“STUDY OF THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS”

Dissertation submitted to

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

in partial fulfilment of the regulations

for the award of the degree of

M.D. BRANCH-I (GENERAL MEDICINE)

Registration Number: 200120505501

DEPARTMENT OF GENERAL MEDICINE

TAGORE MEDICAL COLLEGE AND HOSPITAL

CHENNAI -600 127

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

CHENNAI, TAMILNADU

MAY-2023

CERTIFICATE

This is to certify that this Dissertation entitled **"STUDY OF THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS"** Is the bonafide original work of **Dr. MANIKANDAN G** in partial fulfillment of the requirement for an M.D., in General Medicine examination of the Tamil Nadu Dr.M.G.R. Medical University to be held in May 2023.

GUIDE

Dr. RAJASEKAR.D M.D.,
Department of General Medicine,
Tagore medical college and hospital,
Chennai -600127.

Dr. D. RAJASEKAR
M.D. D.M. (Nephro)
Reg. No: 77825
TAGORE MEDICAL COLLEGE AND HOSPITAL
Rathinamangalam, Chennai-600 127.

HOD

Prof.Dr. T.K.V. SHARAVANAN M.D
Department of General Medicine,
Tagore medical college and hospital,
Chennai -600127.

DEAN

TAGORE MEDICAL COLLEGE & HOSPITAL
RATHINAMANGALAM, MELAKOTTAIYUR POST,
CHENNAI-600 127.

Prof.DR.J.MUTHUKUMARAN,M.S.,M.CH
Tagore medical college and hospital,
Chennai -600127

DECLARATION

I, **DR. MANIKANDAN G,** solemnly declare that the dissertation entitled **"STUDY OF THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS"** is the bonafide work done by me at the department of General Medicine, Tagore Medical College and Hospital under the expert guidance and supervision of **Prof. Dr.T.K.V. SHARAVANAN.M.D.,** Professor of General Medicine, Department of General Medicine, Tagore Medical College and hospital. The dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards partial fulfillment of the requirement for the award of an M.D., Degree in General Medicine.

Place: Chennai

Date:

Signature of Candidate

Dr. MANIKANDAN G

REG.NO: 200120505501

GUIDE CERTIFICATE

Guide: Dr. Rajasekar.D M.D.,

Guide and Associate Professor,

Department of General Medicine,

Tagore Medical College and Hospital (TMCH),

Chennai - 600 127.

Remark of the Guide:

The work done by **DR.MANIKANDAN G,** titled **"STUDY OF THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS"** is under my supervision and I assure that the candidate abided by the rules of the ethical committee.

Dr. RAJASEKAR.D M.D,
Guide and Associate Professor,
Department of General Medicine,
Tagore medical college and hospital,
Chennai -600127.

Dr. D. RAJASEKAR
M.D. D.M. (Nephro)
Reg. No: 77825
TAGORE MEDICAL COLLEGE AND HOSPITAL
Rathinamangalam, Chennai-600 127.

SPECIAL ACKNOWLEDGEMENT

I express my sincere thanks to **DR. J.MUTHUKUMARAN, M.S.,M.ch, Dean,** Tagore medical college and hospital, Chennai for permitting me to utilize the facilities of the institution for my study.

The chairperson of Tagore medical college and hospital**, Dr. M. MALA, M.A., M.Phil.,** has my heartfelt gratitude for her unwavering dedication to the progress of the postgraduate students at the institution.

ACKNOWLEDGEMENT

I would like to express my humble gratitude to The Head of the Department and my guide **Prof.T.K.V.Sharavanan M.D.**, sir for accepting the study and also for his enthusiastic support and guidance throughout the study.

My special thanks to my beloved professors **DR.K.B.PRASANNA.M.D.**, **DR.NASREEN BEGUM.M.D,** all the faculties and colleagues from the Department of Medicine for their valuable support throughout the PG course.

CERTIFICATE – II

This is to certify that this dissertation work titled **"STUDY OF THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS"** of the candidate **DR. MANIKANDAN G** with registration number **200120505501** for the award of **M.D.,GENERAL MEDICINE**. I personally verified the urkund.com website for Plagiarism check. The uploaded thesis file contains from introduction to the conclusion and the results show **14% Percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with seal

Dr. D. RAJASEKAR
M.D. D.M. (Nephro)
Reg. No: 77825
TAGORE MEDICAL COLLEGE AND HOSPITAL
Rathinamangalam, Chennai-600 127.

ABBREVIATIONS

ADA	American Diabetes Association
WHO	World Health Organization
HBa1C	Glycated Haemoglobin
TD	Thyroid Dysfunction
AITD	Autoimmune Thyroid Disease
TG	Thyroglobulin
TSH	Thyroid Stimulating Hormone
T4	Thyroxine
T3	Triiodothyronine
TPO	Thyroid Peroxidase
TRH	Thyrotropin Releasing Hormone
THBI	Thyroid Hormone Binding Inhibitor
HPLC	High Performance Liquid Chromatography
IDF	International Diabetes Federation
SCH	Subclinical Hypothyroidism

CONTENTS

ABSTRACT

Background:

Diabetes Mellitus (DM) is the most common metabolic disease characterized by features of hyperglycemia and metabolic disturbances caused due to pancreatic beta-cell dysfunction, increased renal glucose reabsorptionand hyperglucagonemia. Conversely, DM could variably affect thyroid function. For example, the effect of TSH to thyrotropin-releasing hormone have been shown to be impaired in DM, leading to the hypothyroidism and concomitant lower T3 values.

Objective

Primary objective of the study is to measure the thyroid profile level in type 2 diabetics individuals and to compare the level of thyroid profile in type 2 diabetic individual and non-diabetic individuals with euthyroid.

Methodology

Samples will be collected from patients presented with thyroid dysfunction in type 2 diabetes. Blood samples collected will be investigated for glycemic, lipid and thyroid profile. The data will analysed by SPSS software

Results

Thyroid dysfunction was detected in 43.3% among 150 type2 DM patients studied, out of which 22.7% was found to be hypothyroidism,5.3% of hyperthyroidism,12% of subclinical hypothyroidism and 3.3% of subclinical hyperthyroidism. Hyperthyroidism was more in prevalent in elderly type 2 DM patients and among males. But hypothyroidism was more prevalent among type 2DM female patients and among middle age group patients.

Conclusion:

The present study shows that DM have a higher prevalence of thyroid disorders than the normal population. Thyroid disease is found in both types 1 and 2 diabetes. Studies have found that thyroid dysfunction is much common in diabetic population compared to non-diabetic population, diabetes and thyroid disorders have been shown to influence each other mutually because of intersecting pathology

Key words: Diabetes Mellitus, Thyroid dysfunction,

INTRODUCTION

Diabetes mellitus is the most common metabolic disease characterized by features of hyperglycemia and metabolic disturbances of carbohydrates, proteins, &lipids which is principally caused by pancreatic beta-cell dysfunction,increased renal glucose reabsorptionand hyperglucagonemia1. Diabetes is rapidly becoming one of the most major health problems in worldwide. Thus estimated global prevalence of Diabetes was 2.8% in 2000 and would predicted to increase to 4.4% in 2030[2].

Diabetes Mellitusand thyroid dysfunction are the 2 most common endocrine disorders in routine clinical practice[3]. The association between TD and DM is widely known, with the first studies which was published in 1979[4]. Since then, several studies in different countries were conducted to estimate the prevalence of TD in diabetic patients. There is great variability in the prevalence of TD in general population, which is ranging from 6.6% up to 13.4%[5]. In DM patients, the prevalence is still much greater and may vary from 10 up to 24%[6]. These differences can be explained by different diagnostic criteria of Thyroid dysfunction, the degree of iodine intake among different regions, different sensitivities of the TSH assays and the large population diversity[7]. The relationship between Thyroid dysfunction and DM is characterized by aspecific complex interactions of interdependence. Screening of Thyroid dysfunction,

especially the subclinical state, in patients with Diabetes is justified because most of the patients can be asymptomatic.

Diabetes patients have a greater prevalence of thyroid diseases than the normal population. Thyroid disorder is found in both types I and II diabetes. Autoimmune type is associated thyroid dysfunction and is commonly seen in type I diabetes. Type II diabetes is a metabolic disease caused by the insulin resistance, which occurs primarily within cells of muscles, liver& fat tissue. Since Thyroxine regulate carbohydrate, lipid& protein metabolism, with insulin and thyroxin being intimately involved in the cellular metabolism and thus causes excess or deficit of either of the hormones will result in the functional derangement of the other also[8]. The termthyroid diabetes‟ was fisrtcoined in the early period literature to depict the pattern of influence of thyroid hormone alterations in the deprivation of glucose control.

Thyroid dysfunction is a group of disorders of the thyroid gland in which manifests as either hyper or hypothyroidism and is inflicted in circulation of TSH level. There is a deep, fundamental relation between DM and TD[9]. Studies also found that TD is much common in diabetic population compared to those of non-diabetic population, DM and thyroid diseases have been shown to stimulate each other mutually because of the intersecting pathology[10]. Thyroid hormones levels cause anraise in the hepatocyte type

concentration of glucose-6-phosphate, which is glucose transporter 2 (GLUT 2) thereby leading to elevated hepatic glucose output and abnormal glucose metabolism giving rise to the overproduction of lactate entering Cori's cycle and further promotes hepatic gluconeogenesis. Thyroid hormones also cause an increase in gut glucose absorption and increased lipolysis which further promotes hepatic gluconeogenesis[11]. Thus, thyroid dysfunction may lead to the development of insulin resistance. DM also influences the thyroid function at 2 different sites. Firstly, at the particular level of the hypothalamic control of TSH release and next at the level of peripheral tissue by converting T4 to T3. Hyperglycaemia causes a reduction in the hepatic concentration of T4-T5 deiodinase, low serum concentration of T3, raised, normal or low T4[12]. A possible genetic interaction has also been noted between the development of thyroid dysfunction and type-2 Diabetes Mellitus. Few genes like protein kinase B, Inhibitory G protein, GLUT2, phosphoenolpyruvate kinase [9] have been identified.

Thyroid hormones were essential for its metabolism energy homeostasis &participate in the insulin action and regulation of glucose [13,14]. Previous studies have reported its higher prevalence rates of thyroid diseases in DM patients compared with non-diabetic persons, and overt type hypothyroidism was frequently observed in typeII diabetes mellitus[15]. Moreover, sub-clinical hypothyroidism, a pathological status defined by an elevated serum thyroid stimulating

hormone level with normal concentrations of the free thyroid hormones[16], is receiving major concerns in the recent years. A meta-analysis has also reported that the pooled prevalence of Subclinical hypothyroidism in the Type II DM patients were 10.2% and Chinese patients with the prevalence rate of 18.9% were most frequently affected when compared with those from othercountries[17]. Meanwhile, high values of TSH and low values of free triiodothyroninewithin the normal range are related to more risk of chronic kidney disease[18]. Also, the low values of serum FT3 were found to be independently related with theurinary protein in Type II DM patients[19]. In addition, factors of genetic and environment are related to prevalence of DM and these effects of potential risk factors (such as thyroid dysfunction) on the processes of DM complications; although these mechanismsmights still remain unclear, these geographical variabilities in manifestations also exist[17,20].

Recently, evidence has also suggested that low circulating values of thyroid hormone, even within the range of normal reference concentrations, might be related to an increased risk of developing Type II DM, especially within the pre-diabetic populations[21]. Like DM, thyroid dysfunction also results from dysregulated parts of hormone secretion. Recent data analysis from the Colorado Thyroid Disease Prevalence study also showed that the 9.5% of 25,862 participants has an increased thyroidstimulating

hormone; conversely, 2.2% also had low TSH[22]. The thyroid hormone axis level includes TSH, thyroxine, and triiodothyronine, all of which were required to maintain the normal functioning of the thyroid. The imbalance of these hormones may lead to metabolic overactivity (hyperthyroidism) or underactivity (hypothyroidism). Based on this severity of the imbalance, hyperthyroidism & hypothyroidism could be diagnosed as either clinical or subclinical disease, of which the latter part is the most prevalent[23]. Sub-clinical thyroid dysregulation is commonly known as having an abnormal TSH level but normal T4 concentration. The presence or absence of symptoms might be independent of T4 values[24]. Despite being mild part, sub-clinical thyroid dysregulation has been linked to the several complications, including of cardiovascular disease[25], chronic kidney disease[26], and type IDM in children[27]. Thyroid dysfunction have been reported to be related with Type II DM in several studies. Some researches have suggested a bidirectional influence of DM and thyroid disorders upon each other[28]. The National Health and Nutrition Examination Survey III, a large cross-sectional survey study which has included 17,353 members in USA, revealed that hypothyroidism were present in about 4.6% of the study population& hyperthyroidism in about 1.3% of subjects[29]. In addition, NHANES III found an elevated frequency of thyroid dysregulation in participants with diabetes compared to those without DM. Thyroid hormone has been found to regulate carbohydrate metabolism and also pancreatic function[30].

