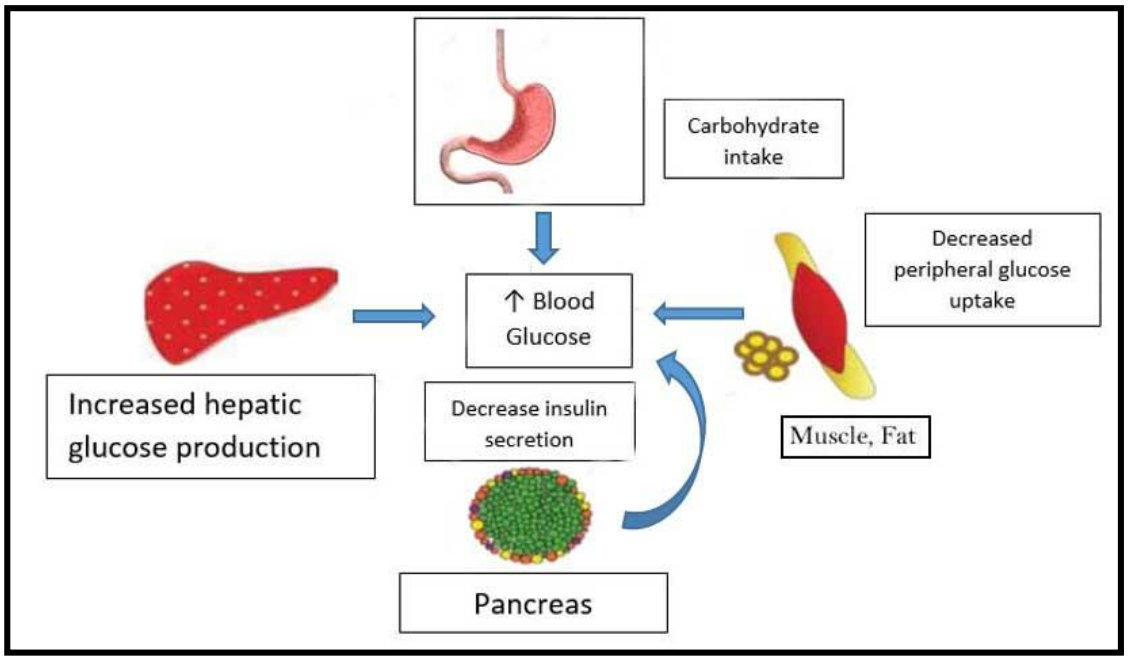
7. Blurring of vision
8. Pruritus vulvae, balanitis
9. Nausea, headache
10. Mood change, irritability, difficulty in concentrating, apathy

The above are the symptoms of diabetes. There is an increased risk of developing number of serious health problems in people with diabetes.[1, 15]

Pathophysiology

Lack of endogenous insulin results in hyperglycemia, the deficiency of which, is either absolute, as in type 1 diabetes mellitus, or relative, as in type 2 diabetes mellitus. Resistance to the actions of insulin results in relative insulin deficiency in muscle, fat, and the liver and an inadequate response by the pancreatic beta cell. Insulin resistance has been attributed to elevated levels of free fatty acids in plasma,[22] and can lead to decreased glucose transport in muscle, elevated hepatic gluconeogenesis, and increased fat breakdown.

Figure 1. Pathophysiology of type 2 diabetes mellitus[2]



It is presumed that when a sedentary lifestyle is superimposed on a susceptible genotype the defects of type 2 diabetes occurs. The body mass index varies with different racial groups, at which the risk for diabetes increases. For example, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight when compared with persons of European ancestry.[23] A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

For microvascular and metabolic complications, hyperglycemia is known to be a major determinant. However, there is lesser effect on the macrovascular complications due to glycemia. Cardiovascular risk is determined by insulin resistance with associated abnormalities in lipid metabolism (i.e., small dense low-density lipoprotein [LDL] particles, low high-density lipoprotein-cholesterol [HDL-C] levels, elevated triglyceride-rich remnant lipoproteins) and thrombotic (ie, elevated

type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen) abnormalities, as well as the conventional atherosclerotic risk factors (e.g., family history, smoking, hypertension, elevated low-density lipoprotein-cholesterol [LDL-C], low HDL-C).[24]

Diagnosis

If a diagnosis of diabetes is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and lifelong.

The World Health Organization and National Diabetes Data Group have issued diagnostic criteria for DM based on the following premises:[24]

***Criteria for the Diagnosis of Diabetes Mellitus*[25]**

- Symptoms of diabetes plus random blood glucose concentration 11.1mmol/L (200 mg/dL)* *or*
- Fasting plasma glucose 7.0 mmol/L (126 mg/dL)** *or*
- Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test***

* Random is defined as without regard to time since the last meal.

** Fasting is defined as no caloric intake for at least 8 h.

*** The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Complications

Uncontrolled diabetes can lead to long-term complications of diabetes including retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot

joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms, sexual dysfunction and pregnancy complications. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.[25] It can also lead to life-threatening complications, such as diabetes ketoacidosis and hyperosmolar coma due to acute biochemical.[8,26]

Acute complications

- ✓ Diabetic ketoacidosis
- ✓ Hyperglycemic Hyperosmolar state
- ✓ Hypoglycemia

Chronic Complications [27-33]

The chronic complications of DM affect many organ systems and those may be responsible for the majority of morbidity and/or mortality associated with the disease.

Figure 2. Microvascular complications seen in diabetes mellitus

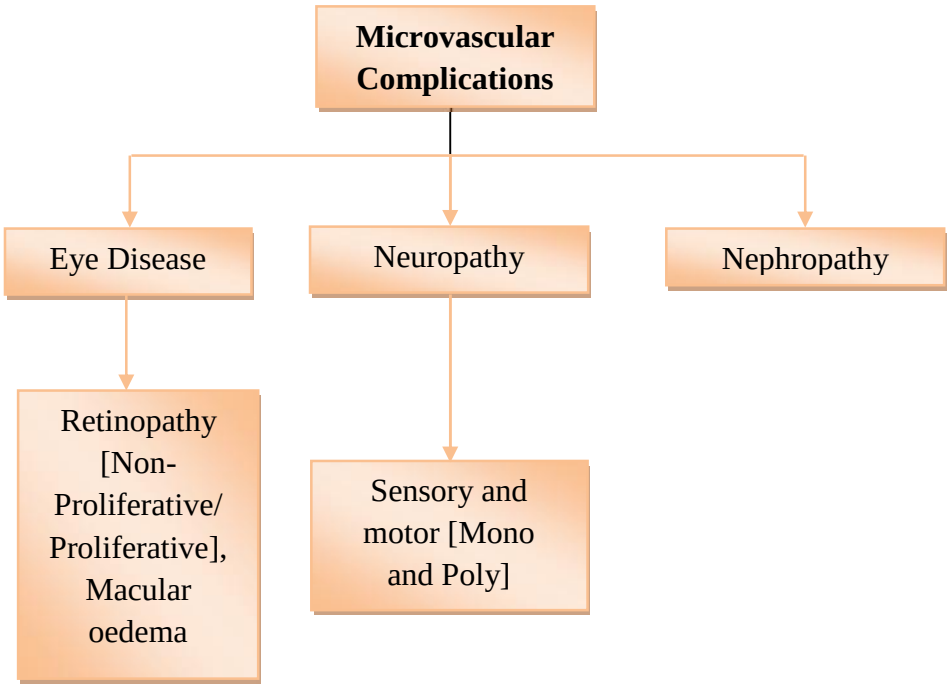
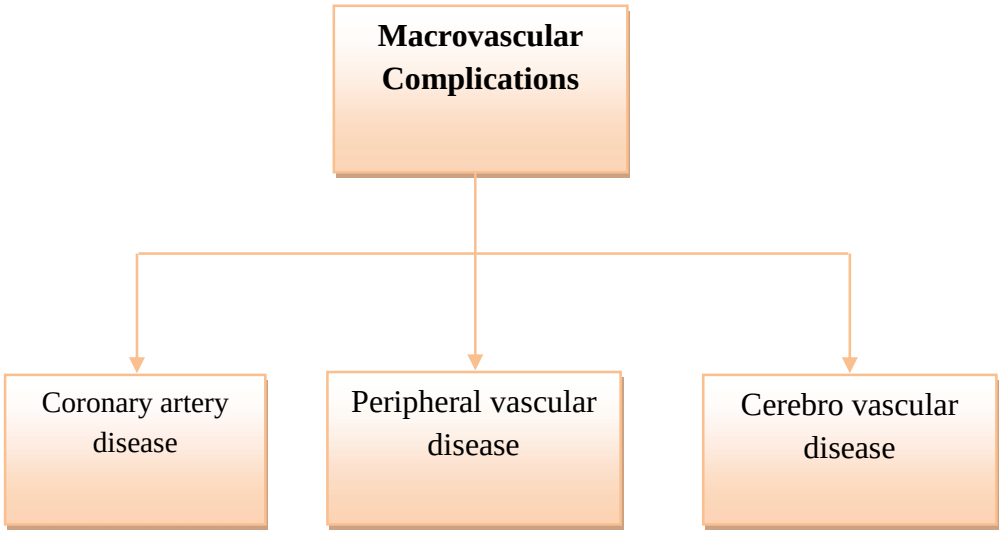


Figure 3. Macrovascular complications seen in diabetes mellitus



Other complications seen in diabetes mellitus:[27-33]

- ✓ Gastro-intestinal problems [Gastroparesis, diarrhea]
- ✓ Genitor-urinary problems [Uropathy / Sexual dysfunction]
- ✓ Dermatologic problems.
- ✓ Infections.

- UTI
- Tuberculosis
- Candidiasis – oral / volvovaginal
- Mucormycosis
- Necrotising fasciitis
- Periodontitis

✓ Cataracts and Glaucomas.

✓ Duputrens contracture, Pseudogout

Mechanisms of Complications

The mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown, although chronic hyperglycemia is an important etiologic factor. [18]

The pathophysiology of chronic complications in DM has been explained by four theories.[2,24,34]

First theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylation of intra- and extracellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs are known to cross-link proteins (for example collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as glomerular filtration rate declines.[35]

A second theory is based on the observation that hyperglycemia increases glucose metabolism via the sorbitol pathway. Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters the redox potential, increases cellular osmolality, generates reactive oxygen species and leads to other types of cellular dysfunction. However, use of aldose reductase inhibitors, has not demonstrated significant beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy.

A third theory proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PKC). Among other actions, PKC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons. Inhibitors of PKC are being studied in clinical trials.

A fourth theory proposes that hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. The hexosamine pathway causes glycosylation of proteins such as endothelial nitric oxide synthase and also regulates changes in gene expression of transforming growth factor B (TGF-B) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors

Growth factors appear to play an important role in DM-related complications, and the above mentioned pathways increases their production. Vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic proliferative retinopathy. TGF-B is increased in diabetic nephropathy and stimulates the production of collagen

and fibronectin by mesangial cells. There is also a role of other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor and insulin in DM-related complications. A unifying mechanism could be that hyperglycemia leads to increased production of reactive oxygen species in the mitochondria and these compounds may activate all four of the pathways. Hence, although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.[36]

Glycemic Control and Complications

The reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM is the definitive proof provided by The Diabetes Control and Complications Trial (DCCT). This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support. Individuals in the conventional diabetes management group received twice-daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).[37]

The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events during the trial (most individuals were young and had a low risk of cardiovascular disease). The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from ESRD, and 5.6 years free from lower extremity amputations. If all complications of DM were combined, individuals in the intensive diabetes management group would experience 15.3 more years of life without significant microvascular or neurologic complications of DM, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened. For example, individuals in the intensive diabetes management group for a mean of 6.5 years had a 42–57% reduction in cardiovascular events [nonfatal myocardial infarction (MI), stroke, or death from a cardiovascular event] at a mean follow-up of 17 years, even though their subsequent glycemic control was the same as those in the conventional diabetes management group.[37]

The benefits of an improvement in glycemic control occurred over the entire range of A1C values, suggesting that at any A1C level, an improvement in glycemic control is beneficial. The goal of therapy is to achieve an A1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.[37]

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each percentage point reduction in A1C was associated with a 35% reduction in microvascular complications. Similar reductions in the risks of retinopathy and nephropathy were also seen in a small trial of lean Japanese individuals with type 2 DM randomized to either intensive glycemic control or standard therapy with insulin (Kumamoto study). These results demonstrate the effectiveness of improved glycemic control in individuals of different ethnicity and presumably, a different etiology of DM (that is phenotypically different from those in the UKPDS).[38]

The findings of the UKPDS, and Kumamoto study support the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications. These landmark studies prove the value of metabolic control and emphasize the importance of intensive glycemic control in all forms of DM.[38,39]

HbA1C is a widely used marker of chronic glycemia, reflecting average blood glucose levels over a 2 to 3 months period of time. The test plays a critical role in the management of the patient with diabeties, since it correlates well with both micro vascular and, to a lesser extent, macrovascular complications and is widely used as the standard biomarker for the adequacy of glycemic management.[25]

DIABETIC RETINOPATHY

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for approximately 10,000 new cases of blindness every year in the United States alone. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia.[24] Development of diabetic retinopathy in patients with type 2

diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K. Prospective Diabetes Study (UKPDS).[33,40] Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes. There are several proposed pathological mechanisms by which diabetes may lead to development of retinopathy.

Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway. This pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. In animal models, sugar alcohol accumulation has been linked to microaneurysm formation, thickening of basement membranes, and loss of pericytes. Treatment studies with aldose reductase inhibitors, however, have been disappointing.[24,39]

Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs). In animal models, these substances have also been associated with formation of microaneurysms and pericyte loss. Evaluations of AGE inhibitors are underway.[39]

Oxidative stress may also play an important role in cellular injury from hyperglycemia. High glucose levels can stimulate free radical production and reactive oxygen species formation. Animal studies have suggested that treatment with antioxidants, such as vitamin E, may attenuate some vascular dysfunction associated

with diabetes, but treatment with antioxidants has not yet been shown to alter the development or progression of retinopathy or other microvascular complications of diabetes. Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy.[24,39]

Diabetic retinopathy is generally classified as either non proliferative or proliferative. It is important to have a general understanding of the features of each to interpret eye examination reports and advise patients of disease progression and prognosis.

CLASSIFICATION (MODIFIED FROM AMERICAN ACADEMY OF OPTHALMOLOGY)[41]

Non Proliferative Diabetic Retinopathy (NPDR)

1. Mild NPDR

   At least one retinal microaneurysm and one or more of the following : retinal hemorrhage, hard exudate, soft exudate.

2. Moderate NPDR

   Hemorrhages or microaneurysms or both in atleast on quadrant and one or more of the following: soft exudates, venous beading and IRMA.

3. Severe NPDR

   Hemorrhages or microaneurysms or both in all quadrants, venous beading in two or more quadrants, IRMA in at least one quadrant.

PDR

1. Early PDR

   One or more of the following:

   - NVE
   - NVD
   - Vitreous or preretinal hemorrhage
   - NVE< ½ disc area.

2. High risk PDR

   One or more of the following.

   - NVD > ¼- $^{1}/_{3}$ disc area
   - NVD with vitreous or preretinal hemorrhage
   - NVE > ½ disc area. Preretinal or vitreous hemorrhage.

3. Advanced PDR

   High risk PDR, traction retinal detachment involving macula or vitreous hemorrhage obscuring ability to grade NVD or NVE.

   - IRMA – Intraretinal microvascular abnormalities.
   - NVE – Neovascularisation elsewhere.
   - NVD – Neovascularisation disc.

Diabetic retinopathy progresses from mild non-proliferative abnormalities to moderate and severe non-proliferative diabetic retinopathy to proliferative diabetic retinopathy. Macular edema can develop at all stages of diabetic retinopathy. NPDR usually develops late in first decade or early 2nd decade of type – 2 diabetes mellitus. PDR usually develops within 5 years of NPDR. Pregnancy, poor glycemic control, hypertension and cataract surgery accelerate these changes. UKPDS study revealed

that for every percentage reduction of HbA1C (eg. From 8 to 7%), there was a 35% reduction in risk of retinopathy.[42]

Thyroid

Physiology of thyroid gland

The principal hormones secreted by the thyroid are thyroxine (T4), triiodothyronine (T3), and calcitonin. T3 is also formed in the peripheral tissues by deiodination of T4. Both T4 and T3 are iodine-containing aminoacids. Small amounts of reverse triiodothyronine (RT3) is also formed, but RT3 is inactive. T3 is more active than T4. Naturally occurring forms of T4 are L isomers.[2,24]

About 93 per cent of the metabolically active hormones secreted by the thyroid gland is T4, and 7 per cent T3. However, almost all the T4 is eventually converted to T3 in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. T3 is about four times as potent as T4, but it is present in the blood in much smaller quantities and persists for a much shorter time than does T4.[43]

Iodide Pump (Iodide Trapping)

The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called iodide trapping.[2,43]

Thyroglobulin, and Chemistry of Thyroxine and Triiodothyronine Formation and Secretion of Thyroglobulin by the Thyroid Cells.

The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin, with a molecular weight of about 335,000. Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid. The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an oxidized form of iodine, either nascent iodine (I0) or I3- , that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provide a potent system capable of oxidizing iodides. The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.[43,44]

Iodination of Tyrosine and Formation of the Thyroid Hormones- "Organification" of Thyroglobulin.

The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but very slowly with the amino acid tyrosine. In the thyroid cells, however,the oxidized iodine is associated with an iodinase enzyme that causes the process to occur within seconds or minutes. Therefore, almost as rapidly as the thyroglobulin molecule is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle, iodine binds with about one sixth of the tyrosine amino acids within the thyroglobulin molecule. Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another. The major hormonal product of the coupling reaction is the molecule thyroxine that remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine, which represents about one fifteenth of the final hormones.

Storage of Thyroglobulin.

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.[11,43]

Daily Rate of Secretion of Thyroxine and Triiodothyronine

About 93 per cent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 per cent is triiodothyronine. However, during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine. Therefore, the hormone finally delivered to and used by the tissues is mainly triiodothyronine, a total of about 35 micrograms of triiodothyronine per day.[43,44]

Thyroid Hormones Have Slow Onset and Long Duration of Action.

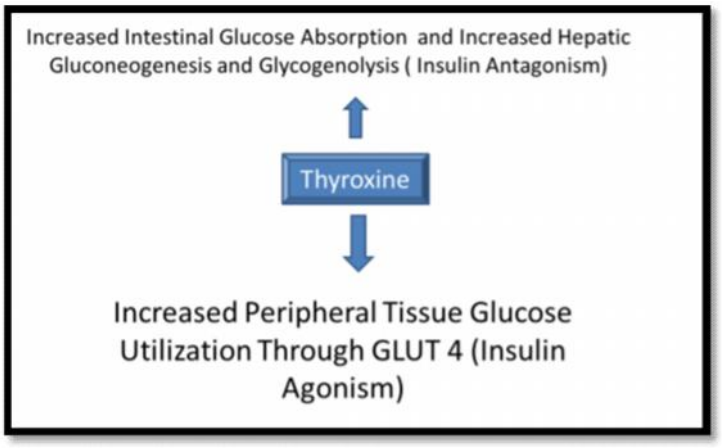
After injection of a large quantity of thyroxine into a human being, essentially no effect on the Metabolic rate can be discerned for 2 to 3 days, thereby demonstrating that there is a long latent period before thyroxine activity begins. Once activity does begin, it increases progressively and reaches a maximum in 10to 12 days. Thereafter, it decreases with a half-life of about 15 days. Some of the activity persists for as long as 6 weeks to 2 months. The actions of triiodothyronine occur about four times as rapidly as those of thyroxine, with a latent period as short as 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days. Most of the latency and prolonged period of actionof these hormones are probably caused by their binding with proteins both in the plasma and in thetissue cells, followed by their slow release.[43]

Thyroid and Diabetes

It has long been known that thyroid hormones act differentially in liver, skeletal muscle and adipose tissue – the main targets of insulin action. While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis,61,62 they up-regulate the expression of genes such as GLUT-4 and

phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin 63,64 in facilitating glucose disposal and utilisation in peripheral tissues.[45,46]

Figure 4. Euthyroidism and glucose homeostasis[45]



Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population.[2] Because patients with one organ-specific autoimmune disease are at risk of developing other autoimmune disorders, and thyroid disorders are more common in females, it is not surprising that up to 30% of female type 1 diabetic patients have thyroid disease.[47,48]

A number of reports have also indicated a higher than normal prevalence of thyroid disorders in type 2 diabetic patients, with hypothyroidism especially subclinical being the most common disorder.[47,50,49]

A number of reports have also indicated a higher than normal prevalence of thyroid disorders in type 2 diabetic patients, with hypothyroidism especially subclinical being the most common disorder. [47,50,49]

How Thyroid Dysfunction May Affect Diabetic Patients

The presence of **Hyperthyoridism** may affect diabetes control. Preexisting diabetes mellitus may be aggravated, one cause being accelerated turnover of insulin.6Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements as insulin clearance is increased.67,68 There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and probably increased insulin resistance. Indeed, thyrotoxicosis may unmask latent diabetes.[47]

Hence in hyperthyroid patients, the diagnosis of glucose intolerance needs to be considered cautiously, since the hyperglycemia may improve with treatment of thyrotoxicosis. Second, underlying hyperthyroidism should be considered in diabetic patients with unexplained

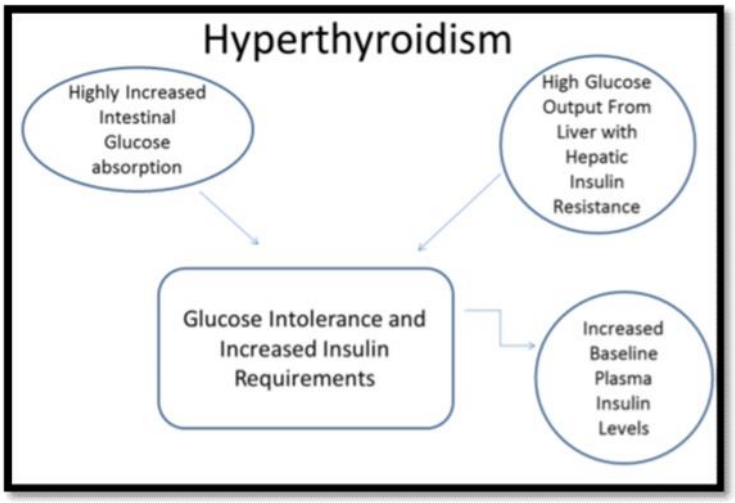
worsening hyperglycemia. Third, in diabetic patients with hyperthyroidism, physicians need to anticipate possible deterioration in glycemic control and adjust treatment accordingly.

Restoration of euthyroidism will lower blood glucose level.[51]

Thyrotoxicosis may lead to ketoacidosis also due to elevated lipolytic actions and increased hepatic β oxidation.[52,53]

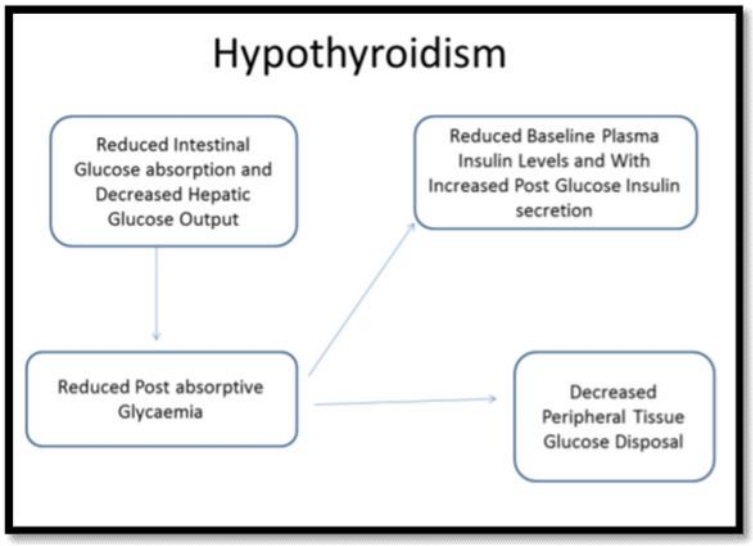
Subclinical hyperthyroidism has also been associated with insulin resistance [54-56] in some but not all studies.[57]

Figure 5. Hyperthyroidism and glucose homeostasis[45]



Hypothyroidism is associated with a reduction in the disposition of glucose to skeletal muscle and adipose tissue.[63] Thyroid hormone has been shown to stimulate expression of the insulin- sensitive glucose transporter (GLUT4), and the levels of this transporter are reduced in hypothyroidism. However, hypothyroidism is also associated with reduced gluconeogenesis, and the net effect of these influences is usually a minimal effect of hypothyroidism on serum glucose levels. Thyroid hormone down regulates expression of prohormone processing enzymes which, therefore, have increased activity in hypothyroidism.[64] Degradation of insulin is slowed, and the sensitivity to exogenous insulin may be increased. In a patient with preexisting diabetes mellitus who develops hypothyroidism, insulin requirements may be reduced.[11] Many studies have shown peripheral insulin resistance in both overt and subclinical hypothyroidism. [58-62]

Figure 6. Hypothyroidism and glucose homeostasis[45]



Among all, insulin resistance has been the most important facet connecting thyroid dysfunction and T2DM. Insulin resistance is a condition which occurs in both hypothyroidism and hyperthyroidism.[65]

More importantly, hypothyroidism is accompanied by a variety of abnormalities in plasma lipid metabolism.[2,19] Even subclinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in type 2 diabetes and further increase the risk of cardiovascular diseases. [66] Adequate thyroxine replacement will reverse the lipid abnormalities.[47,11]

Both the synthesis and the degradation of lipid are depressed in hypothyroidism. However, degradation is reduced to a great extent, with a net effect of accumulation of LDL and triglycerides.[67] Impaired lipolysis of white fat in hypothyroid patients at baseline and in response to catecholamine reflects impaired free fatty acid mobilization.[68,69] All of these abnormalities are relieved bytreatment.[11]

A correlation was shown between total cholesterol and serum TSH levels in hypothyroid individuals identified from among 25,862 participants in a health fair,

including those not aware of being hypothyroid and those on T4replacement.46 An elevation in serum LDL-cholesterol has been associated, in most studies, with overt and subclinical hypothyroidism.[70,71] According to most studies, serum HDL and triglycerides levels are not influenced by hypothyroidism.[67,70]

The reduction in LDL with T4 therapy is generally related to the original magnitude of LDL and TSH elevation: the higher the initial levels, the greater the observed reduction in LDL.[70] A typical reduction in LDL is 5% to10% of the original level.[11]

The benefit of early identification of both diseases has a significant impact on improving cardiovascular function, blood pressure, and lipid profile, thereby reducing long-term cardiovascular risk and improving quality of life for persons with Diabetes.[45,47]

Prevalence of thyroid dysfunction in type 2 diabetics

Celani MF *et al.,* studied 290 type 2 diabetics, 159 females and 131 males aged 40 to 93years. Among them abnormal TSH concentrations were detected in 91 patients (31.4%). Subclinical hypothyroidism was most common (48.3%), followed by subclinical hyperthyroidism (24.2%) and by definite hypothyroidism (23.1%). Definite hyperthyroidism was found in 4 patients (4.4%). They found that prevalence of abnormal thyroid function test results was significantly higher in the female than in the male patients and in the insulin-treated patients than in those receiving oral hypoglycaemic agents. They also found that 30 patients with abnormal thyroid function test results (33.0%) had evidence of thyroid autoimmunity.[50]

In a study conducted by **Papazafiropoulou *et al.,*** they found that out of 1,092 greek type 2 diabetic patients, the prevalence rate of thyroid dysfunction was 12.3%.

In the group with thyroid dysfunction there was an excess of females in comparison with the group without thyroid dysfunction ($P < 0.001$).[72]

Demitrost L *et al.,* did a retrospective study and found that out of 202 type 2 DM patients 139 (68.8%) were euthyroid, 33 (16.3%) had subclinical hypothyroidism , 23 (11.4%) have hypothyroidism, 4 (2%) had subclinical hyperthyroidism and 3 (1.5%) were overt hyperthyroid. Maximum cases were of hypothyroidism (subclinical and clinical) seen in the age group of 45-64 years. They also found that patients with BMI > 25 were at increased risk of having hypothyroidism ($P < 0.016$).[5]

Akbar DH *et al.,* investigated a random sample of 100 Saudi type 2 diabetics and 100 age- and sex-matched controls for thyroid autoimmunity and thyroid dysfunction. In the study they found that thyroid autoimmunity was detected in 10% diabetics vs. 5% controls (p=0.05), while thyroid dysfunction was found in 16% and 7% respectively which was significant (p=0.03).[73]

Perros P *et al*., randomly selected 1310 adult diabetic patients attending a diabetic outpatient clinic and subjected them to thyroid function test. They found that the overall prevalence of thyroid disease was 13.4%, and was highest (31.4%) in Type 1 diabetic females, and lowest in Type 2 diabetic males (6.9%). As a direct result of screening, new thyroid disease was diagnosed in 6.8% (89 patients) of the population screened; the commonest diagnosis was subclinical hypothyroidism (4.8%), followed by hypothyroidism (0.9%), hyperthyroidism (0.5%), and subclinical hyperthyroidism (0.5%). The study concluded that thyroid function should be screened annually in diabetic patients to detect asymptomatic thyroid dysfunction which is increased in frequency in a diabetic population.[74]

Chen HS *et al.*,[75] studied 588 Taiwanese type 2 diabetic patients with sub-clinical hypothyroidism and compared with euthyroid patients. In the cross-sectional analysis, they found that sub-clinical hypothyroidism was associated with a higher frequency of nephropathy. Also they found that after 4 years, sub-clinical hypothyroidism was associated with a higher rate of incident cardiovascular events in patients with type 2 diabetes.[75]

Chubb SA *et al.*,[76] studied 420 adult females with type 2 diabetes randomly selected from participants in the community-based Fremantle Diabetes Study and found that the prevalence of subclinical hypothyroidism was 8.6%. [76]

Melville NA *et al.*, did a cross-sectional study comparing 1,848 adult patients with type 2 diabetes and 3,313 individuals without diabetes, and showed the prevalence of hypothyroidism in the study group to be 5.7% compared with 1.8% in the control group ($P \leq .0001$).They concluded that Patients with type 2 diabetes should be evaluated for thyroid dysfunction as are those with type 1 diabetes.[77]

Yang JK *et al.*, compared 127 type 2 diabetic patients with SCH and 200 randomly selected euthyroid type 2 diabetic patients and showed that severe retinopathy was significantly higher in the SCH group than in the euthyroid group.[78]

A meta-analysis by **Haentjens *et al*.** reported that compared with euthyroid control subjects, subclinical hyperthyroidism yielded a significant 1.49-fold increase in relative likelihood of death from all causes.[79]

A meta-analysis by **Ochs N *et al.*,** and **R azvi S *et al.*,** showed that Subclinical hypothyroidism and hyperthyroidism may be associated with a modest increased risk for coronary heart disease and mortality.[80,81]

Díez JJ *et al.,* screened 318 diabetic patients (191 women, aged 29-89 yr, median duration of diabetes 8yr) for thyroid dysfunction and found that thyroid dysfunction was present in 32.4%. Among them overt hyperthyroidism were 11 (3.5%); subclinical hyperthyroidism, 10 (3.1%); overt hypothyroidism, 48 (15.1%), and subclinical hypothyroidism, 34 patients (10.7%). Logistic regression analysis showed that there were no significant relationships between the presence of thyroid dysfunction and duration of diabetes, hemoglobin A1c levels, and the presence of diabetic complications.[66]

Cardiovascular events and micro- or macro-angiopathies are the counter reflection of resurgence of heavily disturbed lipid metabolism due to thyroid dyscrasias.[81,82] Recent findings have evidenced the intricate bond between subclinical hypothyroidism and diabetes mellitus that deceptively contribute to the major complications such as retinopathy and neuropathy.[79,83] It is also evident from the existing literature that insulin resistance bears an indispensable role in connecting T2DM and thyroid dysfunction. It is important to diagnose thyroid dysfunction in T2DM patients, and this practice should be inculcated in clinical settings to nourish further understanding of thyroid dysfunction and T2DM.[83]

In a study by **Radaideh *et al.,*** [84] (2000), the prevalence of thyroid disease in type 2 diabetics was 12.5%, the most common type being SCH.

Patients with diabetes may require more frequent testing of TSH.[85]

MATERIALS AND METHODS

The present study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with Type 2 Diabetes Mellitus.

Study design

The study design was a hospital based a one year cross-sectional study.

Study period

The present study was conducted from January 2015 to December 2015.

Source of Data

The present study included patients admitted with type 2 diabetes mellitus of duration more than 5 years in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 100 patients with type 2 diabetes mellitus were included in the study.

Sampling procedure

The sample size (n) was calculated using the following formula:

$$N = \frac{1.96^2 \times p \times q}{d^2}$$

Where,

n = Sample size

p = Prevalence (32% as obtained from previous study)[10]

q = 100 – p (68%)

d = Absolute error (7%)

Therefore;

p= 32

q= 68

d= 9

$$n = \frac{1.96^2 \times 32 \times 68}{9^2}$$

n=100

Selection criteria

Inclusion Criteria

- All in patients admitted with known history of Type 2 diabetes mellitus

Exclusion Criteria

The following patients were excluded from the study.

- Non diabetic Patients with history of thyroid disorders on treatment.
- Patients with Diabetic Ketoacidosis and Chronic Renal Failure
- Patients on drugs affecting thyroid profile (Cough syrup, Lithium and Amiodarone)

Ethical clearance

The study was approved by the Institutional Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed consent

Patients presenting with type 2 diabetes mellitus were screened for the eligibility. The patients fulfilling the selection criteria were briefed about the nature of study and included in the study after obtaining a written informed consent (Annexure–I).

Data collection

Patients were interviewed to obtain the demographic characteristics such as age and sex, presenting complaints, diabetic history and history of other comorbid conditions. These patients were subjected to clinical examination and the findings including vitals and systemic examination findings were noted. These findings were recorded on a predesigned and pretested proforma (Annexure-II).

Investigations

Patients were subjected to following investigations.

- Blood sugar levels
    - Fasting blood sugars
    - Post Prandial blood sugars
- Glycosylated hemoglobin.
- Renal function tests
    - Blood Urea
    - Serum Creatinine
- Thyroid functions test

By the aseptic precautions 7 ml of blood will be collected from anticubital vein after 8-12 hours of fasting. Blood will be collected in EDTA vacutainer (2ml) and plain vacutainer (5ml). Urine sample (5ml) will also collected in a clean, dry and sterile container. Blood collected in plain vacutainer will be processed to obtain serum. Serum T3 Serum T4, Serum TSH will be measured by chemiluminescence method in immulite 1000 autoanalyzer. Serum creatinine will be measured by modified Jaffe's method in semi–autoanalyzer using commercially available kit.

Blood collected in EDTA tube will be used for estimation of glycated haemoglobin measured by ion-exchange resin method using commercially available kit.

Guidelines for detection of thyroid dysfunction:

- Normal – when T3, T4 and TSH are in normal range.
- Primary Hypothyroidism – when TSH more than 5.5mIU/ml and T3, T4 less than normal.
- Subclinical Hypothyroidism – when TSH is more than 5.5 mIU/ml and T3, T4 is within normal range.
- Primary Hyperthyroidism – when TSH is less than 0.3mIU/ml and T3, T4 more than normal.
- Subclinical Hyperthyroidism – when TSH is less than 0.3 mIU/ml and T3, T4 is within normal range.

Diabetic retinopathy

Fundoscopy

Dilated fundus examination was done in all the patients using the indirect ophthalmoscope and patients were classified into:

1. No evidence of diabetic retinopathy
2. Non proliferative diabetic retinopathy (NPDR)
3. Proliferative diabetic retinopathy (PDR)

STATISTICAL METHODS

The data obtained was entered into the Microsoft excel spreadsheet (Annexure III). The data was analysed using SPSS statistical software version 20.0. The categorial data was expressed in terms of rates, ratios and percentages and comparison was done using chi-square test. The continuous data was expressed as mean +- standard deviation and comparison was done using independent 't' test. A Probability value (p- value) of less than or equal to 0.05 was considered as statistically significant.