Conversely, DM could variably affect thyroid function. For example, the effect of TSH to thyrotropin-releasing hormone have been shown to be impaired in DM, leading to the hypothyroidism and concomitant lower T3 values. It have been related that lower T3 values might also be explained by a lower value of conversion of T3 & T4 in DM based on studies of hyperglycemia-induced reversible decrease to deiodinase action and hepatic concentration of thyroid hormone[3]. Other researches have suggested that short-term T3 excess might induce insulin resistance; hence causing to T2DM[31]. However, this relationship between thyroxine levels and Type II DM risk remains highly significant and human studies has demonstrated conflict findings. Several studies have suggested a positive impact of high TSH level and low free thyroxine values on hyperglycemia& insulin resistance[32,33], but some has claimed that no relationship found in those researches[34]. Therefore, it have become apparent that some comprehensive evaluation of the relation between TSH, free T4, and Type II DM is needed.

There are contradictory reports regarding the prevalence of thyroid dysfunction among normal and patients with type II DM[35]. Hence the study was designed to assess the status of thyroid function in type II DM.

AIMS AND OBJECTIVES

Primary objective:

To measure the thyroid profile level in type 2 diabetics individuals.

Secondary objective:

To compare the level of thyroid profile in type 2 diabetic individual and non-diabetic individuals with euthyroid.

REVIEW OF LITERATURE

Review of Literature

Background & Justification for the conduct of the study:

The association between diabetes and thyroid dysfunction were first published in 1979[36]. QUICK RESPONSE CODE DOI: 10.13040/IJPSR.0975-8232.7(9).3877-80 Article can be accessed online on: www.ijpsr.com DOI link: http://dx.doi.org/10. 13040/IJPSR. 0975-8232.7 (9).3877-80 .

Thyroid dysregulation is a disease of the thyroid gland which almost manifests either as hyperthyroidism or hypothyroidism and is even reflected in the values of thyroid stimulating hormone[37].Diabetes Mellitus is the most commonendocrine disease, causing leading death worldwide[38].The WHO estimated DM prevalence were 2.8% in 2000 & 4.4% in 2030. The total number of people with DM is projected to increase from 171 million in 2000 to about 366 million in the year 2030[39].Thyroid also the commonest endocrine disorder in the worldwide population after DM[40].After ,1979 a number of researches estimated the prevalence of thyroid dysregulation among DM patients ranging from 2.2-17 %[41,42,43].However, fewer researches have estimated increased prevalence of thyro-diabetics of about 31% and 46.5% respectively[44,45]. Defective insulin production leads to various metabolic alterations in Type II DM, ranging from hyperglycemia

due to the defective insulin-regulated glucose uptake & up-regulated hepatic glucose synthesis, along with dyslipidaemia, which may includes impaired metabolism of fatty acids, TGs, and of lipoproteins[46]. Diabetes appears to have influence thyroid regulation in two sites; Firstly at the part of hypothalamic control of TSH secretion and secondly at peripheral tissue level by converting T4 to T3.Hyperglycemiaresults in reduction in hepatic values of T4-5 deiodinase, decreased serum concentration of T3,increased levels of reverse T3 & low, normal, or of high value of T4. Thyroxine regulate metabolism and DM could alter metabolism[47].

Anatomy

The thyroid gland is the most important part of the endocrine function and has weight of about 15-20gm. It is soft and is red in colour. This organ is mostly located between the C5-T1 vertebrae level of columnavertebralis, in front of the tracheal portion and below the larynxpart. It is comprised of 2 lobes (lobus dexter and lobus sinister) and the isthmus part that binds them almost together. Capsule glandular which is internal & external folium of thyroid gland is almost wrapped up by a fibrotic capsule named thyroid. Thyroid gland is nourished by a thyroidea superior that is the branch of artery carotis external and inferior thyroid artery that is the branch of a subclavian artery[48,49].

Physiology

Functions of Thyroid hormone

The thyroid hormones, triiodothyronine and its prohormone, thyroxine are tyrosine-based hormones which is synthesised by the thyroid gland that are commonly responsible for regulation of its metabolism. T3 and T4 are partially composed of iodine molecule. A deficiency of iodine factor leads to decreased production of T3 &T4, enlarges the thyroid gland and would cause the disorder known as simple goitre. T4 elevates the spectacular apoptosis of the parts of the larval gills, tail and fins. In Contrary to amphibian metamorphosis model, hypothyroidism and thyroidectomy in the mammals might be considered as sort of phylogenetic & metabolic regression to a forestage of reptilian life model. Indeed, many diseases that seem to affect hypothyroid humans has reptilian-like features, likescaly, dry, hairless, cold skin and a general decrease of digestion, metabolism, heart rate , and nervous stimulation, with lethargic cerebration, hypothermia and hyperuricemia [50].

Thyroid hormone plays an important role in various metabolic processes like carbohydrate, lipid metabolism and pancreatic functions. Alteration of thyroid hormone levels directly affects the basal metabolic rate[51].

Prevalence of Thyroid Disease:

The prevalence of the thyroid disease in general population has a great variability varying from 6.6% to 13.4%[52]. This difference may be due to difference in diagnostic criteria of thyroid disease, degree of iodine intake among various regions, difference in sensitivities of the TSH assays and the 9 large population diversity[53]. Thyroid dysfunction is more common in female than male and this may be due to inhibition of disease activity by androgens and also exacerbation by estrogens[54].

Thyroid diseases are more common with a variable prevalence in different populations. Data analysed from the Whickham survey, a study that conducted in the late 1970s in the northern England showed a prevalence rate of 6.6% of 27 thyroid dysreglation in the adult population. In the Colorado Thyroid Disorder Prevalence study involving about 25,862 participants attending a state health fair, about 9.5% of the studied population are found to have an elevated level of TSH, while 2.2 percent had a reduced level of TSH[55]. In the NHANES part III study, a survey of 17,353 participants representing the US population, hypothyroidism were seen in about 4.6% and hyperthyroidism in about 1.3% of subjects. Latter further studies observed an greater frequency of thyroid dysregulation with an advancing age and aincreased prevalence of thyroid disorder in women when compared to menpopoulation and in DM subjects compared to non-diabetic subjects. Many reports

documented aelevated prevalence of thyroid dysregulation in the DM population. Particularly, Perros et al.[55] demonstrated an overall prevalence of 13.4% of thyroid disorders seen in diabetics with the higher prevalence in type I female DM patients (31.4%) and lowest prevalence in type II male DM patients (6.9%). Recently, a prevalence of about 12.3% were reported that among Greek diabetic patients & 16% of Saudi patients with type IIDM were found to have thyroid dysregulation. In Jordan a study has described that thyroid dysregulation were present in 12.5% of type II diabetes mellitus subjects. However, thyroid diseases were found to be most commonly seen in those subjects with type I diabetes compared to those with type IIDM.

Diabetes Mellitus

Epidemiology

Diabetes is found in every population in the world and in all regions, including rural parts of low- and middle-income countries. The number of people with diabetes is steadily rising, with WHO estimating there were 422 million adults with diabetes worldwide in 2014. The age-adjusted prevalence in adults rose from 4.7% in 1980 to 8.5% in 2014, with the greatest rise in low- and middle-income countries compared to high-income countries. In addition, the International Diabetes Federation (IDF) estimates that 1.1 million children and adolescents aged 14–19 years have T1DM. Without interventions to halt the increase in diabetes, there will be at least 629 million people living with diabetes by 2045. High blood glucose

causes almost 4 million deaths each year, and the IDF estimates that the annual global health care spending on diabetes among adults was US$ 850 billion in 2017.

The effects of diabetes extend beyond the individual to affect their families and whole societies. It has broad socio-economic consequences and threatens national productivity and economies, especially in low- and middle-income countries where diabetes is often accompanied by other diseases.

Types of DM: WHO

Type1diabetes
Type2diabetes
Hybridformsofdiabetes
Slowlyevolvingimmune-mediateddiabetesofadults
Ketosispronetype2diabetes
Otherspecifictypes(seeTables)
Monogenicdiabetes
-Monogenicdefectsofβ-cellfunction
-Monogenicdefectsininsulinaction
Diseasesoftheexocrinepancreas
Endocrinedisorders
Drug-orchemical-induced
Infections
Uncommonspecificformsofimmune-mediateddiabetes
Othergeneticsyndromessometimesassociatedwithdiabetes
Unclassifieddiabetes
Thiscategoryshouldbeusedtemporarilywhenthereisnotacleardiagnosticcategoryespeciallyclosetothetimeofdiagnosis ofdiabetes
Hyperglyacemiafirstdetectedduringpregnancy
Diabetesmellitusinpregnancy
Gestationaldiabetesmellitus

Effect of Thyroid hormones on glucose homeostasis

Thyroxinehave an effect on glucose metabolism with several mechanisms. Hyperthyroidism have long been recognized to stimulate increased blood glucose. During hyperthyroidism state, the half-life of insulin is reduced most likely secondary to an elevated rate of degradation and an intensified stimulant of biologically inactive insulin precursors. In elevated pro-insulin values in response to a meal was observed in a study by Bech et al. In addition, untreated hyperthyroidism was affiliated with a decreased C-peptide to pro-insulin ratio implicating an fundamental defection in pro-insulin function. Another mechanism which explaining that the relation between hyperglycemia and hyperthyroidism is the raise in glucose gut absorption which is intervened by the surplus thyroxine. Endogenous synthesis of glucose is also elevated in hyperthyroidism via several functions. Thyroid hormones producesanraise in the hepatocyte plasma membrane levels of GLUT2 which is the main glucose transporter in the hepatic, and accordingly, the increased values of GLUT-2 also contribute to the elevated hepatic glucose output & unusual glucose metabolism. Furthermore, an elevated lipolysis is also noticed in hyperthyroidism state resulting in an increase in FFA which trigger the hepatic gluconeogenesis. The elevated release of FFA will relatively be explained by an strong catecholamine-stimulated lipolysis stimulated by the excess thyroid hormones . Moreover, the nonoxidative glucose disposal in the hyperthyroidism is increased

resulting in an elevated production of lactate which enters the Cori cycle and stimulates further hepatic gluconeogenesismetabloism. The increase in glucagon, GH and catecholamine values integrated with hyperthyroidism which further contributes to the impaired glucose tolerance. It is of well known that DM patients with hyperthyroidism state experience worsening of itsglycemic control in blood and thyrotoxicosis have been prone to DKA in subjects with DM. In hypothyroidism, glucose metabolism is affected via several factors[56]. Aelevated rate of liver glucose synthesis is observed in hypothyroidism state and it is also a cause for the reduction in insulin requirement in hypothyroid DM patients.

Pathological mechanisms common to thyroid disorders and diabetes:

Thyroid hormones act variably in hepatic, skeletal muscle and of adipose tissue which are the main targets of insulin action. Thyroid disorders have a major impact on glucose control. When thyroid dysfunction ensues the glucose homeostatic balance is broken. Insulin resistance, mainly associated with increased hepatic gluconeogenesis, is characteristic of an excess of thyroid hormones and explains why glucose control deteriorates when diabetic patients develop hyperthyroidism. Thyrotoxic patients show an increased glucose turnover with increased glucose absorption through the gastrointestinal tract, postabsorptive hyperglycaemia and elevated hepatic glucose output, along with elevated fasting or

postprandial insulin and proinsulin levels, elevated free fatty acid concentrations and elevated peripheral glucose transport and utilization. In peripheral tissues there is a large arrival of glucose to the tissues that overwhelms the function of Krebs cycle resulting in an increased metabolism of glucose through the nonoxidative pathway. Lactate produced in great quantities in the cells returns to the liver and participates in the regulation Cori cycle where 4 ATP molecules are wasted for each of the glucose molecule that is created. Although glucose uptake regulation in peripheral cells has been described as either normal or raised reduced insulin afflicted peripheral glucose utilization have also been demonstrated in the hyperthyroidism[56].

The Link between TD and T2DM

Thyroxineexert a direct influence on insulin secretion. Hypothyroidism resulted in a decrease in insulin production via beta cells whereas hyperthyroidism led to an increase in beta-cell responsiveness to catecholamine or glucose due to increased beta-cell mass. Additionally, thyrotoxicosis results in an increase in insulin clearance. All of these changes occur as a result of alternations in thyroid hormone which increases the risk of developing T2DM and can lead to diabetic complications or can worsen diabetic symptoms.

Hyperthyroidism and T2DM

Increased production of glucose from liver is an important factor in development of the peripheral insulin resistance, hyperinsulinemia and glucose intolerance. In case of thyrotoxicosis, glucose tolerance is mainly triggered by an increase inglucose output in liver and also an increase in the glycogenolysis[58]. This process contributes to progression of diabetes sub clinically and exacerbation of the hyperglycaemias in type 2 diabetes. Research have also described that both Type 2 Diabetes and hyperthyroidism have similar pathological features. For example, Type 2 DM is characterized by alterations the in B-cell mass, reduced insulin secretion, and increase in intestinal glucose absorption, this increase in glucagon secretion, rise in insulin breakdown, insulin resistance, and raised levels of catecholamines. These factors plays an important part of hyperthyroidism[59]. Among the mentioned factors, insulin resistance has been recognized as the most important link between thyroid malfunction and T2DM. Hepatic insulin resistance is broadcasted by raised production of glucose rather than the fasting hyperinsulinemia. Furthermore, increased hepatic glucose output has been noted to be a critical regulator of elevated fasting plasma glucose concentrations in Type 2 DM patients[60]. During insulin resistance, muscle glucose is raised even though uptake efficiency is reduced. Decreased glucose uptake into muscles and increased hepatic glucose output results in a worsening of glucose metabolism. It is worth observing that insulin resistance

may occur in both hyperthyroidism and hypothyroidism. According to current discoveries, insulin resistance also impairs lipid metabolism. Thus, insulin resistance seems to have possible connection between thyroid dysfunction and Type 2 DM.