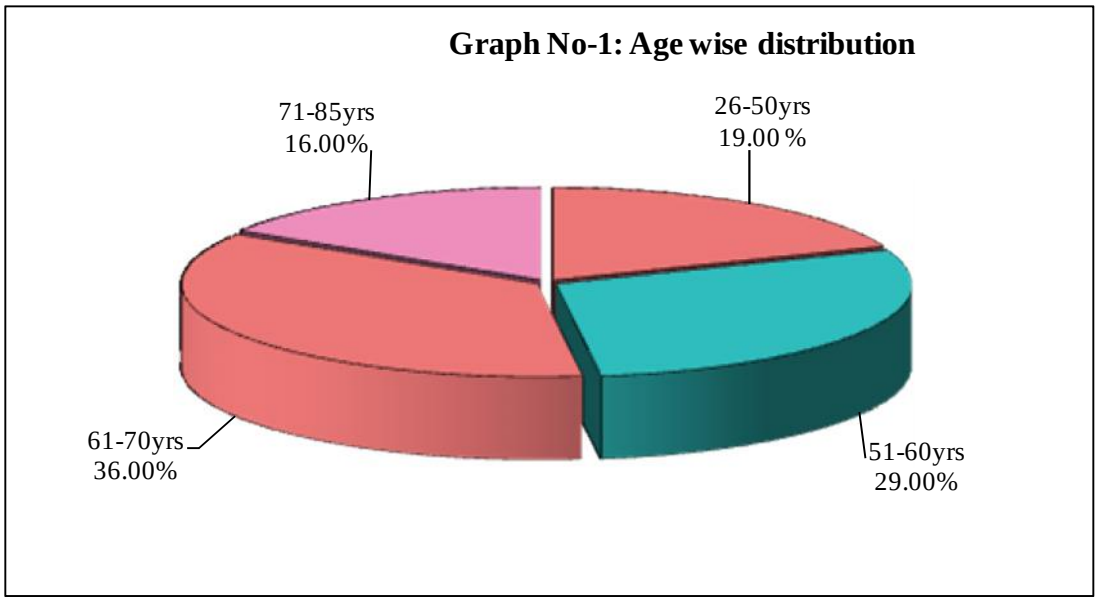
RESULTS

The present study was conducted in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital & Medical Research Center, Belagavi from January 2015 to December 2015. A total of 100 patients with Type 2 Diabetes Mellitus were studied.

The data obtained was analysed and the final results and observations were tabulated as below.

Table No-1 : Distribution of patients by age groups

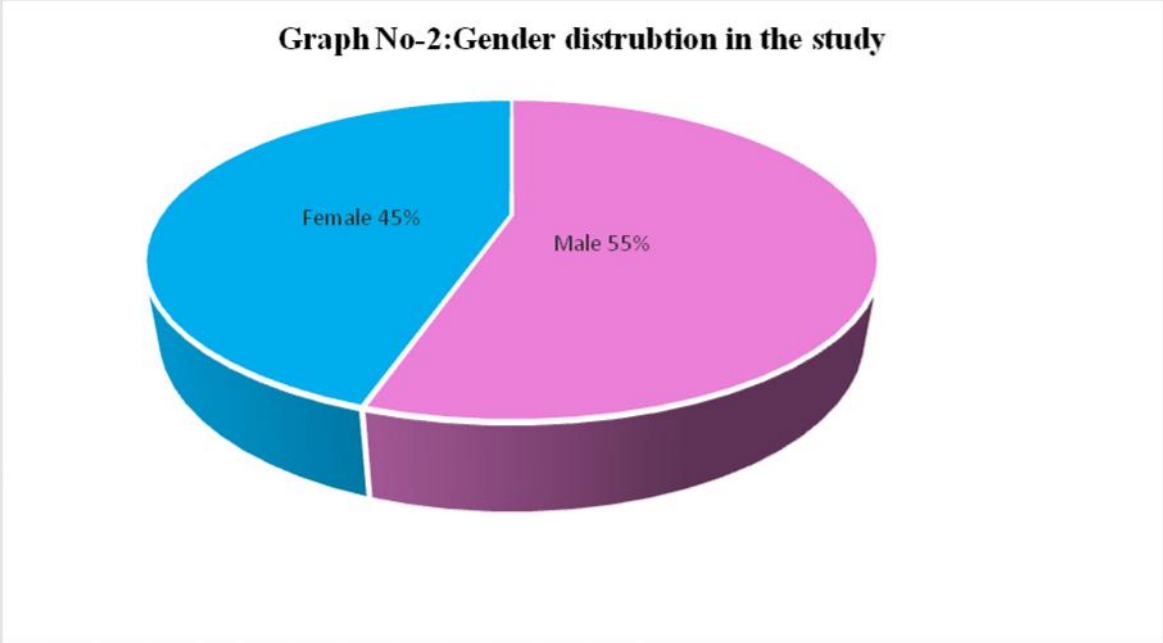
Age groups	No of patients	% of patients
26-50yrs	19	19.00
51-60yrs	29	29.00
61-70yrs	36	36.00
71-85yrs	16	16.00
Total	100	100.00



Age group ranges from 26 years to 85 years. Majority were in the age group of 61 to 70 years age group (36%). The mean age was 60.03 with standard deviation of 11.02.

Table No-2: Gender distribution in the study

Gender	No of patients	% of patients
Male	55	55
Female	45	45
Total	100	100.00

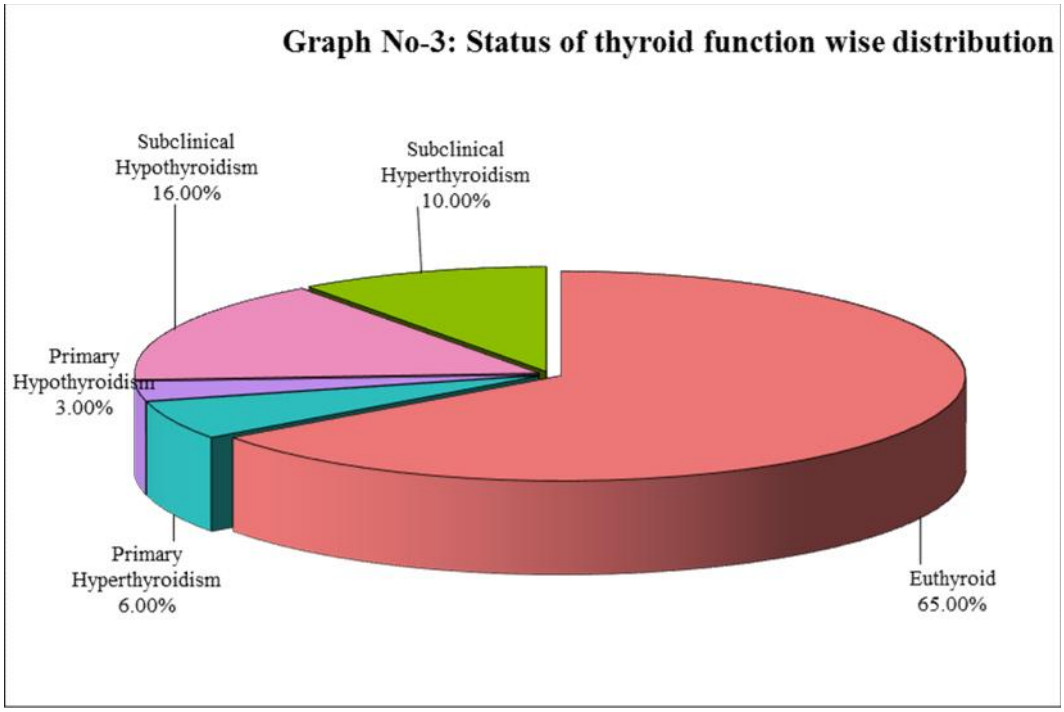


We studied 100 patients of which majority patients in the study were Males (55%) compared to Females (45%).

The Male to Female ratio was 3:2.

Table No-3: Distribution of patients with status of thyroid Function

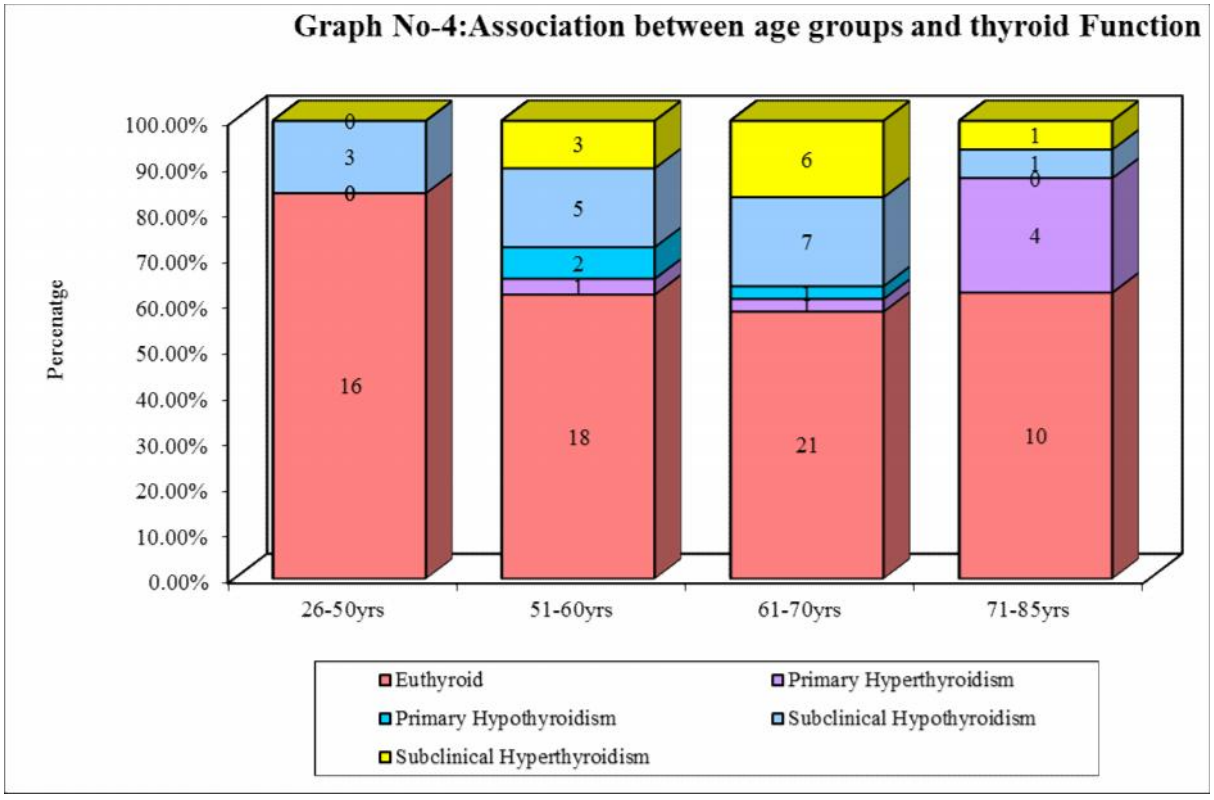
Thyroid Function	No of patients	% of patients
Euthyroid	65	65.00
Primary Hyperthyroidism	6	6.00
Primary Hypothyroidism	3	3.00
Subclinical Hypothyroidism	16	16.00
Subclinical Hyperthyroidism	10	10.00
Total	100	100.00



The prevalence of Thyroid Disorder in this study was 35%. Of them 16% had Subclinical Hypothyroidism,10% had Subclinical Hyperthyroidism, 6% had Primary Hyperthyroidism and 3% had Primary Hypothyroidism. 65% of the patients were Euthyroid.