Similarly, another study disclosed that beta-cell dysfunction and insulin resistance both are negatively associated to TSH, that can be explained by thyroid hormones' insulin-antagonistic properties shared with a rise in TSH. A raised blood T3 and T4 levels frequently result in reduced TSH levels through a negative feedback process. Thyroid hormone levels reduces as TSH levels decrease and insulin-antagonistic effects are lessened and when TSH level decreases, thyroid levels increase and insulin-antagonistic effects are raised. Though, the mechanism which leads to hyperthyroidism insulin resistance is not known but it is most commonly happening phenomenon detected in diabetic patients with hyperthyroidism.

Genetic Variations, Hyperthyroidism, and T2DM

Thyroid hormone's interaction with skeletal muscles is controlled by the mitochondrial uncoupling protein, GLUT1, GLUT4, "PPAR gamma coactivator-1 alpha (PGC-1 alpha)," and phosphoglycerate kinase (PGK) genes. UCP-3 and GLUT-4 are two of the many newly identified genes that have been the subject of in-depth study. T3 mediates GLUT-4 in skeletal muscles and has been

shown to enhance both basal and also insulin-induced glucose transport. A recently discovered gene called "mitochondrial uncoupling protein 3" (UCP 3) has been connected to reduced fatty acid oxidation and improved glucose metabolism61. Furthermore, studies have noted that this gene is important for the downregulation of "Akt/PKB signalling and 5′ adenosine monophosphate-activated protein kinase"62. The potential function of T2 has been studied, and it has determined that it is related to sarcolemma GLUT-4. Similar to this, phosphofructokinase & glycolytic enzymes have been connected to T262-mediated GLUT 4 activity. Additionally, many genes have been discovered to play a role in the peripheral glucose metabolism. For instance, T3 connects to thyroid hormone receptors and also activates a variety of genes involved in glucose metabolism. These receptors come from, in that order, TR1, TR2, TR3, and TR1. These are T3 bindings four main isoforms63. The metabolic effects of thyroid hormones are thought to be modulated by TR 1. The preservation of the "hypothalamic-pituitary-thyroid axis" and the preservation of normal thyroid function are related64.

Similar to T4, T4 is the source of 3,5,3-triiodothyronine. By removing the iodine atom from phenolic ring, type 2 or the type 1 iodothyronine deiodinases might cause it (D2). Type 3 deiodinase, on the other hand, renders thyroid hormone inactive by removing an iodine atom from tyrosyl ring. The modulation bioavailability of T3

and, consequently, the insulin response is mediated by deiodinase. The expression of deiodinases in diverse tissues is influenced by thyroid hormones. They control T3 bioavailability, that affects insulin sensitivity. A novel missense variant is connected to T3 elevations (Thr92Ala). Insulin resistance and this are related. Furthermore, it is connected with an increase in clearance of insulin-induced glucose and turnover of glucose in skeletal muscle and also in adipose tissue. "Intracellular triiodothyronine" (T3) was found to be connected to abnormalities in insulin sensitivity in a meta-analysis64. According to studies, GLUT 2 expression was increased in hyperthyroidism when compared with euthyroid phase65. A connection between thyroid hormone and insulin resistance is further shown by abnormalities in lipid metabolism. Additionally, hypothyroidism causes a reduction in glucose oxidation whereas thyrotoxicosis causes a rise in lipid peroxidation. LDL clearance leads to lower levels of triglycerides and LDL cholesterol. Adipocytes are lipolyzed as a result of TH's stimulation of catecholamine activity, which also raises the level of fatty acids in the blood. The TH-mediated boost of the hepatic long-chain fatty acids oxidative pathway, which is implicated in glucogenesis, is countered by increased FA supply. The aetiology of type 2 diabetes is significantly influenced by all of these genes connected to thyroid hormones.

Hypothyroidism and T2DM

Reduced GI glucose absorption, extended peripheral glucose accumulation, the gluconeogenesis, reduced hepatic glucose synthesis, and reduced glucose elimination are all symptoms of hypothyroidism. Different ways in which hypothyroidism might impact type 2 diabetes' glucose metabolism. For instance, subclinical hypothyroidism can lead to insulin resistance because of reduced rate of insulin-stimulated transfer of glucose brought on by GLUT 2 gene translocation. In addition, research found that the physiological requirement for insulin was reduced in hypothyroidism because of lower insulin clearance by kidneys. Additionally, anorectic conditions may also be a factor in hypothyroidism's decreased insulin production. Additionally, hypothyroidism & insulin resistance have been connected in a number of preclinical and in vitro studies where it was observed that peripheral muscles lose their sensitivity to insulin in hypothyroid states. Dysregulated leptin metabolism has been proposed as a possible function for such illness. In addition, a number of writers have demonstrated a direct connection between hypothyroidism and also insulin resistance. However, several researchers have noted contradictory results, underlining the requirement for more study in this area.

Thyroid diseases and T2DM

Thyroid cancer incidence and T2DM may or may not be connected. Women with type 2 diabetes mellitus had more incidence of differentiated thyroid carcinoma, according to large prospective cohort studies[66]. There is no proof that thyroid cancer and the diabetes are significantly related, according to separate sizable prospective research and a pooled review of multiple prospective trials[67]. Furthermore, a previous analysis of the literature found that the likelihood of any association between thyroid cancer and also T2DM was low[68]. Though, early T2DM patients had a reduced incidence of the thyroid cancer, and this benefit persisted for up to six years after T2DM was discovered, according to Korean research[69]. Additionally, T2DM was associated with a markedly elevated risk of cancer in thyroid in Chinese women, according to research retrospectively that was published in 2018. Evidence also demonstrates that subclinical hyperthyroidism or hypothyroidism increases blood pressure and also cholesterol levels, inhibits insulin secretion, and degrades micro-vascular and macrovascular function, raising risk of the peripheral neuropathy, peripheral artery disease, and diabetic nephropathy. Different research, however, suggested that subclinical hypothyroidism may help T2DM patients avoid cardiovascular mortality. Prior research also looked at the connection between the subclinical hypothyroidism and diabetes complications. This meta-analysis found that diabetes sequelae such as peripheral neuropathy, nephropathy, and retinopathy were likely

to occur in T2DM individuals who presented with subclinical hypothyroidism. It is plausible to deduce from the facts above that thyroid disorders can aggravate diabetes symptoms or raise risk of diabetic complications. Future investigation into the connection between cancer in thyroid and diabetes mellitus is strongly advised, though.

Effect of type 2 diabetes on thyroid diseases:

Diabetes mellitus affects thyroid function in two different ways: first, by controlling TSH release at hypothalamus level[70], and second, by converting T4 to T3 in peripheral tissues[71]. Reduced hepatic T4-T3 conversion, lower serum T3 levels, and increased reverse T3 intensity are all potential effects of hyperglycemia. In diabetics with inadequate glycemic control, the levels of thyroid hormone is altered. Patients with DM have lower nocturnal TSH levels and worse TRH responsiveness[72]. TSH and insulin resistance are inversely correlated, which may be due to thyroid hormone's insulin-antagonistic actions along with rise in TSH. Through a negative feedback loop, greater serum TSH often results in reduced thyroid hormone levels.

The likelihood of developing hypothyroidism in type 2 DM is increased by older age, obesity, female sex, hospitalisation, and the thyroid peroxidase antibody positivity. Diabetes alters the levels of the hormone thyroid-stimulating hormone (TSH) and interferes with

the process by which thyroxine (T4) is converted to triiodothyronine in peripheral tissues[49], both of which affect thyroid function. The nocturnal TSH peak may be missing or reduced in euthyroid diabetic individuals, and TSH response to thyrotropin-releasing hormone might be impaired. But persistent hyperglycemia may worsen thyroid dysfunction over time. Because of this, it is crucial to remember when understanding thyroid function tests, like to other systemic illnesses, diabetic ketoacidosis can cause a decline in T3 and T4 levels while TSH levels might remain normal. Furthermore, goiter[50] is brought on by insulin resistance and also by hyperinsulinemia, both of which encourage the growth of thyroid tissue. Additionally, goitre orbitopathy in diabetics increases the incidence of dysthyroid optic neuropathy compared to non-diabetics. Numerous studies have also demonstrated that there may be a bilateral relationship between thyroid function and diabetes. For instance, type 2 diabetes or even prediabetes in the early stages might worsen thyroid tissue hyperplasia, which causes the thyroid gland to expand and nodules to form. On the other hand, diabetes's glucose metabolism is impacted by thyroid disease. Furthermore, it is generally known that subclinical hypothyroidism is increasingly common as people become older. Obesity has been shown to be substantially related with hypothyroidism[73], and males and females have different thyroid malfunction predispositions. An analysis of 36 studies found that subclinical hypothyroidism is more common in Type 2 DM females above the age of 60. Additionally, a cross-

sectional study conducted in India with 1,508 Type 2 DM patients noted a clear risk of hypothyroidism in obese and non-obese patients along with a significantly higher risk of hypothyroidism in older type 2 diabetic patients who are more than 65 years with an OR of 4.2. This proposes that thyroid dysfunction and Type 2 DM can also be influenced by factors such as BMI, age, gender, and sex hormones.

Relationship between thyroid disorder and glycemic status

The primary determinants of dysfunction of thyroid in diabetes are glycaemic state and TRH and TSH levels. The presence of thyroid hormone binding inhibitors (THBI), which reduced the excess thyroidal conversion of the T4 to T3, also had an impact. Due to an increase in beta cell mass in hyperthyroidism, the beta cells' sensitivity to glucose or even catecholamine is heightened[74]. Glycogenesis and glycogenolysis result in a rise in the liver's endogenous glucose synthesis and reduced sensitivity of the liver to insulin. In hyperthyroidism, there is an increase in FFA levels because of enhanced lipolysis, which promotes hepatic gluconeogenesis. FFA levels also rise because of lipolysis that is catecholamine-stimulated by elevated thyroid hormone levels. Skeletal muscle glucose use has increased, and this is mediated by insulin-stimulated glucose oxidation rate[75]. Thyroid illness in diabetes is challenging to diagnose clinically. In addition, severe DM nephropathy may be misinterpreted for hypothyroidism

(edoema, weight gain, and pallor)[76] due to the symptoms of poor DM management being similar to those of hyperthyroidism (weight loss, increased hunger, and weariness).

Review of Studies:

In retrospective research in 2012 by Demitrost L. et al., the thyroid stimulating hormone levels of 202 Type 2 DM patients who visited the diabetes clinic at the Regional Institute of Medical Sciences in Imphal between January 2011 and July 2012 were examined. Type 2 DM instances that are well-known serve as inclusion criteria. Patients with a history of hypothyroidism and those taking medications that affect the thyroid profile are excluded from the study. Of the 202 subjects, type 2 DM patients included in the analysis—61 men and 141 women—139. 68.8% are euthyroid, 16.3% have subclinical hypothyroidism, 11.4% have hypothyroidism, 2% have subclinical hyperthyroidism. The age range of 45 to 64 years had the highest prevalence of subclinical and symptomatic hypothyroidism patients. Patients who had a BMI greater than 25 had a higher chance of developing hypothyroidism. Hypothyroidism is extremely common in type 2 DM individuals older than 45, and it is more common if the BMI is higher than 25[77].

To determine the incidence of various forms of thyroid dysfunction and its risk variables, Metab Al-Geffari et al. conducted cross-sectional retrospective randomised hospital-based research of 411 Type 2 diabetes Saudi patients older than 25 years in 2013. 28.5% of people have some form of thyroid malfunction, of which 25.3% have hypothyroidism, with clinical, subclinical, and with overt hypothyroidism being represented by 15.3%, 9.5%, and 0.5%, respectively. 3.2% of people have hyperthyroidism, of which 2.7% have subclinical instances and 0.5% have overt hyperthyroidism. Family history of thyroid illness, being a woman, and having diabetes for more than 10 years are risk factors for dysfunction of the thyroid in Saudi Type 2 diabetics, although the risk was not significant in patients with a history of goitre and patients older than 60. Parity and smoking exhibit a nonsignificant lower risk. This study found that family history of thyroid illness, being a woman, and having diabetes for more than ten years are the biggest risk factors for dysfunction of thyroid among Saudi Type 2 diabetic patients[10].

In 2016, Maxzud et al noted that 48% of type 2 diabetes patients (n = 92) had thyroid disease. 40% (n = 37) of participants with no history of TD had subclinical hypothyroidism, which affected 15 of them (a rate of 45%). The incidence of subclinical hypothyroidism was 8% throughout the entire research group. Anti-TPO prevalence was 13% (n = 25) and subclinical DT prevalence

was 9% (n = 17) globally. Given the high rate of newly diagnosed cases and elevated cardiovascular risk associated with undiagnosed thyroid dysfunction, early detection of dysfunction of thyroid in patients with type 2 diabetes mellitus should be routinely carried out[78].

Thyroid function was measured in 2016 by Chaker et al. (mean age 65 years), who also assessed the incidence of diabetes over time. Thyroid function was determined by thyroid-stimulating hormone (TSH) and free thyroxine (FT4). The relationship between TSH and FT4 and diabetes and the transition from prediabetes to the diabetes was examined using Cox-models. Age, sex, baseline levels of high-density lipoprotein cholesterol, and blood sugar were all modified in multivariable models. 798 new instances of diabetes were reported throughout an average follow-up of 7.9 years. Even when TSH levels were within the reference range for thyroid, greater TSH levels were linked to a higher risk of diabetes. In both patients with thyroid function within the reference range and in all participants, higher FT4 levels were linked to a decreased risk of developing diabetes. Low-normal thyroid function was associated with a greater risk of developing diabetes. With greater FT4 levels within the normal range, the absolute risk of developing type 2 diabetes in individuals with prediabetes dropped from 35% to roughly 15%. They came to the conclusion that low and low-normal thyroid function, particularly in subjects with prediabetes, are risk factors for incident diabetes. Future research should examine the

benefits of diagnosing and treating (subclinical) hypothyroidism in those at risk of acquiring diabetes[79].

A total of 50 patients diagnosed with type-2 DM and 50 healthy controls were taken into account randomly in 2016, according to Shubhankar Mishra. Chemiluminescence assays were used to perform thyroid function testing. After tabulation, it underwent statistical analysis. Use of Statistical Analysis For categorical variables, the Chi-square test was used in statistical analysis. The significance between the means was determined using the Student's t-test. The term "P-value of 0.05" denoted significance. Significantly more type-2 DM (16%) than healthy controls (4%) were reported to have thyroid abnormalities. Six (75%) of the eight diabetes patients with thyroid dysfunction were female. In diabetic individuals with thyroid disease, the mean BMI was high. Patients with thyroid impairment reported elevated HbA1c values. Compared to euthyroid diabetics and controls, those with thyroid disease had a higher mean total cholesterol level. In 4% of type-2 DM patients, goitre was discovered. This study found a strong correlation between type-2 DM and thyroid conditions. The two most prevalent thyroid abnormalities in type-2 DM were subclinical hypothyroidism and overt hypothyroidism. Improved dyslipidemia in type-2 DM was linked to thyroid dysfunction[80].

Mehalingam et al did a cross-sectional study in 2016 in the departments of medicine and endocrinology at JIPMER, Pondicherry. The study enrolled 331 type 2 diabetes patients who were outpatients and had no prior history of thyroid disease, any chronic liver disease, or any other acute sickness. For diabetes complications, every participant underwent screening. Chemiluminescent immunoassay was used to examine each subject's thyroid function. 13.9% of the research participants had hypothyroidism, whereas 3.6% had hyperthyroidism. The prevalence of dysfunction of the thyroid was higher in women when compared with men. In this patients, there was no association between thyroid dysfunction and diabetes complications. According to this study, 17.5% of individuals with type 2 diabetes mellitus had thyroid impairment. Diabetes problems and thyroid dysfunction did not correlate at all[81].

In 2016, Datchinamoorthi and associates T3, T4, and TSH thyroid function tests were performed on DM patients. Fasting blood glucose levels and lipid markers were connected with the outcomes of 50 healthy volunteers who were treated as controls and matched for age and the sex. The outcomes revealed a sizable distinction between the patients and the controls. This investigation may lead to the conclusion that DM patients have hypothyroidism[82].

To determine prevalence of thyroid dysfunction, Jali MV et al. conducted a cross-sectional hospital-based investigation in 2017. The survey has 713 people with type 2 diabetes mellitus as participants. Fasting blood sugar (FBS), glycosylated haemoglobin (HbA1c), total triiodothyronine (T3), total thyroxine (T4), and thyroid-stimulating hormone were all measured in these participants (TSH). 16.2% of T2DM patients had thyroid impairment, it was discovered. Females (25%) had a greater gender-specific prevalence rate than men (10.1%). Age group 50 yrs. reported to have increased age-specific prevalence. In comparison to other age groups, (19%) Higher prevalence (27.9%) was seen in the subjects who had poor glycemiccontro). The thyroid dysfunction was more common (19.8%) in subjects with long-standing T2DM, though the association was not statistically significant. This study found that women had more probable than men for this thyroid dysfunction with T2DM (16.2%), with hypothyroidism being more common. One of the main factors contributing to ineffective diabetes management may be the failure to recognise dysfunction of thyroid in T2DM patients. They advise routine thyroid dysfunction monitoring and universal thyroid dysfunction screening for T2DM patients[83].

Research by Raja Rao et al. was undertaken in 2017 with a total of 140 participants who had Type 2 DM. 31.42% of people had thyroid conditions. In 28 cases, the thyroid function was low, whereas in 16, the thyroid function was hyperactive. Three

individuals had overt hypothyroidism, 25 had subclinical hypothyroidism, and 16 had hyperthyroidism. In this study, there were 70 male patients and 70 female patients. Thyroid diseases were more common in women (44.28%) than in men (17.14%). Elderly individuals were more expected to have subclinical hypothyroidism (39.02%). Subclinical hypothyroidism was very common in elderly ladies (17.14%). In 16 cases, there were signs of hyperthyroidism. The glycemic control of patients with hyperthyroidism was subpar. There was no connection between prevalence of thyroid disorders and diabetes duration. Sub-clinical hypothyroidism was seen in patients with uncontrolled diabetes and microvascular complications. They reported that 31.42% of diabetics had thyroid problems. More elderly people were present. The prevalence of sub-clinical hypothyroidism was high in women. The glycemic control of diabetics with hyperthyroidism was poor. Patients with subclinical hypothyroidism were shown to have serious diabetes consequences. Thyroid dysfunction was unaffected by the duration of diabetes[84].

A cross-sectional study was carried out in 2017 by Subekti I et al in Mangunkusumo Hospital. Patients with type 2 diabetes mellitus who are willing to undergo thyroid laboratory testing and are under the age of 18 are included in this study. In this study, hyperthyroidism is defined as TSH less than 0.4 mIU/L with eCLIA and hypothyroidism as TSH greater than 4.0 mIU/L. 303 of the 364

patients enrolled from the Endocrine and Diabetes Polyclinic at CiptoMangunkusumo Hospital underwent this trial all the way to analysis. Ninety one percent (90.1%) of the 273 participants were euthyroid, whereas seven (2.31%) were hyperthyroid and twenty-three (7.59%) were hypothyroid. Most of the patients had subclinical hypothyroidism (56.5% according to the Zulewski and Billewicz Score and 65.2% according to the fT4 laboratory result), whereas 42.9% and 71.4% of the subjects had clinical hyperthyroidism according to the clinical appearance and fT4 laboratory result, respectively. According to this study, the percentage of hypothyroidism and hyperthyroidism among diabetics was 7.59% and 2.31 respectively, while the percentage of overall thyroid dysfunction was 9.9%. It is recommended that individuals with type 2 diabetes mellitus who are in high-risk conditions get a thyroid dysfunction test as part of comprehensive management[85].

Sotak S. et al. conducted a study in 2018 involving two groups. 60 patients with T2DM who had no prior history of thyroid illness made up the first group. The second group included 60 thyroid illness patients who had no prior history of glucose metabolism impairment. 100 people in the control group (CG) had no prior history of thyroid illness or impaired glucose metabolism. Blood tests were used to assess thyroid and glucose metabolism parameters. When compared to CG, individuals with T2DM had a considerably greater frequency of thyroid disorders. Free

triiodothyronine (fT3), thyroid-stimulating hormone (TSH), and anti-thyroid peroxidase (anti-TPO) autoantibodies were all shown to be present at higher blood levels in T2DM patients. No statistically significant difference was discovered in the frequency of T2DM in individuals with thyroid disorders and CG. In terms of glucose metabolism parameters, individuals with hyperthyroidism and autoimmune thyroid disease (AITD) only had higher fasting glucose levels. This study also came to the conclusion that patients with T2DM had a greater prevalence of both primary hypothyroidism and AITD. We did not discover a greater frequency of T2DM in thyroid disease patients[86].

A study on thyroid function in people with type 2 diabetes (T2DM) and diabetic nephropathy was carried out in 2018 by Wei Zhao et al. They used 139 people with DN, 100 T2DM patients without DN, and 103 healthy volunteers. Body mass index, blood pressure, and laboratory tests of thyroid, kidney, and glycosylated haemoglobin were all taken as part of physical examinations. Results. TSH levels were higher and free T3 levels were lower in DN patients compared to those without DN. In comparison to controls and patients without DN, patients with DN had a prevalence of SCH and low FT3 syndrome that was 10.8% and 20.9% higher, respectively (p 0.05). Through Pearson correlation or Spearman rank correlation analysis, there were positive relationships between TSH and urine albumin-to-creatinine ratio and

estimated glomerular filtration rate in DN patients as well as between FT3 and eGFR with statistical significance. This study came to the conclusion that T2DM patients with DN had high TSH levels and low FT3 levels. The control of thyroid dysfunction may be a viable therapeutic approach for DN. Routine thyroid function monitoring is required in people with DN[87].

In 2018. A prospective case control research was carried out at the Adichunchanagiri Institute of Medical Sciences in B.G. Nagar, Nagamangala Taluk by Shenoy R. et al. Its location in a rural area makes it primarily a service to a sizable community. 54 patients out of 108 analysed individuals were cases and 54 were controls. The study excluded patients with pre-existing liver or renal disease, those taking medications that affect thyroid function, patients with pre-existing thyroid dysfunction, and pregnant women. Written permission was obtained. A thorough history and physical were taken. The following tests were run: FBS, PPBS, HbA1c, serum creatinine, fasting lipid profile, and thyroid profile. fT4, if necessary. In cases, there were 21 (38.8%) men and 33 (61.2%) women, whereas among controls, there were 15 (27.7%) men and 39 (72.3%) women. Patients in 19 instances (35.2%) exhibited thyroid dysfunction. Six (11.1%) people had overt hypothyroidism, whereas 13 (24.1%) presents subclinical hypothyroidism. In the control group, 4 (7.5%) individuals had thyroid issues. This study

demonstrates that people with type 2 DM have a higher frequency of thyroid impairment than the general population[88].

Romesh Sharma et al. reported that among 150 type 2 DM patients they evaluated, 43.3% had thyroid dysfunction, of which 22.7% had hypothyroidism, 5.3% had hyperthyroidism, 12% had subclinical hypothyroidism, and 3.3% had preclinical hyperthyroidism. Males and older type 2 DM patients were more likely to have hyperthyroidism, whereas women and individuals in the medium age range were more likely to have hypothyroidism. As the duration of diabetes increased, there was an increase in occurrences of hyperthyroidism. Compared to patients who were hypothyroid (mean HbA1c=7.71.0%) and euthyroid (mean HbA1c=7.61.8%), hyperthyroid patients (mean HbA1c=8.51.9%) had worse glycemic control[89].

A sub-dataset of the National Health Insurance Research Database (NHIRD) was used in this study by Chen et al. in 2019. Patients over the age of 18 who had recently received a diagnosis of thyroid disease (including hyper- and hypothyroidism) between 2000 and 2012 were chosen for the study. The control group was made up of individuals chosen at random who had never had a thyroid condition identified and whose frequency was four times higher than that of the thyroid illness group. T2D was the cohort's event. The thyroid disease group was compared to the control group

in the primary analysis, and the hyperthyroidism subgroup, hypothyroidism subgroup, and control group were compared in the secondary analysis. With a hazard ratio of 1.23, T2D was more common in the thyroid illness group than in the control group. Significantly more cases of hyperthyroidism and hypothyroidism than in the control group. Additionally, individuals who were female and in the categories of 40 to 64 years old and 18 to 39 years old were shown to have significantly higher HR. Thyroid illness patients without co-morbid conditions also had a higher rate of T2D M than those in the control group, with an HR of 1.47. In the half-year follow-up, the highest HR was discovered. Patients with thyroid dysfunction had a disproportionately greater chance of developing T2D, particularly in the 0.5 to 1 year window following the diagnosis of thyroid dysfunction. The findings advise administering blood sugar testing to thyroid disease sufferers in order to identify and treat T2DM early[90].

Three hundred and fifty-four T2DM patients and 118 non-diabetic individuals (controls) were included in research done by Ogbonna and Ezeani in 2020. After adequate justifications, a pretested questionnaire was completed for each subject. Following the examination of the participants, anthropometric measurements and clinical data were recorded. Their HbA1c, fT3, fT4, and TSH levels were examined in blood samples. The data were analysed using the student t-test, chi-square test, and regression analysis.

they considered statistical significance to be P 0.05. Approximately 56.5% of the T2DM participants in this research were female, compared to 62.7% of the controls. BMI was significantly higher in T2DM patients compared to controls. Mean HbA1c in T2DM patients was substantially higher than in controls. In this study, thyroid dysfunction in T2DM patients was significantly associated with female gender, central obesity, DM nephropathy, HbA1c 7%, and duration of DM >5 years. This study revealed that among type 2 DM patients, female gender, central adiposity, nephropathy, above-normal HbA1c, and also duration of DM were risk factors for thyroid dysfunction[91].