Table No-4: Association between age groups and thyroid Function

Thyroid Function	26-50 yrs	%	51-60 yrs	%	61-70 yrs	%	71-85 yrs	%	Total
Euthyroid	16	24.62	18	27.69	21	32.31	10	15.38	65
Primary Hyperthyroidism	0	0.00	1	16.67	1	16.67	4	66.67	6
Primary Hypothyroidism	0	0.00	2	66.67	1	33.33	0	0.00	3
Subclinical Hypothyroidism	3	18.75	5	31.25	7	43.75	1	6.25	16
Subclinical Hyperthyroidism	0	0.00	3	30.00	6	60.00	1	10.00	10
Total	19	19.00	29	29.00	36	36.00	16	16.00	100
Chi-square= 20.5812 p=0.0569									

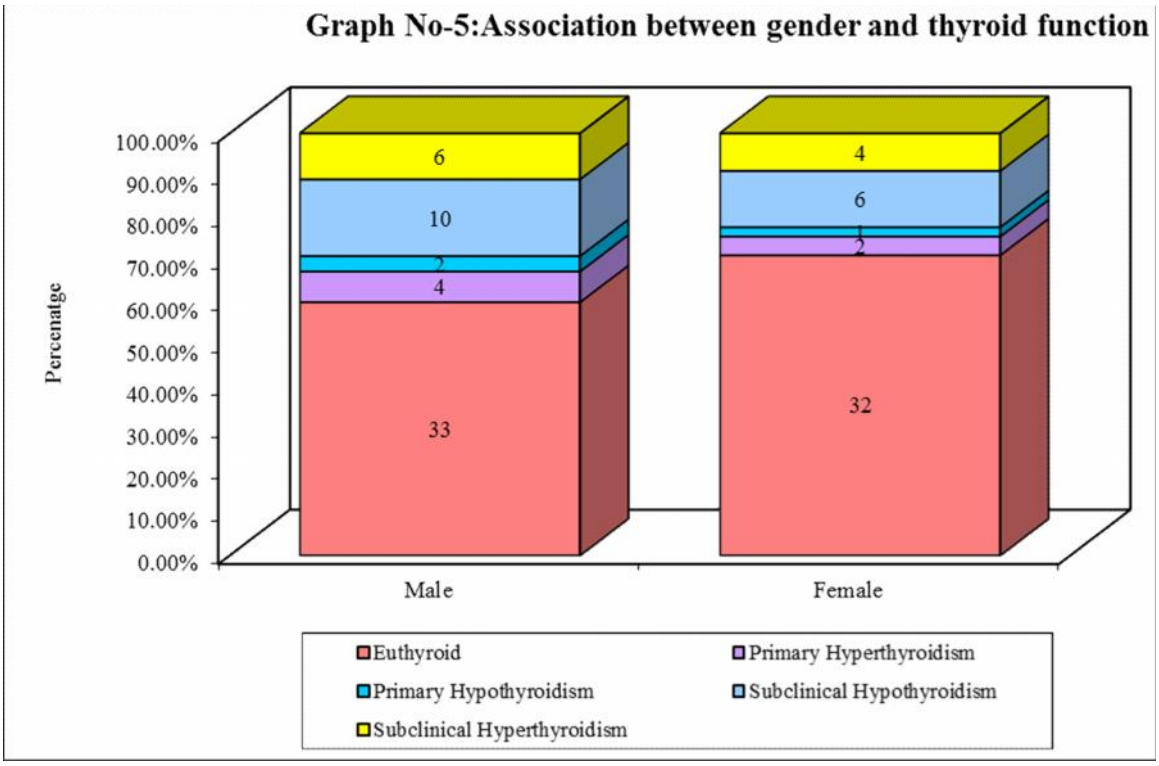


In the age group of 26 to 50 years 19 patients were there , of whome 3 patients had Thyroid Disorder. Out of 29 patients in the age group of 51 to 60 years , 11 patients had Thyroid Disorder. Out of 36 patients in the age group of 61 to 70 years , 15 patients had Thyroid Disorder. 6 out of 16 patients in the age group of 71 to 85 years had Thyroid Disorder.

But there was no statistical significance ($p = 0.0569$)

Table No-5: Association between gender and thyroid Function

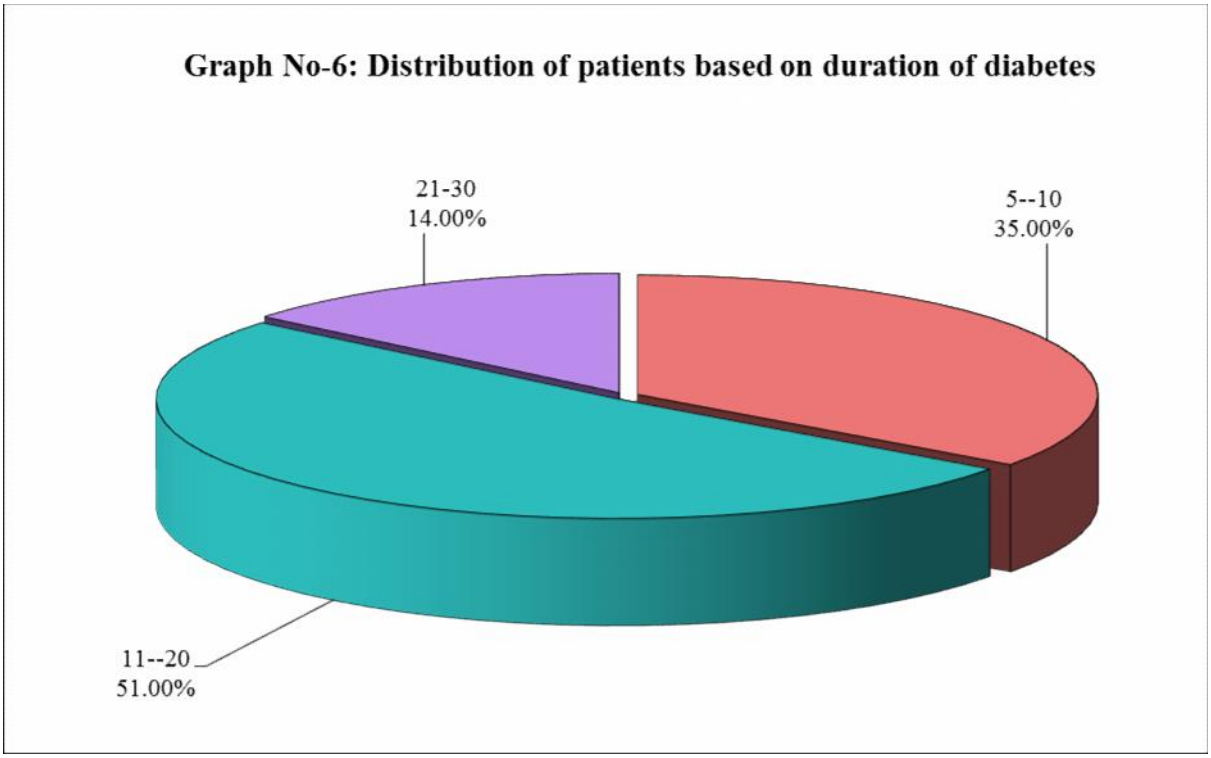
Thyroid Function	Male	%	Female	%	Total
Euthyroid	33	50.77	32	49.23	65
Primary Hyperthyroidism	4	66.67	2	33.33	6
Primary Hypothyroidism	2	66.67	1	33.33	3
Subclinical Hypothyroidism	10	62.50	6	37.50	16
Subclinical Hyperthyroidism	6	60.00	4	40.00	10
Total	55	55.00	45	45.00	100
Chi-square= 1.4304 p=0.8390					



Out of 55 male patients, 22 of the males had Thyroid Disorder. In that 62.50% of the males had Subclinical Hypothyroidism. Out of 45 female patients, 13 of the females had Thyroid Disorder, in that 37.50% of the females had Subclinical Hypothyroidism. But there was no statistical significance (p= 0.8390)

Table No-6: Distribution of patients based on duration of Diabetes

Duration in years	Number of Patients	Percentage %
5--10	35	35.00
11-20	51	51.00
21-30	14	14.00
Total	100	100.00

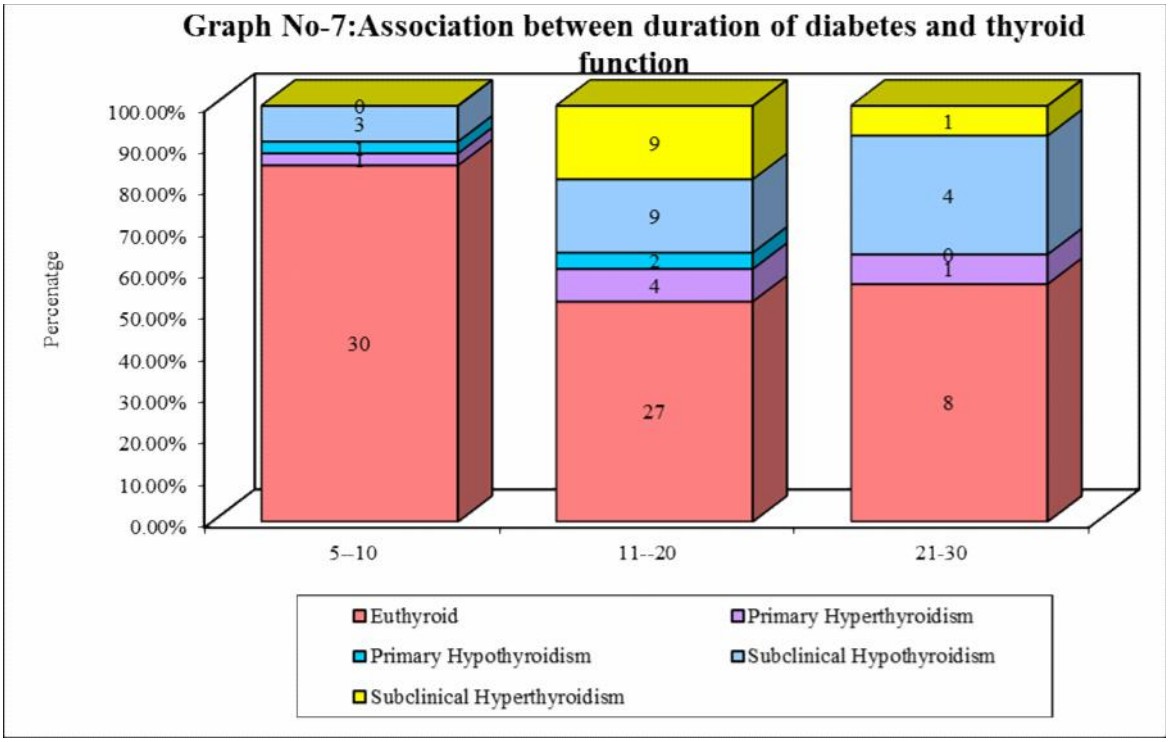


Most of the patients in our study fell in the group of 11 to 20 years of duration of Diabetes (51%).

Table No-7: Association between duration of diabetes and thyroid Function

Thyroid Function	5-10yrs	%	11-20yrs	%	21-30yrs	%	Total
Euthyroid	30	46.15	27	41.54	8	12.31	65
Primary Hyperthyroidism	1	16.67	4	66.67	1	16.67	6
Primary Hypothyroidism	1	33.33	2	66.67	0	0.00	3
Subclinical Hypothyroidism	3	18.75	9	56.25	4	25.00	16
Subclinical Hyperthyroidism	0	0.00	9	90.00	1	10.00	10
Total	35	35.00	51	51.00	14	14.00	100
Chi-square= 17.6458 p=0.0240*							

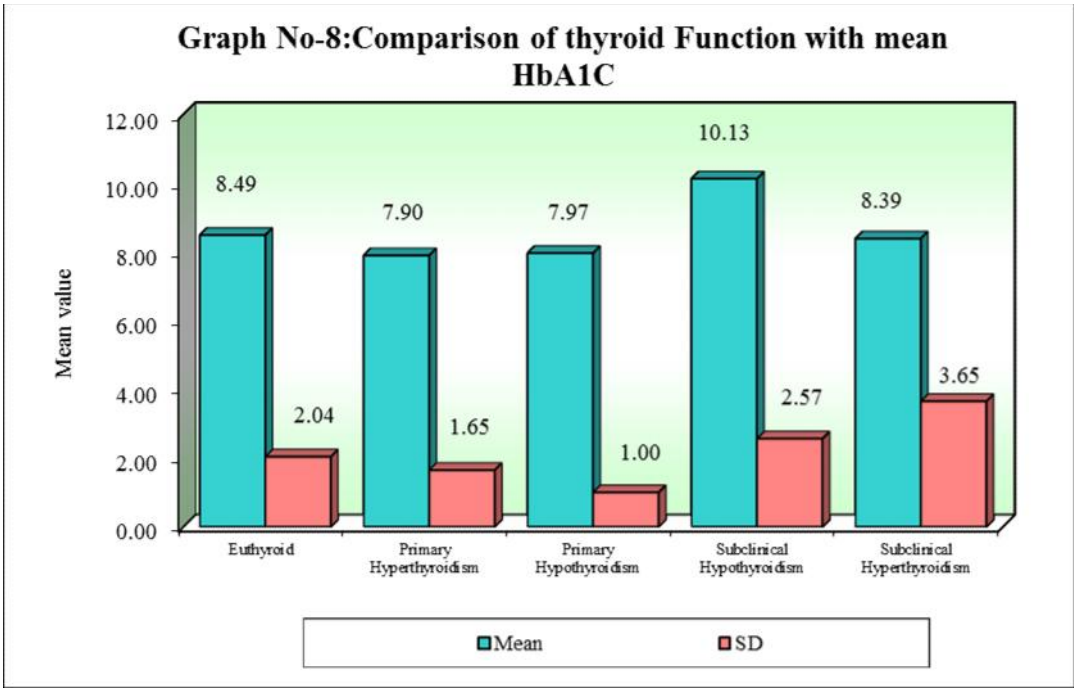
*p<0.05



Out of 35 patients in the group of 5 to 10 years duration of Diabetes, 5 patients had Thyroid Disorder. Out of 51 patients in the group of 11 to 20 years, 24 patients had Thyroid Disorder. 6 out of 14 patients in group 21 to 30 years duration of diabetes had Thyroid Disorder, which was statistically significant.(p= 0.0240)

Table No-8: Comparison of thyroid Function with mean HbA1C by one way ANOVA

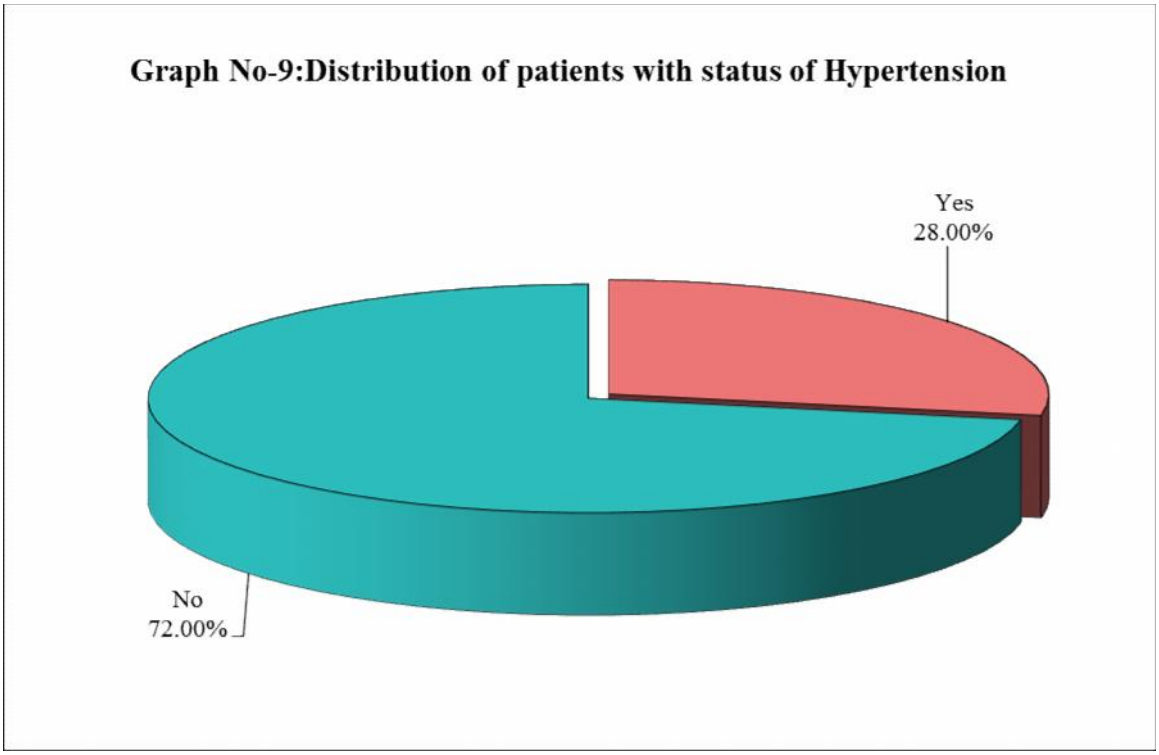
HbA1C	Mean HbA1C	SD HbA1C
Euthyroid	8.49	2.04
Primary Hyperthyroidism	7.90	1.65
Primary Hypothyroidism	7.97	1.00
Subclinical Hypothyroidism	10.13	2.57
Subclinical Hyperthyroidism	8.39	3.65
Total	8.69	2.34
F-value	1.9906	
P-value	0.1021	



The mean HbA1c in Euthyroid Diabetics was 8.49. The mean HbA1c in Primary Hyperthyriod, Primary Hypothyroid, Subclinical Hypothyroid and Subclinical Hyperthyroid diabetics was 7.90, 7.97, 10.13 and 8.39 respectively. The difference was not stastitically significant (p= 0.1021)

Table No-9: Distribution of patients with status of hypertension

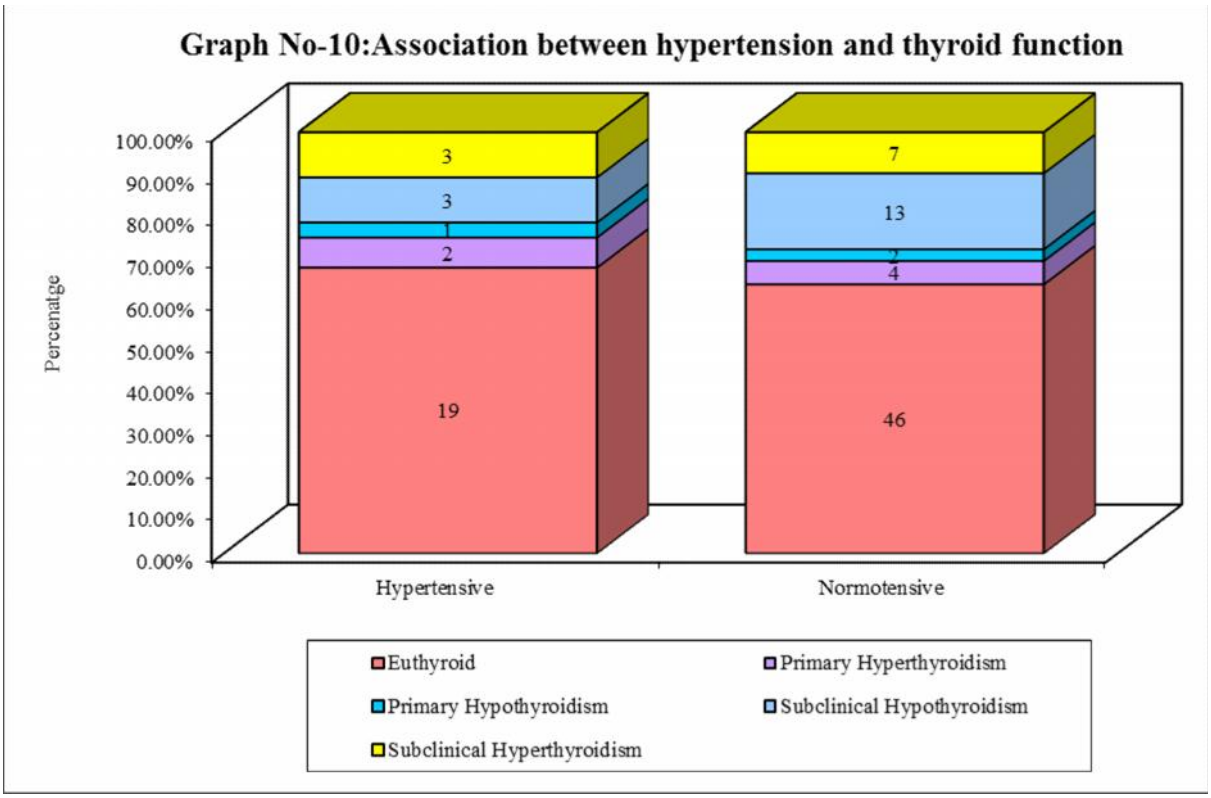
Hypertension	No of patients	% of patients
Yes	28	28.00
No	72	72.00
Total	100	100.00



Out of 100 Diabetic patients 28% of patients were Hypertensive.

Table No-10: Association between hypertension and thyroid function

Thyroid Function	Hypertensive	%	Normotensive	%	Total
Euthyroid	19	29.23	46	70.77	65
Primary Hyperthyroidism	2	33.33	4	66.67	6
Primary Hypothyroidism	1	33.33	2	66.67	3
Subclinical Hypothyroidism	3	18.75	13	81.25	16
Subclinical Hyperthyroidism	3	30.00	7	70.00	10
Total	28	28.00	72	72.00	100
Chi-square= 0.8754 p=0.9281					

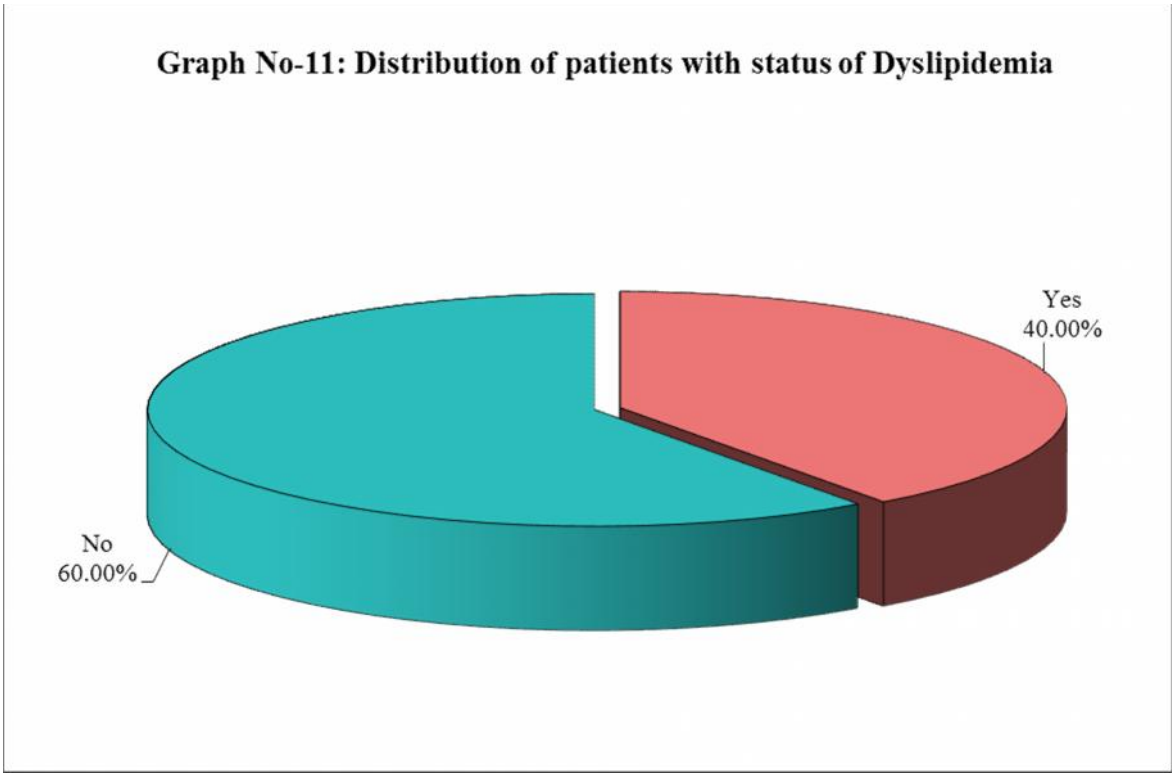


A total of 28 Diabetic patients were Hypertensive, of which 9 had Thyroid Disorder. The rest 72 Diabetic patients were Normotensive and 26 out of 72 Normotensive had Thyroid Disorder. The difference was not significant. (p=0.9281)

Table No-11: Distribution of patients with status of Dyslipidemia

Dyslipidemia	No of patients	% of patients
Yes	40	40.00
No	60	60.00
Total	100	100.00

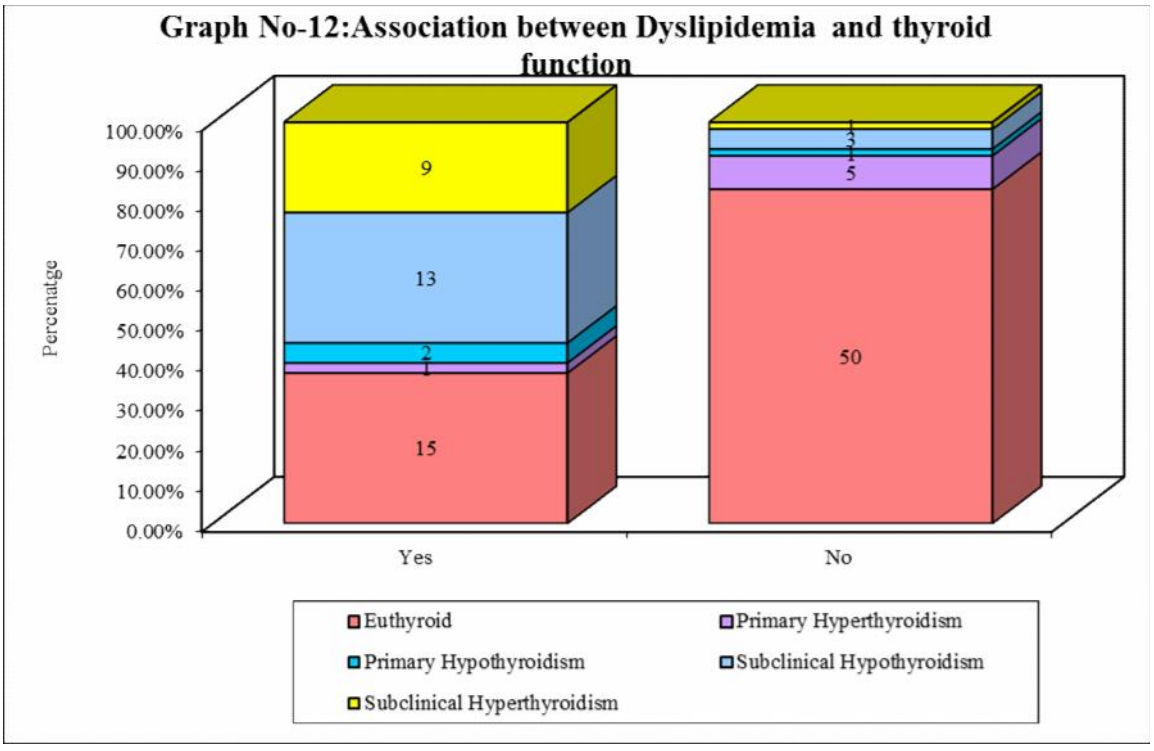
Graph No-11: Distribution of patients with status of Dyslipidemia



40% of the patients had Dyslipidemia out of the 100 Diabetic patients.