In 2020, Ishitha Reddy et al conducted a cross-sectional study with 500 T2DM patients in a tertiary medical facility in Andhra Pradesh's south coast. 98 (19.6%) subjects had thyroid dysfunction, with subclinical hypothyroidism (n = 66, 13.2%) being the most prevalent type (n = 98, 19.6%). Patients who were obese (16.2% vs 7.6%, p = 0.007) and metformin users (9.6% vs 18.7%, p = 0.0044) had a higher incidence of subclinical hypothyroidism (SCH). In comparison to euthyroid T2DM patients, SCH patients had considerably higher rates of diabetic retinopathy. This study found that T2DM patients from south-coastal Andhra Pradesh had a high prevalence of thyroid dysfunction, particularly that of SCH; SCH was more common in obese people and people who took

nonmetformin, and it was linked to an increased risk of diabetic retinopathy[92].

A total of 1341 people were enrolled in the trial in 2020, according to Khassawneh et al. 60.14 12.21 for the mean SD, and 47.9% of the population were female. 140 (14%) of T2DM patients had thyroid conditions known to exist; as a direct result of screening, 126 (12.6%) additional instances of thyroid conditions were identified. Thus, it was discovered that T2DM patients had a prevalence of thyroid disorders overall of 26.7%, which was significantly higher than the controls (13.7%). The most prevalent was subclinical hypothyroidism. Age 50 years, with an adjusted OR of 3.895, was the risk factor for thyroid dysfunction among T2DM patients after adjusting for age, gender, obesity, smoking, anaemia, the presence of goitre, the duration of the disease, and poorly controlled diabetes. Thyroid issues did not, however, significantly correlate with the severity or duration of diabetes ($p>0.050$). This study concluded that T2DM patients were shown to have a significant frequency of thyroid problems. Therefore, we advocate regular thyroid dysfunction screenings for diabetes individuals. Among T2DM patients, goitre, old age, being a woman, and poorly controlled diabetes have been linked to dysfunction of thyroid. As a result, effective diabetes management and control may reduce the risk of thyroid dysfunction, and vice versa[93].

Jalal et al. in 2020 there were 50 total cases (diagnosed Type 2 DM cases) and 50 randomly selected healthy controls. Chemiluminescence assays were used to perform thyroid function testing. After tabulation, it underwent statistical analysis. The Chi-square test for categorical variables was used for statistical analysis. The significance between the means was determined using the Student's t-test. Statistics were considered significant at "P 0.05". Significantly more type 2 DM (16%) than healthy controls (4%) were noted to have thyroid dysfunction. Six (75%) of the eight diabetes patients with dysfunction of thyroid were female. In diabetic individuals with thyroid disease, the mean BMI was high. Patients who had thyroid dysfunction had high haemoglobin A1c levels. Compared to euthyroid diabetics and controls, those with thyroid disease had a higher mean total cholesterol level. In 4% of Type 2 DM cases, goitre was discovered. This study came to the conclusion that there is a substantial link between Type 2 DM and also thyroid conditions. The two types of hypothyroidism that are most prevalent in Type 2 DM are subclinical and overt hypothyroidism. Dyslipidemia in these Type 2 DM was worsened by thyroid dysfunction[94].

100 patients with known Type 2 DM were included in study by BalaKoteswara Rao et al. in 2020. By analysing their thyroid profiles, all of patients were assessed for thyroid dysfunction (triiodothyronine, thyroxine, and thyroid-stimulating hormone).

Hemoglobin A1C, age distribution, prevalence of thyroid disorders, and the length of diabetes were all examined. The findings were statistically analysed after the observations and interpretations were recorded. In this study, 100 people with diabetes mellitus had thyroid disorders screened for. 16 (16%) patients with type 2 diabetes mellitus had abnormal thyroid function tests, while the other 84 (84%) did not. 16 patients with diabetes were found to have low thyroid function in 14 patients and hyperthyroidism in 2 patients. Females are more likely than males to have a thyroid abnormality. They came to the conclusion that subclinical hypothyroidism is the most prevalent form of dysfunction of thyroid among Type 2 DM patients, occurring very frequently (16%). To lower the death rate, thyroid dysfunction must be evaluated in all Type 2 DM patients[95].

A cross-sectional study by VAMSHIDHAR et al. was carried out in 2020 at the MGM Hospital in Warangal, India, and the departments of physiology and general medicine at Kakatiya Medical College. 50 consecutive patients with the diabetes mellitus type 2 were chosen as cases, and an equal number of normoglycemic people with similar age & sex were chosen as controls. Following an overnight fast of eight hours, measurements of fasting blood sugar and HbA1c levels, serum triglycerides, and serum TSH, FT3, and FT4 were made in the lab using chemiluminescence immunoassay. Eight (16%) of type 2 diabetes mellitus overall—6%

of female patients and 10% of male patients—presented thyroid disorders. Four cases (8%) were found to have thyroid disorders overall, two (4%) of which were in males and two (2%), respectively. A Pearson correlation coefficient of +0.70 was calculated using the values of TSH IU/ml and FBS mg/dl in type 2 diabetes mellitus cases, indicating a positive correlation between the two variables. In individuals with type 2 diabetes, the values of HbA1c were plotted together with TSH levels, and a Pearson correlation coefficient of +0.76 was determined. According to this study, it may be said that people with type 2 diabetes have a high prevalence of thyroid dysfunctions. Additionally, a consistent positive connection between TSH, FBS, and HbA1c was discovered. Therefore, it is advised that diabetic patients undergo periodic screening for their coexistence in thyroid dysfunctions[96].

In 2021, Rong et al. used a database search of MEDLINE and Embase until May 1, 2021, to find prospective studies that evaluated diabetes incidence. The associations and dose-response correlations between thyroid function/hormone levels and risk of T2DM and cardiovascular disease among T2DM patients were assessed using the Sidik-Jonkman random-effects model and cubic spline model. There were 12 prospective studies altogether. In contrast to normal TSH levels, we discovered that high baseline TSH levels were associated with a 17% higher risk of T2DM. Low FT3 and also FT4 levels were significantly correlated with the risk of T2DM. Cubic

spline model showed an inverted-J relationship with FT3 and FT4, but a J-shaped relationship with TSH. Despite being prospectively assessed in four investigations, impaired thyroid function was not linked to CVD events or all-cause mortality. This meta-analysis showed a J-shaped association with TSH and an inverted-J-shaped relationship with FT3 and also FT4, indicating that an aberrant thyroid hormone level is related to an increased risk of T2DM[97].

MATERIALS AND METHODS

Methodology

- Study type – observational study
- Study design – cross sectional study
- Study setting/area – study will be conducted on Tagore Medical College And hospital
- Study period – 1 year
- Sample size – 100 [50 will be type 2 diabetic patients ,50 will be euthyroid non diabetics]
- As per criteria of American diabetes association 2016 along with standard guidelines of thyroid dysfunction
- Sampling population: From April 2021 to April 2022 all consecutive patients attending the General Medicine Outpatient department will be screened for presence of thyroid dysfunction in type 2 diabetes mellitus as per study eligibility criteria. All of these patients will be explained about the study details and willingness to participate. Data will be collected until 100 participants are reached and analysed for study objectives

SAMPLING METHOD:

- consecutive sampling

Inclusion criteria:

- Diabetic patients attending diabetic clinic OPD and admitted in medical wards in Tagore medical college and hospital.
- Patients who are willing to give written informed consent for the study
- Patients who have hyperthyroidism and hypothyroidism, according to American Thyroid Association guidelines
- Patients who give diabetic history
- Patients who have normal blood sugar value
- Patients who have Normal Thyroid function, according to American Thyroid Association guidelines
- Sex: both sexes
- Age group (35-60 Years) will be included.

Exclusion criteria:

- Patients with Type 1 diabetic history and Type 1 Diabetic mellitus, according to American Diabetic Association guidelines[2]
- Patient with Diabetic keto acidosis
- Patient with Chronic renal failure
- Patient on Drugs like Lithium and Amiodarone

Methodology of study:

- All Complete blood count samples from patients who are diagnosed with type 2 diabetic mellitus received in the department of general medicine, Tagore medical college and hospital after considering inclusive and exclusive criteria shall be included in the study Prevalence 30%
- Sample Size N: Z^2PQ/d^2,Z=1.96,P=30%,Q=70%,d=10%

  =1.96*1.96*0.30*0.70/0.10*0.10

  =81

Final sample size=Effective sample size /(1-non response rate anticipated)

(We anticipate a non-response or drop out Percentage as10%)

so, final sample size =100

- Intervention: Nil
- Control: Non diabetic Euthyroid Subjects
- Dosages of drug & frequency with duration: Not Applicable

Investigations /procedures to be done etc.:

Methods:

- T3 and T4 estimated by using ChemiLuminationImmuno Assay (CLIA) method
- TSH was estimated using Ultra Sensitive CLIA method.
- FBS was measured by ERBA CHEM -5 PLUS V2 (SEMI AUTO ANALYSER) method

- HbA1c by Hyper performance Lipid Chromatography (HPLC) method
- TG by Enzymatic Colonometry method
- HDL, LDL VLDL by Homogenous Enzymatic Colonometry

  Assay method;
- Urea by Ultra Violet Kinetic method
- Creatinine by Picrate method

PROCEDURE:

- After obtaining Institutional ethical committee clearance, cases will be selected as per the inclusion criteria mentioned above and written informed consent will be taken.
- Venous Blood sample will be drawn from the antecubital vein using 5ml syringe and will be immediately mixed in EDTA vacutainers.
- Sample will be run immediately within 2 hours using venepuncture .using 5 part differentiated hematology analyser sysmex XN-330 will be used to assess thyroid function tests such T3, T4 and TSH.
- Samples for plasma glucose estimation and HBA1C will be collected in sodium flouride and EDTA vacutainers respectively.

- The estimation of plasma glucose levels (FBS,PPBS) will be carried out by glucose oxidase method in semi auto analyser and hba1c by high performance liquid chromatography method
- All the relevant clinical history along with FBS,PPBS,HbA1c, LIPID PROFILE, RFT from case sheets will be taken.
- Patients will be grouped hyperthyroid Hypothyroid and Euthyroid based on TSH T3 T4 LEVELS as per American Thyroid Association guidelines14 and patients will be grouped as Non-Diabetic, Prediabetic, Diabetic Based on HbA1c, FBS, PPBS levels as per ADA guidelines15.
- Thyroid function levels will be studied in patients who are diabetic with hyper\hyothyroidism and non-diabetic with euthyroid level.

STATISTICAL ANALYSIS

- Statistical analysis will be performed by using SPSS software, Student ‘t’ test and Pearson’s correlation was used and if the P* value is< 0.005. then it is considered to be statistically significant and using Microsoft office
- Type of randomization & method used: From April 2021 to April 2022 all consecutive patients attending the General Medicine Outpatient department will be screened for presence of THYROID DYSFUNCTION IN TYPE 2 DIABETICS MELLITUS as per study eligibility criteria. All of these patients will be explained about the study details and willingness to participate. Data will be collected until 100 participants are reached and analysed for study objectives.

RESULTS

Results

Table 1: Age Distribution of Study Groups

Group	Number	Mean	S.D	t	P value
Diabetic	50	49.09	2.3	0.08	0.93
Non diabetic	50	48.63	2.4		

Mean age in both the groups are comparable There is statistically no significant difference between both the groups.

Figure1: Age Distribution of Study Groups

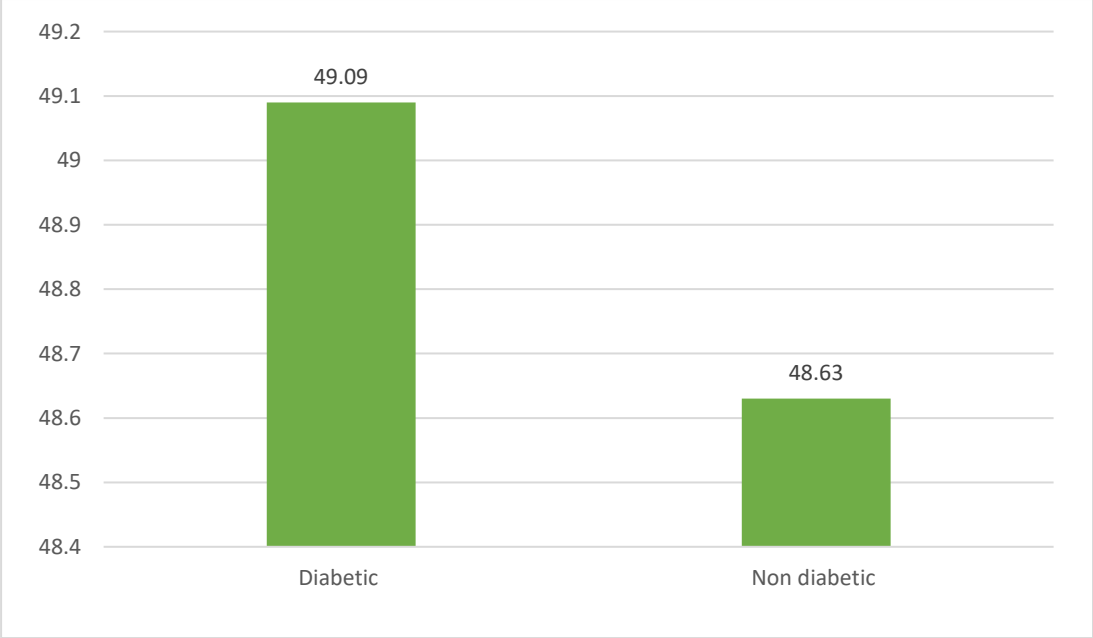


Table 2: Sexwise distribution of study groups

Group	Male	Female	Total	df	CHI Square	P value
Diabetic	32	18	50	1	0.577	0.44
Non diabetic	30	20	50			
Total	62	38	100			

Figure 2: Sexwise distribution of study groups

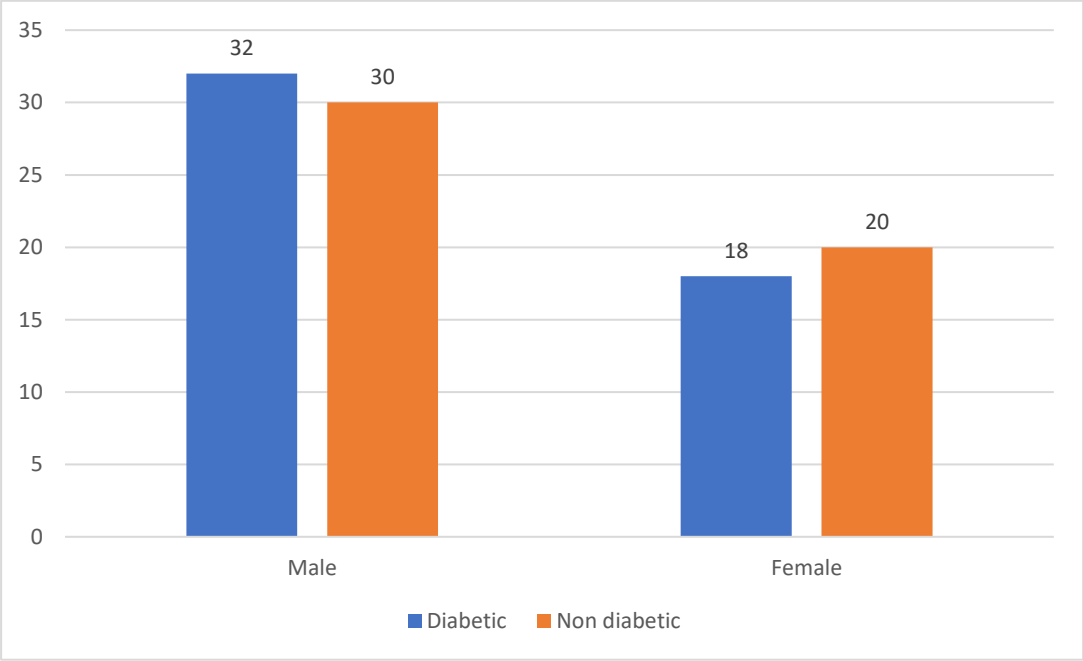


Table 3:Biochemical parameters among study participants

Parameters	Diabetic		Non diabetic		P
	Mean	SD	Mean	SD	
SBP	121.53	2.52	121.83	2.41	0.77
DBP	88.23	3.21	84.21	3.11	0.53
FBS	110.40	2.34	96.50	2.24	0.04
PPBS	223.90	3.46	152.30	3.36	0.01
HbA1C	8.62	1.2	5.18	1.4	0.96
BMI	23.62	8.6	25.68	6.7	0.84
Urea	20.68	2.1	18.68	3.2	0.96
Creatinine	0.98	0.01	0.92	0.01	0.89

The two groups are comparable with respect to biochemical parameters like systolic blood pressure, diastolic blood pressure, body mass index ,urea and creatinine. There is statistically significant difference between both the groups with respect to fasting, postprandial blood sugar .(P<0.05)

Figure 3:Biochemical parameters among study participants

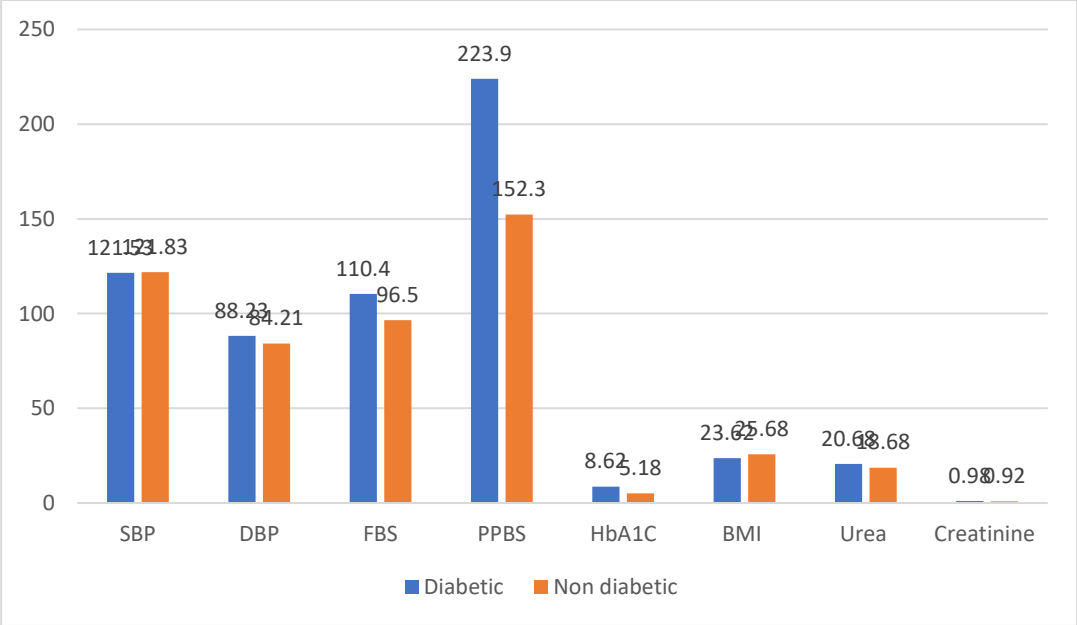


Table 4:Lipid parameters among study groups

Parameters	Diabetic		Non diabetic		P
	Mean	SD	Mean	SD	
T.cholesterol	189.09	11.21	183.21	0.6	0.04
TGL	139.12	10.12	129.21	8.68	0.03
HDL	44.2	1.2	52,12	2.4	0.05
LDL	127.2	11.2	108.1	10.6	0.001

The two groups are different with respect to lipid parameters like T.cholesterol, TGL,HDL and LDL (P<0.05).Lipid parameters are better in normal individuals compared to diabetic individuals .

Figure 4: Lipid parameters among study groups

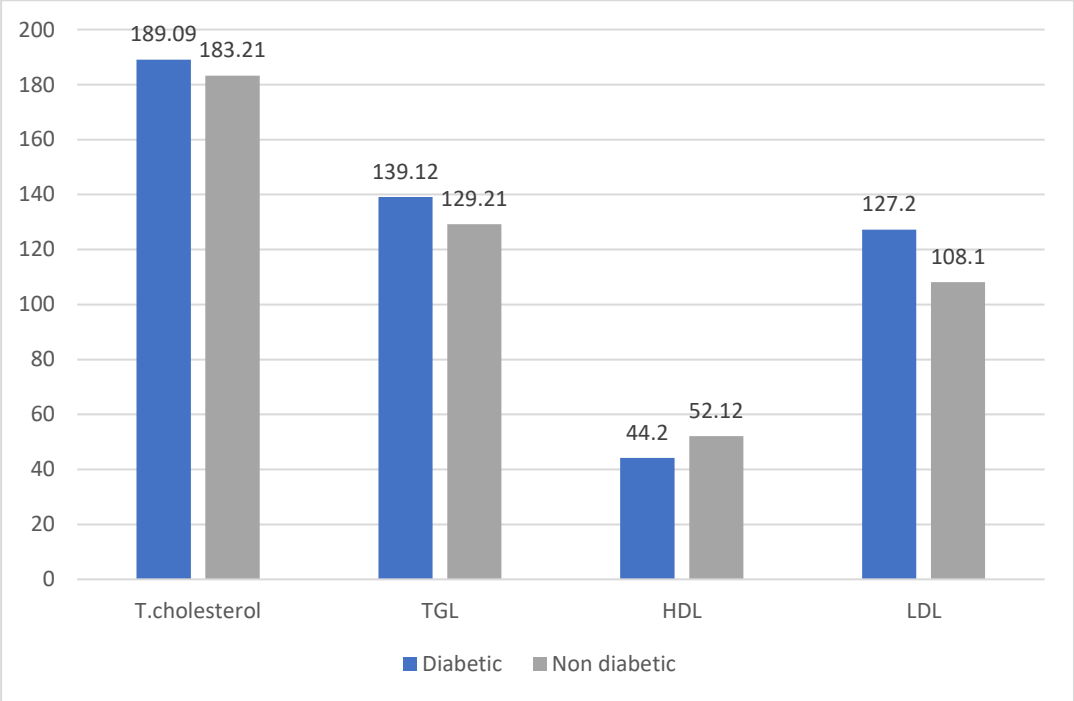
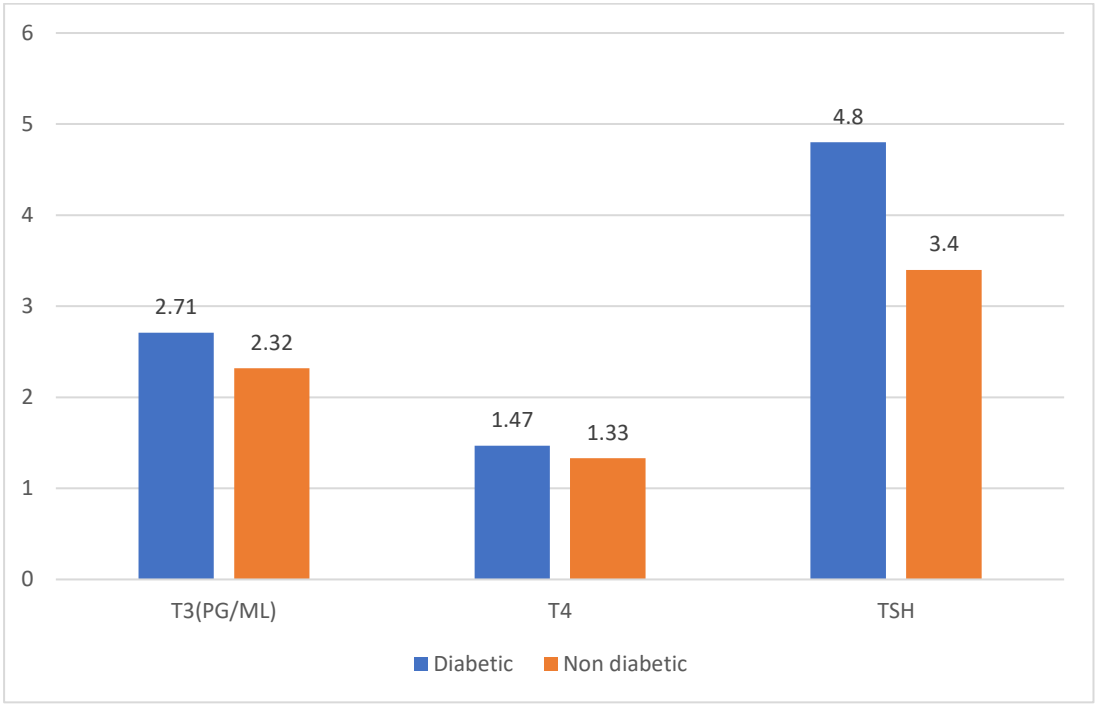


Table 5:Thyroid profile among study participants

Parameters	Diabetic		Non diabetic		P
	Mean	SD	Mean	SD	
T3(PG/ML)	2.71	0.21	2.32	0.4	0.78
T4	1.47	0.86	1.33	0.92	0.87
TSH	4.8	1.2	3.4	0.92	0.03

Thyroid parameters like TSH,T3 and T4 are better in normal individuals compared to diabetics .The two groups are statistically different with respect to TSH .($P<0.05$)

Figure 5: Thyroid profile among study participants



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DISCUSSION

The prevalence of the thyroid disease in general population has a great variability varying from 6.6% to 13.4%[52]. This difference may be due to difference in diagnostic criteria of thyroid disease, degree of iodine intake among various regions, difference in sensitivities of the TSH assays and the 9 large population diversity[53]. Thyroid dysfunction is more common in female than male and this may be due to inhibition of disease activity by androgens and also exacerbation by estrogen. Thyroid disorders are more common with variable prevalence among the different populations. Thyroid hormones have an effect on glucose metabolism via several mechanisms. Hyperthyroidism has long been recognized to encourage increased blood glucose. Hence the present study is carried out to add to the existing literature. Present study is a cross sectional study conducted among 50 diabetic and 50 nondiabetic individuals.