Table No-12: Association between Dyslipidemia and thyroid Function

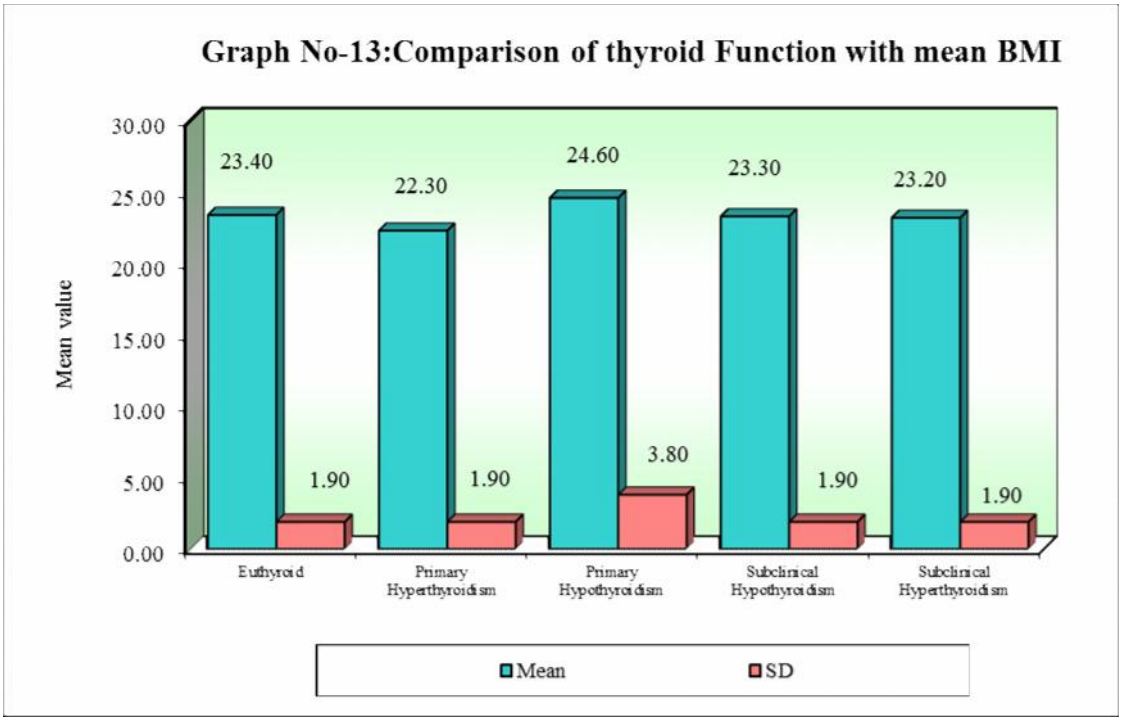
Thyroid Function	Yes	%	No	%	Total
Euthyroid	15	23.07	50	76.92	65
Primary Hyperthyroidism	1	16.66	5	83.33	6
Primary Hypothyroidism	2	66.67	1	33.33	3
Subclinical Hypothyroidism	13	81.25	3	18.75	16
Subclinical Hyperthyroidism	9	90.00	1	10.00	10
Total	40	40.00	60	60.00	100
Chi-square= 3.4704 p=0.4825					



25 patients had Thyroid Disorder out of 40 Dyslipidemic patients. But there was no statistical significance(p=0.4825)

Table No-13: Comparison of thyroid Function with mean BMI by one way ANOVA

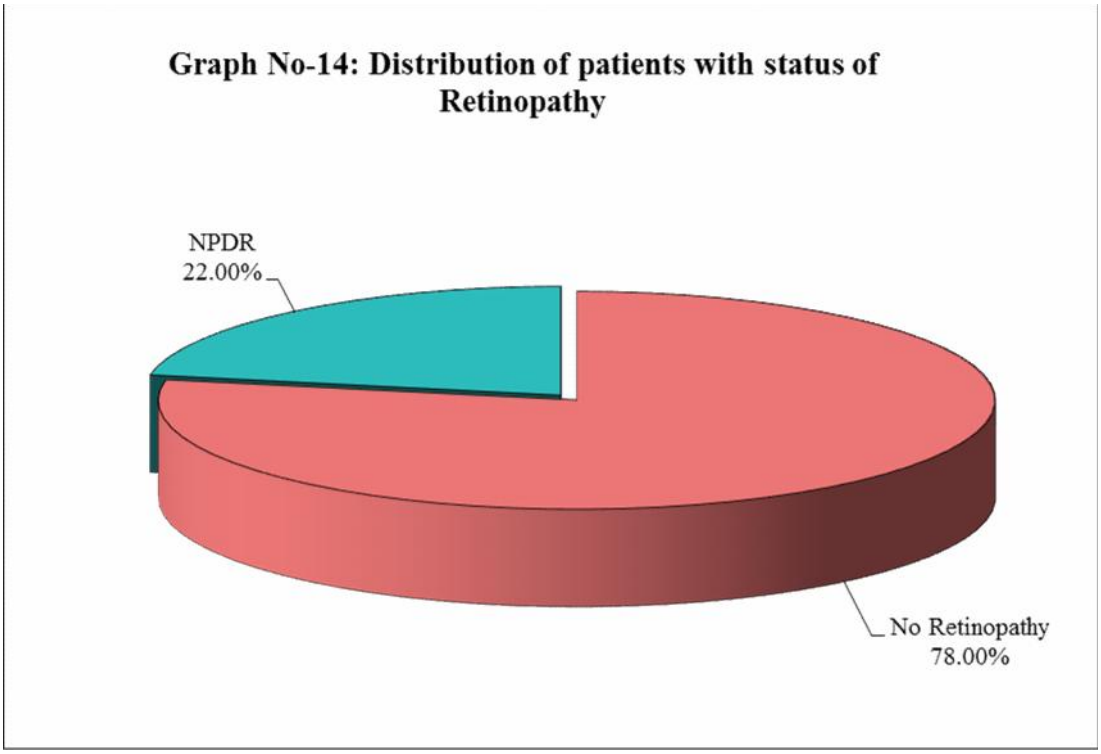
Thyroid Function	Mean BMI	SD BMI
Euthyroid	23.4	1.9
Primary Hyperthyroidism	22.3	1.9
Primary Hypothyroidism	24.6	3.8
Subclinical Hypothyroidism	23.3	1.9
Subclinical Hyperthyroidism	23.2	1.9
Total	23.3	1.9
F-value	0.7446	
P-value	0.5640	



The mean BMI in Euthyroid Diabetics was 23.4.The mean BMI in Primary Hyperthyriod, Primary Hypothyroid, Subclinical Hypothyroid and Subclinical Hyperthyroid diabetics was 22.3, 24.6, 23.3 and 23.2 respectively. The difference was statistically not significant. (p= 0.5640)

Table No-14: Distribution of patients with status of Fundoscopy

Fundoscopy	No of patients	% of patients
No Retinopathy	78	78.00
NPDR	22	22.00
Total	100	100.00

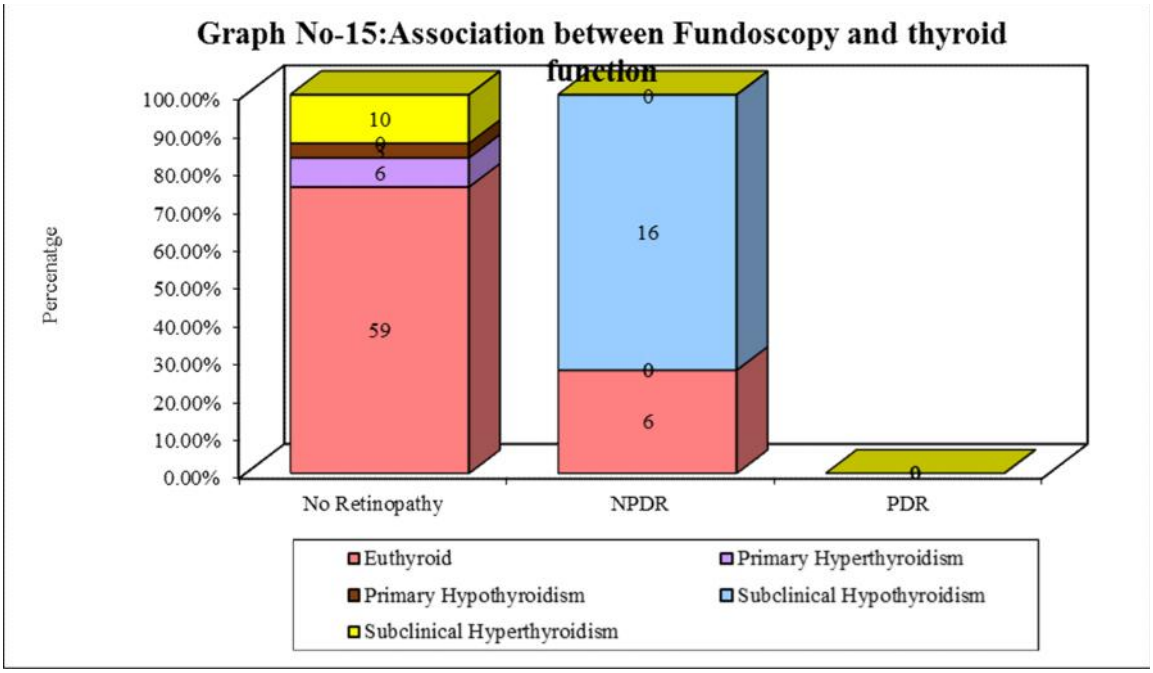


In this study fundoscopy reveled NPDR in 22% of the patients

Table No-15: Association between Fundoscopy and thyroid Function

Thyroid Function	No Retinopathy	%	NPDR	%	PDR	%	Total
Euthyroid	59	90.76	6	9.23	0	0.00	65
Primary Hyperthyroidism	6	100	0	0.00	0	0.00	6
Primary Hypothyroidism	3	100	0	0.00	0	0.00	3
Subclinical Hypothyroidism	0	0.00	16	100	0	0.00	16
Subclinical Hyperthyroidism	10	100	0	0.00	0	0.00	10
Total	78	78.00	22	22.00	0	0.00	100
Chi-square= 16.6458 p=0.0340*							

*p<0.05



Out of the 22% patients with NPDR 16 patients had Subclinical Hypothyroidism and 6 patients were Euthyroid. No Retinopathy was seen in Primary Hyperthyriod, Primary Hypothyroid and Subclinical Hyperthyroid diabetics. The difference was statistically significant. (p=0.0340).

DISCUSSION

Type 2 diabetes mellitus and Thyroid diseases are the most common endocrine disorders among the global health challenges encountered in physicians practice. It has been shown to have mutual influence of Diabetes and thyroid disorders on each other and association between both the conditions has long been reported.[3]

In the present study, out of the 100 diabetic patients, 35% patients had thyroid disorder and 65% patients were found to be Euthyroid. The findings of our study are consistent with studies of Vikhe *et al*[86] (overall prevalence of thyroid disorder was 30%), Demitrost *et al*[5] (overall prevalence of thyroid disorder was 31.2%), Diez *et al*[7] (overall prevalence of thyroid disorder was 32.4%) and Celani MF *et al*[50] (overall prevalence of thyroid disorder was 31.4%).