Results

The two groups are comparable with respect to age and sex. The two groups are comparable with respect to biochemical parameters like systolic blood pressure, diastolic blood pressure, body mass index, urea and creatinine. There is statistically significant difference between both the groups with respect to fasting, postprandial blood sugar.($P<0.05$). The two groups are

different with respect to lipid parameters like T.cholesterol, TGL,HDL and LDL (P<0.05).Lipid parameters are better in normal individuals compared to diabetic individuals . Thyroid parameters like TSH,T3 and T4 are better in normal individuals compared to diabetics .The two groups are statistically different with respect to TSH .(P<0.05)

Comparison with other studies

In a study done by Demitrost L et alMaximum cases were of hypothyroidism (subclinical and clinical) seen in the age group of 45-64 years. Patients with BMI > 25 were at increased risk of having hypothyroidism (P < 0.016). Prevalence of hypothyroidism is quite high in type 2 DM patients above 45 years and more so if their BMI is over 25[77].

In a study done by chakeretal higher TSH levels were associated with a higher diabetes risk The risk of progression from prediabetes to diabetes was higher with low-normal thyroid function Absolute risk of developing diabetes type 2 in participants with prediabetes decreased from 35 % to almost 15 % with higher FT4 levels within the normal range. They concluded that low and low-normal thyroid function are risk factors for incident diabetes, especially in individuals with prediabetes.[79]

In the study done by Shubhankar Mishra et al , The HbA1c levels in patients who had thyroid dysfunction were high. Those with thyroid dysfunction had a mean total cholesterol level higher than euthyroid diabetics and controls. Goitre was found to be present in 4% of cases of type-2 DM. This study noted that type-2 DM and thyroid diseases have a significant association. Subclinical hypothyroidism and hypothyroidism (overt) were the commonest thyroid abnormality in type-2 DM. Thyroid dysfunction was associated with worsening dyslipidemia in type-2 DM[80].

In study done by Datchinamoorthi et al. DM patients were screened for thyroid function studies viz T3, T4 & TSH. 50 age and sex matched healthy volunteers were treated as controls and the results were correlated with fasting blood glucose levels and lipid parameters. The results showed a significant difference among the controls and the patients. It may be concluded from this study that there is hypothyroidsm in DM patients[82].

In a study done by Rajaraoetal, Patients with uncontrolled diabetes with micro vascular complication had sub- clinical hypothyroidism. They noted that the prevalence of thyroid disorders in Diabetics was 31.42%. Elderly population had more incidence. Sub-clinical hypothyroidism was more common among females. Diabetics with hyperthyroidism had poor glycemic control. Severe diabetic complications were noted in patients with sub-clinical

hypothyroidism. Duration of Diabetes had not impact on thyroid dysfunction[84]

In a study done by Romesh Sharma et al, Thyroid dysfunction was detected in 43.3% among 150 type2 DM patients studied, out of which 22.7% was found to be hypothyroidism,5.3% of hyperthyroidism,12% of subclinical hypothyroidism and 3.3% of subclinical hyperthyroidism. Hyperthyroidism was more in prevalent in elderly type 2 DM patients and among males. Buthypothyroidism was more prevalent among type 2DM female patients and among middle age group patients. [89]

In a study done by, ishitha Reddy et al, T2DM patients from south-coastal Andhra Pradesh the prevalence of thyroid dysfunction, especially that of SCH was high; SCH was more frequent among obese and nonmetformin users and was associated was associated with increased risk of diabetic retinopathy[92].

In a study done by Jalal, et al. A total of 50 cases (diagnosed case of Type 2 DM) and 50 healthy controls were taken into consideration randomly. Thyroid function tests were conducted using the chemiluminescence assay. Thyroid dysfunction was found to be more in type 2 DM (16%) than in healthy controls (4%) which were significant.

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CONCLUSION

Diabetes patients have a higher prevalence of thyroid disorders than the normal population. Thyroid disease is found in both types 1 and 2 diabetes. Studies have found that thyroid dysfunction is much common in diabetic population compared to non-diabetic population, diabetes and thyroid disorders have been shown to influence each other mutually because of intersecting pathology. Results of our study is consistent with previous studies. More studies to be conducted in future so that necessary actions can be taken at the earliest

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ANNEXURES

PROFOMA

DEMOGRAPHICS

Name:

Age :

Sex:

Address:

Qualification:

CHIEF COMPLAINTS:

PRESENTING ILLNESS:

PAST HISTORY:

TREATMENT HISTORY:

PERSONAL HISTIORY:

FAMILY HISTORY:

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS

RS

CNS

PER ABDOMEN

RISK FACTOR ASSESSMENT:

T2DM

DURATION

TREATMENT

H/O THYROID DISORDERS:

Hypothyroid/hyperthyroid

duration

LAB INVESTIGATION

FBS

PPBS

HbA1C

FT3

FT4

TSH

LDL

HDL

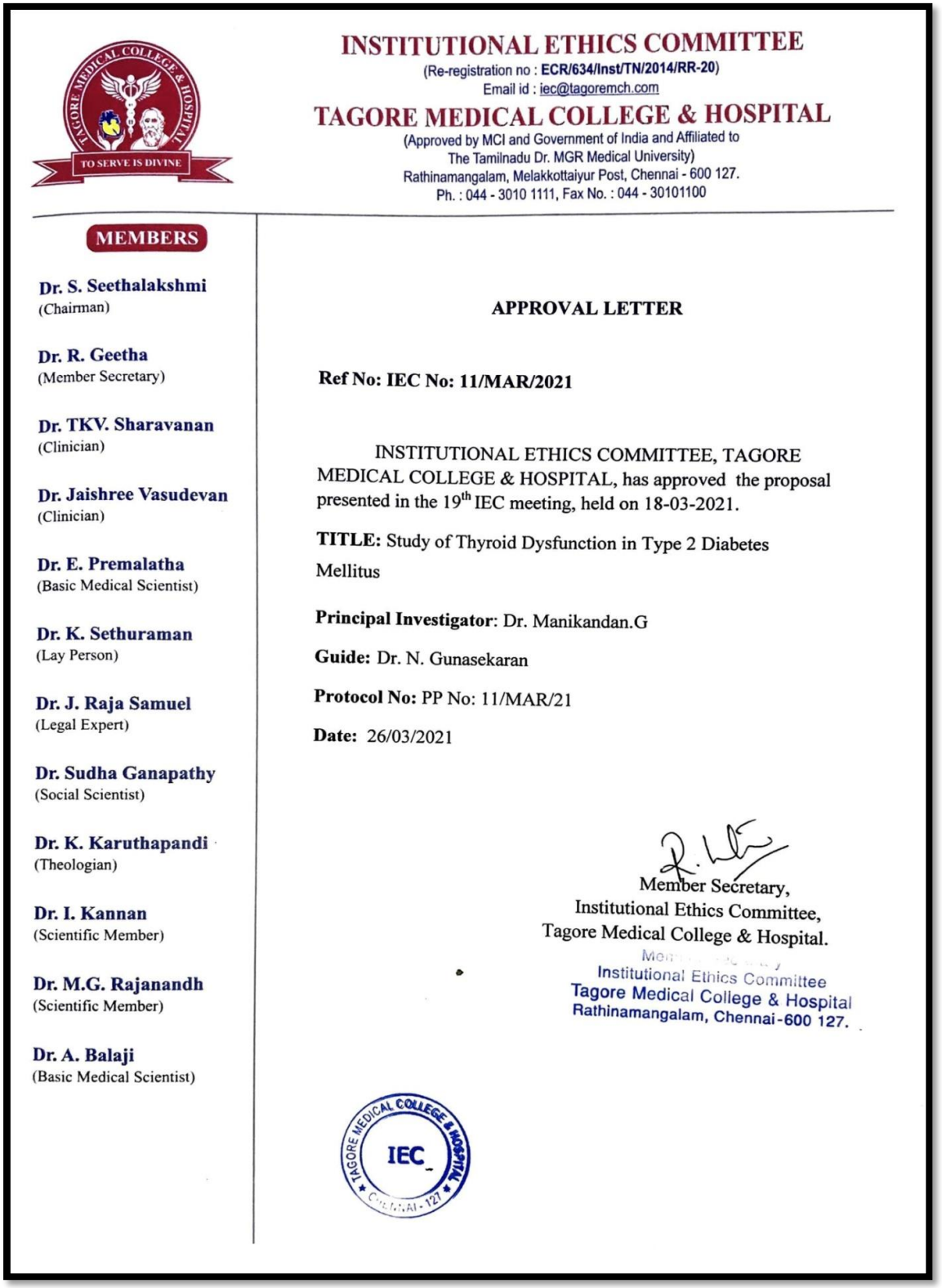
VLDL

TRIGLYCERIDE

SR.UREA

SR.CREATININE

INSTITUTIONAL ETHICS COMMITTEE APPROVAL CERTIFICATE



INSTITUTIONAL ETHICS COMMITTEE
(Re-registration no : ECR/634/Inst/TN/2014/RR-20)
Email id : iec@tagoremch.com
TAGORE MEDICAL COLLEGE & HOSPITAL
(Approved by MCI and Government of India and Affiliated to
The Tamilnadu Dr. MGR Medical University)
Rathinamangalam, Melakkottaiyur Post, Chennai - 600 127.
Ph. : 044 - 3010 1111, Fax No. : 044 - 30101100

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Dr. M.G. Rajanandh (Scientific Member)
Dr. A. Balaji (Basic Medical Scientist)

APPROVAL LETTER

Ref No: IEC No: 11/MAR/2021

INSTITUTIONAL ETHICS COMMITTEE, TAGORE MEDICAL COLLEGE & HOSPITAL, has approved the proposal presented in the 19th IEC meeting, held on 18-03-2021.

TITLE: Study of Thyroid Dysfunction in Type 2 Diabetes Mellitus

Principal Investigator: Dr. Manikandan.G

Guide: Dr. N. Gunasekaran

Protocol No: PP No: 11/MAR/21

Date: 26/03/2021

Member Secretary,
Institutional Ethics Committee,
Tagore Medical College & Hospital.

Institutional Ethics Committee
Tagore Medical College & Hospital
Rathinamangalam, Chennai-600 127.

PLAGIARISM CERTIFICATE

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by Turnitin

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Similarity	14%
Analysis address	bgmgmk1994.tnmg@analysis.urkund.com

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INFORMED CONSENT

I_____ agree to take part in the study conducted by Dr. Manikandan G, PG resident of Tagore Medical college and Hospital.

TITLE OF RESEARCH PROJECT: Study of Thyroid Dysfunction in type 2 diabetes mellitus. I acknowledge that I have read the information and the same has been explained to me clearly by the principal investigator.

I know about - Possible risks in the study

Benefits of the study

Compensation if any and if applicable

Confidentiality of all information

Withdrawal from the study

If more information is required, whom to contact

Complaints regarding the study, whom to contact

I agree to give necessary information and participate in the study

Patient signature & Date

ஒப்புதல்சான்றிதழ்

தாகூர் மருத்துவக் கல்லூரி மற்றும் மருத்துவமனையில் பி.ஜி.

குடியிருப்பாளர் டாக்டர் **மணிகண்டன்.க**

நடத்திய ஆய்வில் பங்கேற்க _____ ஆகிய நான் ஒப்புக்கொள்கிறேன்.

ஆராய்ச்சி திட்டத்தின் தலைப்பு:

வகை 2 நீரிழிவு நோயில் தைராய்டு செயலிழப்பு பற்றிய ஆய்வு

நான் தகவலைப் படித்திருக்கிறேன் என்பதை ஒப்புக் கொள்கிறேன், அதையே முதன்மை புலனாய்வாளர் தெளிவாக விளக்கினேன்.

எனக்கு தெரியும் - ஆய்வில் சாத்தியமான அபாயங்கள்

ஆய்வின் நன்மைகள்

இழப்பீடு ஏதேனும் இருந்தால் பொருந்தும்

அனைத்து தகவல்களும் இரகசியத்தன்மை

படிப்பிலிருந்து திரும்பப் பெறுதல்

மேலும் தகவல் தேவைப்பட்டால், யாரை தொடர்பு கொள்ள வேண்டும்

ஆய்வு தொடர்பான புகார்கள், யாரை தொடர்பு கொள்ள வேண்டும்

தேவையான தகவல்களை வழங்கவும், ஆய்வில் பங்கேற்கவும் ஒப்புக்கொள்கிறேன்.