Subclinical hypothyroidism was the most prevalent disorder in diabetic patients in our study, occurring in 16%, followed by subclinical hyperthyroidism in 10%, primary hyperthyroidism in 6% and primary hypothyroidism in 3% of total 100 diabetic patients. Thus, among thyroid disorders maximum prevalence was found to be of subclinical hypothyroidism whereas primary hypothyroidism was least found. Our results are in concordance with the results of Vikhe *et al*[86] in which Hypothyroidism was present in 22 % (14% subclinical hypothyroidism and 8 % primary hypothyroidism) and hyperthyroidism is present in 8 % (all Primary hyperthyroid subjects) of diabetic subjects. Similarly another study was conducted by Laloo Demitrost *et al*[5] they observed 33 (16.3%) had subclinical hypothyroidism (10 males and 23 females), 23 (11.4%) had hypothyroidism (6 males and 17 females), 4 (2%) had subclinical hyperthyroidism, 3 (1.5%) were hyperthyroidism cases and (68.8%) were Euthyroid.

In this study majority of the patients were in the age group of 61 to 70 years (36%) and the mean age was 60.03 years with a standard deviation of 11.02.

In the study of Al-Geffari *et al*[87] the mean age was 59.0 ± 10.8 years which is similar to present study.

It is reported that, the prevalence of diabetes is higher in men than women.[10-16] The same was true in the present study as males (55%) where more than females (45%) with male to female ratio 3:2. These findings suggest higher prevalence of diabetes among males in this study which was consistent with the previous literature.[10-16]

In this study, out of 55 male patients,22 of the males had Thyroid Disorder. In that 62.50% of the males had Subclinical Hypothyroidism. Out of 45 female patients , 13 of the females had Thyroid Disorder, in that 37.50% of the females had Subclinical Hypothyroidism. But there was no statistical significance.

Yang GR et al.,[83] studied 371 diabetics, in which 83 subjects (22.4%) were diagnosed as SCH of whom 12.1% were males and 29.9% were females.[78] In many of the studies it shows that thyroid disorders are more common in females with Type 2 Diabetes –Celani MF et al.[50], Singh et al., Babu K et al.,[49] etc.

Out of 35 diabetic patients who had thyroid disorders, 5 had duration of diabetes between 5 to 10 years, 24 had duration of diabetes between 11 to 20 years and 6 had duration of diabetes between 21 to 30 years. However, this difference when evaluated statistically was significant. (p=0.024)

This association of duration of diabetes and thyroid disorder did not correlate with other studies.

The mean HbA1C was higher in patients with thyroid disorder compared to Euthyroid patients. The difference was not statistically significant. (p=0.1021) which is similar to the study done by Diez JJ et al.,.[66]

The study done by Kim et al., who retrospectively evaluated type 2 diabetics with SCH concluded that patients with SCH had poor glycemic control.[88,89]

In the present study the mean BMI in Euthyroid Diabetics was 23.4kg/m^2. The mean BMI in Primary Hyperthyroid, Primary Hypothyroid, Subclinical Hypothyroid and Subclinical Hyperthyroid diabetics was 22.3, 24.6, 23.3 and 23.2kg/m^2 respectively. The difference was statistically not significant. (p= 0.5640). It was comparatively similar to the study done by Proces S *el al*.,[90]

In this study 9% of the hypertensive patients had Thyroid disorder and 26% normotensives had Thyroid disorder. But the difference was not significant. (p=0.9281) Kim et al., showed that though the mean SBP and DBP was higher in patients with thyroid dysfunction although it was not significant.93 [88]

In the present study we found that Non proliferative diabetic retinopathy was present in 22% of the patients. It was noted that out of 22 patients with retinopathy, a significantly number of patients i.e 16 patients had Subclinical Hypothyroidism ($p<0.001$), There was a significant difference in prevalence of Thyroid Disorder in diabetics with, and without retinopathy.

In a study by Yang JK et al, they found 127 type 2 diabetic patients with subclinical hypothyroidism and 200 randomly selected euthyroid patients were compared. The trend for severe retinopathy was significantly higher in the SCH group than in the euthyroid group (P = 0.000). SCH was associated with greater prevalence of diabetic retinopathy, especially NPDR.[78]

In another study by Manjunath, et al, they found that diabetic retinopathy was detected in 6 SCH patients, i.e. 46% of SCH patients in the study. All 6 of these patients had non-proliferative diabetic retinopathy.[91]

A meta-analysis done by Wu J et al, they analysed 8 studies and found there is association between Diabetic Retinopathy and Subclinical Hypothyroidism, and it demonstrated that diabetic patients suffering from Subclinical Hypothyroidism could increase the risk of Diabetic Retinopathy.[92]

25% of the Dyslipidemic patients had Thyroid disorder as compared to 10% of patients without Dyslipidemia.there was no statistical significance. (p=0.4825)

In our study there was no significant correlation between Dyslipidemia and Thyroid disorder.

The association between dyslipidemia & thyroid dysfunction were significant with each lipid parameter except LDL, which failed to reach the significance, was concluded by the study done by Chubb SA et al.,[76]

In a study by Kim et al,[88] SCH patients had relatively higher mean values of serum TC, LDL, HDL, compared to euthyroid subjects and relatively lower mean TG compared to euthyroid counterparts; but none of the above parameters showed any statistically significant difference between the two groups.

This study reveals a strong association between Thyroid disorder and type 2 diabetes mellitus. Hence it could be suggested that routine surveillance for Thyroid disorder is done in patients of type 2 diabetes mellitus.

CONCLUSION

- The mean age of the study group was 60.03 years
- Males out numbered females in the study.
- The prevalence of Thyroid disorder in our study was 35% of which Subclinical hypothyroidism was 16%, followed by subclinical hyperthyroidism in 10%, primary hyperthyroidism in 6% and primary hypothyroidism in 3% of the total diabetics.
- The prevalence of subclinical hypothyroidism was highest in the Thyroid disorders in our study.
- The prevalence of Thyroid disorder was more in males as compared to females in our study.
- The prevalence of NPDR was 22% in the study and 16 patients had NPDR with Subclinical Hypothyroidism.
- 28% of the Diabetics were hypertensive and 40% of the Diabetics had dyslipidemia.
- The correlation between age, duration of diabetes, HbA1C levels or BMI between Euthyroid patients and patients with thyroid disorder was not significant.
- The study population had an obvious Thyroid Dysfunction , hence it is prudent to screen for or to ask for Thyroid panel in Diabetics.

SUMMARY

There is high frequency of Thyroid disorder in patients with type 2 diabetes mellitus and it may lead to several hindrance in the control of type 2 DM. This study was aimed to evaluate the Thyroid disorders in patients with type 2 DM.

The present study was a one year hospital based cross-sectional study which was done on 100 patients with type 2 diabetes mellitus from January 2015 to December 2015 in Department of Medicine, KLES Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

In the present study the commonest age group was 61 to 70 years and the mean age was 60.03 years. Majority of the patients were males (55%) and male to female ratio was 3:2. The duration of Diabetes in 51% of the patients was 11 to 20 years.

The prevalence of Thyroid disorders in this study was 35%. In them 16% had Subclinical hypothyroidism, 10% had Subclinical hyperthyroidism, 6% had Primary hyperthyroidism and 3% had Primary hypothyroidism.

In the present study diabetic retinopathy was seen in 22% of the patients and non-proliferative diabetic retinopathy was seen in 16% of subclinical hypothyroid patients.

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ANNEXURE-I- CONSENT FORM

CONSENT FOR PARTICIPATING IN A RESEARCH STUDY

J.N. Medical College, K.L.E. University, Belgaum- 590010

Mr/ Mrs/ Ms _____ You are invited to participate in our research study titled "**PREVALENCE OF THYROID DISORDERS IN TYPE 2 DIABETIC PATIENTS – A ONE YEAR CROSS SECTIONAL STUDY"**

Conducted by

Dr**.** _____ , Postgraduate student in the department of Medicine, J.N. Medical College, Belgaum under the guidance of

Dr. _____ Professor in the Department of Medicine, J.N. Medical College, Belgaum

Respected Sir/Madam we request you to enrol yourself to participate in our study as you are eligible to participate in the study. Your participation in research is voluntary. If you decide to participate, you are free to withdraw anytime.

Purpose of the Study: The purpose of this study is to find the thyroid disorders in type 2 diabetics like hypothyroidism or hyperthyroidism there by to treat and prevent the complications caused by thyroid dysfunction.

Procedure of the Study : If you agree to enrol in the study, you will be asked about your present, past and family history. You will be clinically examined and data of relevant investigations like FBS, PPBS, HBA1C,T3,T4 and TSH will be obtained. The hence obtained data will be monitored and documented.

Risks and Benefits: . Phlebotomy is safe when done by a health professional. You may get a small bruise at the puncture site. In rare cases, the vein may become inflamed after the blood sample is taken. This condition is called phlebitis . There is also a small risk of infection at the puncture site.

Your participation may benefit you and others suffering from the same ailment in the future by helping us achieve the purpose of this study.

Alternatives: If you are not willing to participate, you will be treated according to the existing protocol and it will not affect your relationship with this hospital.

Costs for participating in this research: The participant will have to pay for the investigations which are the part of the existing management protocol for this ailment. There is no commitment for any reimbursement or any other compensation for the participant.

Privacy and Confidentiality: No information about you or information provided by you during the research will be disclosed to others without your written permission

Authorization to publish results: when the results if the research are publishes or discussed, in a conference, no information would be divulged that would disclose your identity.

Compensation:

In the event of any injury related to the study, treatment will be made available through KLES Prabhakar Kore Hospital and MRC, Belgaum. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions:

If you have any questions about the research you may please contact:

1) **Dr._____**

   Chief Investigator, P.G., Department of Medicine, JNMC, Belgaum.

2) **Dr. _____**

   Guide, Professor, Department of Medicine, JNMC, Belgaum

   If you need any futher information regarding your rights as a study participant contact.

3) **Dr. Ganga S. Pilli**,

   Chairperson of Institutional Ethics Committee, Contact number: 9448863866

Consent Statement

I, Mr./Mrs./Ms. _____ voluntarily agree for the participation as a subject of this study. By signing this consent form I am not giving any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me, in my own vernacular language, including the risks and benefits and after having all my questions answered.

Subject's name: _____

Signature or the Left thumb Print of the Subject: _____

Witness' name: _____

Signature of the witness: _____

Investigator's Name: _____

Investigator's Signature: _____

Date:

Place: Belgaum

ANNEXURE-II- PROFORMA

PREVALENCE OF THYROID DISORDERS IN TYPE 2 DIABETIC PATIENTS – A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR. PRABHAKAR KORE HOSPITAL AND MRC.

Name Occupation ID No.

Age / Sex Address

Ip/op no.

Symptoms of hypothyroidism: Yes / No

Symptoms of hyperthyroidism: Yes / No

Duration of diabetes mellitus :

Drugs for DM: OHAs

Insulin

Past history:

IHD

Cerebrovascular disease

Peripheral artery disease

Systemic hypertension

Dyslipidemia

COPD

Family history:

Diabetes Mellitus

Thyroid disease

Drug history:

Anti-hypertensive drugs

Other drugs like Amiodarone, Lithium etc

Personal history:

Diet

Appetite

Sleep

Bowel / Bladder

Habits

General Physical Examination:

Height Weight BMI

Pulse BP RR Temperature

Pallor / icterus / cyanosis / clubbing / lymphadenopathy / edema

Local examination of the neck : Goiter

Operative scar

Signs of hyperlipidemia:

Systemic examination:

Cardiovascular system

Respiratory system

Abdomen examination

Central nervous system

Markers of endocrine disorders

Investigations:

HbA1C

FT3

FT4

TSH

RBS

Others

Remarks :

ANNEXURE-III- KEY TO MASTER CHART

N	No retinopathy
HTN	Hypertension
TSH	Thyroid stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
Creat	Creatinine
HbA1c	Glycosylated haemoglobin
NPDR	Non proliferative diabetic retinopathy
IP No	In patient number
T2DM	Type 2 diabetes mellitus
RBS	Random blood sugar
BMI	Body mass index
SCH	Subclinical hypothyroidism