நோயாளியின் கையொப்பம் & தேதி:

MASTER CHART

AGE	SEX	HEIGHT cm	WT	BMI	Syst.BP mm Hg	Dias.BP mm Hg	FBS mg/dl	PPBS mg/dl	HbA1C %	UREA mg/dl	CREATININE mg/dl	T.CHO mg/dl	TRIGLY mg/dl	LDL mg/dl	HDL mg/dl	T3 pg/ml	T4 ng/dl	TSH m IU/ml	group
57	M	165	70	25.71166	120	80	150	356	6	28	1.3	160	87	78	57	1.5	1.6	1.3	diabetic
55	F	155	54	22.47659	130	86	95	119	5.2	23	0.7	185	127	112	40	2.2	1.4	18.9	diabetic
49	F	152	64	27.70083	130	90	138	160	6.2	20	0.8	190	136	109	40	2.8	1.2	4	diabetic
57	M	165	70	25.71166	120	80	150	356	6	28	1.3	160	87	78	57	1.5	1.6	1.3	diabetic
60	F	160	78	30.46875	136	90	233	341	9.6	15	0.9	189	73	163	39	4	1.9	8.1	diabetic
45	M	175	65	21.22449	120	80	83	188	5.9	24	1	165	111	84	47	3.9	1.5	1	diabetic
38	F	142	60	29.756	110	70	341	486	10.4	15	0.7	190	234	118	35	2	1.7	1.7	diabetic
60	M	165	80	29.38476	140	78	160	241	6.4	18	0.8	153	84	87	47	2.8	1.4	1.2	diabetic
58	F	150	60	26.66667	140	86	110	153	5.9	19	0.7	218	117	139	51	2.9	1.4	1.2	diabetic
59	M	164	70	26.02618	130	80	100	130	6	16	0.8	156	64	91	39	2.2	1.6	1.2	diabetic
55	F	155	54	22.47659	130	86	95	119	5.2	23	0.7	185	127	112	40	2.2	1.4	18.9	diabetic
58	F	152	60	25.96953	140	94	99	174	6.3	29	0.9	284	222	105	51	3.2	1.4	1.3	diabetic
44	F	145	65	30.91558	140	90	123	150	5.6	17	0.8	192	124	113	41	3.1	0.9	13.3	diabetic
49	F	152	64	27.70083	130	90	138	160	6.2	20	0.8	190	136	109	40	2.8	1.2	4	diabetic
47	F	156	70	28.76397	120	80	218	378	10.9	35	0.9	208	265	105	69	2.5	1.7	5.8	diabetic
60	M	172	50	16.90103	146	80	131	266	6.8	27	0.9	166	112	95	38	3	1.3	4.5	diabetic
53	M	165	72	26.44628	130	96	168	260	8.6	29	1	220	116	136	50	1.4	1.4	2.4	diabetic
57	F	150	62	27.55556	130	70	172	301	10.8	17	0.7	281	98	105	52	2.1	1.5	1.8	diabetic
52	M	180	78	24.07407	140	90	145	315	10.6	22	0.6	169	80	96	49	3.1	1.5	1.8	diabetic
61	M	163	70	26.34649	130	90	141	271	6.5	31	0.9	127	366	73	18	1.9	1.6	4.4	diabetic
65	M	165	72	26.44628	140	90	225	463	9.8	42	1	202	103	136	34	2.7	1.7	4.3	diabetic
37	M	172	75	25.35154	120	80	85	161	5.7	18	1	192	168	108	44	3	1.6	3.9	diabetic
43	M	165	70	25.71166	110	70	122	214	6.2	19	1	179	182	108	54	3.4	1.5	0.7	diabetic
46	F	165	72	26.44628	160	74	215	339	9.2	15	0.7	163	82	96	51	2.3	1.1	3.6	diabetic
65	M	160	64	25	130	90	104	249	6.6	26	1	139	157	74	35	2.3	2.1	3.6	diabetic
45	M	174	65	21.46915	130	86	125	230	6.9	16	1.1	190	117	110	45	4.5	1.3	1.2	diabetic
62	M	162	55	20.95717	110	70	298	400	10.2	20	1.2	229	132	144	36	2.1	1.3	1.7	diabetic
60	F	165	75	27.54821	156	94	138	229	7	25	0.9	158	154	76	46	2.2	1.4	2.3	diabetic
63	F	155	48	19.97919	110	80	163	322	7.6	16	0.8	214	93	124	59	1.9	0.9	2.4	diabetic
37	F	154	60	25.29938	110	70	235	345	9.6	19	0.7	204	118	146	46	1.3	1.2	4.1	diabetic
44	M	175	65	21.22449	136	80	293	427	9	23	1.1	232	212	137	38	2.7	1.7	2.3	diabetic
37	M	160	71	27.73438	146	84	316	454	10.2	25	1	166	84	82	57	1.8	1	21.5	diabetic
70	M	160	48	18.75	160	90	144	194	5.7	21	1.6	235	80	145	49	2.2	1.4	2	diabetic
58	M	160	64	25	130	80	106	164	5.8	28	1.3	249	181	151	38	2.4	1.5	6.9	diabetic
43	F	156	60	24.65483	130	86	94	168	5.9	15	0.6	149	134	75	38	2.9	1.4	1.1	diabetic
38	F	158	57	22.83288	110	70	93	185	5.7	25	0.8	224	127	169	58	1.5	0.5	35.5	diabetic
78	M	170	70	24.22145	140	90	98	162	5.8	23	1	143	66	81	38	2.9	1.4	4	diabetic
36	M	165	65	23.87512	150	90	101	162	5.8	15	0.9	307	102	196	51	2.6	1.6	4.5	diabetic

33	M	164	57	21.19274	110	70	204	294	6.8	23	0.9	183	193	101	53	2.6	1.5	1.6	diabetic
53	M	162	74	28.19692	130	90	138	276	6	20	1.2	137	128	76	37	2.3	1.3	3.6	diabetic
38	M	165	72	26.44628	126	80	191	373	6.9	16	0.8	163	172	93	47	2.7	1.8	4	diabetic
60	F	150	65	28.88889	140	90	312	424	10.3	28	1	182	149	110	39	2.2	1.4	0.8	diabetic
62	F	152	68	29.43213	130	80	117	316	5.5	24	0.8	202	139	96	42	11.6	4.7	0.05	diabetic
57	F	150	65	28.88889	150	84	125	196	5.4	17	0.7	190	103	108	46	2.8	1.3	2.7	diabetic
46	M	170	65	22.49135	130	80	237	366	10.3	24	0.9	182	94	116	35	2.3	1.3	0.8	diabetic
63	M	164	62	23.05176	130	90	127	252	6.3	25	0.9	157	273	94	32	3	1.2	7.2	diabetic
52	F	160	68	26.5625	130	96	113	123	5.8	15	0.7	220	74	162	65	2.7	1.4	9.7	diabetic
59	F	150	64	28.44444	110	70	135	199	6.2	15	0.8	136	210	72	58	2.4	1	3	diabetic
49	F	150	48	21.33333	120	70	106	167	5.7	19	0.7	169	235	103	45	2.6	1.5	1.5	diabetic
45	M	168	65	23.03005	146	90	139	164	5.6	25	1	211	243	118	39	2.7	1.6	1.5	diabetic
50	F	150	62	27.55556	130	70	221	375	9.2	15	0.7	156	95	84	44	2.3	1.5	3.6	non diabetic
67	F	145	60	28.53746	110	60	120	145	6.1	16	1.1	147	152	71	36	1.6	0.7	4.5	non diabetic
65	F	150	62	27.55556	140	90	104	145	5.7	20	0.8	245	243	149	39	2.2	0.3	2.7	non diabetic
55	M	170	67	23.18339	130	85	118	142	5.4	19	1.4	102	210	46	30	0.5	0.2	37.5	non diabetic
46	F	154	46	19.39619	110	70	92	123	5.3	18	0.7	210	123	120	41	2.1	1.5	2.9	non diabetic
40	M	160	64	25	120	86	98	103	5.2	21	0.8	114	142	80	43	3.1	1.5	2.8	non diabetic
40	F	158	54	21.63115	110	70	87	112	4.8	15	0.9	152	138	75	43	2.8	1.2	3.5	non diabetic
66	M	162	68	25.91068	140	80	92	107	5	30	1.4	161	87	103	29	2.5	1.4	1.3	non diabetic
47	F	156	58	23.83301	110	70	81	98	4.8	15	0.8	182	84	100	38	1.6	1.3	4.7	non diabetic
35	M	164	60	22.30815	110	80	70	94	5.4	21	0.8	240	109	130	57	3	1.3	1.5	non diabetic
49	M	168	63	22.32143	140	90	83	101	5	27	0.9	206	190	120	37	3.4	0.8	7.7	non diabetic
45	M	158	58	23.23346	130	80	84	107	5.1	21	1	203	148	122	40	2.7	1.1	3.4	non diabetic
46	M	157	64	25.96454	110	70	85	129	4.9	18	1	170	79	88	43	2.4	1.2	1	non diabetic
35	F	152	66	28.56648	110	80	91	124	4.9	15	1	195	88	106	43	3	1.6	2.3	non diabetic
38	F	160	72	28.125	110	80	73	106	5.1	15	0.7	181	117	91	49	2.6	1.6	0.9	non diabetic
46	M	168	70	24.80159	130	80	71	94	4.5	15	1.2	203	257	113	35	1.7	1.2	2.3	non diabetic
53	F	164	59	21.93635	120	80	93	104	5.7	19	0.6	188	114	119	33	2.7	0.9	1.7	non diabetic
75	M	160	70	27.34375	140	90	95	105	5	25	1	156	59	99	37	1.8	1.6	3.5	non diabetic
41	M	148	60	27.39226	110	70	102	113	5.5	23	1	214	77	126	60	2.2	1.9	1.4	non diabetic
54	M	156	68	27.94214	110	70	88	99	4.8	16	0.6	170	84	99	116	2	1.4	6.4	non diabetic
39	M	162	58	22.10029	120	80	97	109	5.3	21	1	175	129	95	48	2.9	1.6	1.6	non diabetic
46	M	154	60	25.29938	120	70	99	106	5.2	24	0.8	181	64	105	46	2.7	1.5	1	non diabetic
39	M	152	68	29.43213	120	70	94	103	5	16	1.1	188	248	105	40	1.6	1.9	1.9	non diabetic
45	F	152	58	25.10388	110	70	90	104	5.2	16	0.7	168	117	98	41	2.3	1.2	2	non diabetic
48	M	172	64	21.63332	110	70	94	107	5.4	17	0.8	209	116	128	49	2.2	1.7	1.9	non diabetic
45	M	162	62	23.62445	120	70	91	100	5	20	1	181	116	119	42	2.6	1.2	2.4	non diabetic
48	F	151	63	27.63037	130	80	96	102	4.8	22	0.8	161	68	109	41	2	1.2	4.4	non diabetic
48	M	176	59	19.047	130	90	90	134	5.2	19	0.9	216	141	153	43	2.1	1.3	4.9	non diabetic
36	F	150	57	25.33333	110	70	98	114	5	16	0.7	214	205	125	40	2.2	1.5	1.9	non diabetic

46	F	154	46	19.39619	110	70	92	123	5.3	18	0.7	210	123	120	41	2.1	1.5	2.9	non diabetic
40	M	160	64	25	120	86	98	103	5.2	21	0.8	114	142	80	43	3.1	1.5	2.8	non diabetic
40	F	158	54	21.63115	110	70	87	112	4.8	15	0.9	152	138	75	43	2.8	1.2	3.5	non diabetic
66	M	162	68	25.91068	140	80	92	107	5	30	1.4	161	87	103	29	2.5	1.4	1.3	non diabetic
47	F	156	58	23.83301	110	70	81	98	4.8	15	0.8	182	84	100	38	1.6	1.3	4.7	non diabetic
35	M	164	60	22.30815	110	80	70	94	5.4	21	0.8	240	109	130	57	3	1.3	1.5	non diabetic
49	M	168	63	22.32143	140	90	83	101	5	27	0.9	206	190	120	37	3.4	0.8	7.7	non diabetic
45	M	158	58	23.23346	130	80	84	107	5.1	21	1	203	148	122	40	2.7	1.1	3.4	non diabetic
46	M	157	64	25.96454	110	70	85	129	4.9	18	1	170	79	88	43	2.4	1.2	1	non diabetic
35	F	152	66	28.56648	110	80	91	124	4.9	15	1	195	88	106	43	3	1.6	2.3	non diabetic
38	F	160	72	28.125	110	80	73	106	5.1	15	0.7	181	117	91	49	2.6	1.6	0.9	non diabetic
46	M	168	70	24.80159	130	80	71	94	4.5	15	1.2	203	257	113	35	1.7	1.2	2.3	non diabetic
53	F	164	59	21.93635	120	80	93	104	5.7	19	0.6	188	114	119	33	2.7	0.9	1.7	non diabetic
75	M	160	70	27.34375	140	90	95	105	5	25	1	156	59	99	37	1.8	1.6	3.5	non diabetic
41	M	148	60	27.39226	110	70	102	113	5.5	23	1	214	77	126	60	2.2	1.9	1.4	non diabetic
54	M	156	68	27.94214	110	70	88	99	4.8	16	0.6	170	84	99	116	2	1.4	6.4	non diabetic
39	M	162	58	22.10029	120	80	97	109	5.3	21	1	175	129	95	48	2.9	1.6	1.6	non diabetic
46	M	154	60	25.29938	120	70	99	106	5.2	24	0.8	181	64	105	46	2.7	1.5	1	non diabetic
39	M	152	68	29.43213	120	70	94	103	5	16	1.1	188	248	105	40	1.6	1.9	1.9	non diabetic
45	F	152	58	25.10388	110	70	90	104	5.2	16	0.7	168	117	98	41	2.3	1.2	2	non diabetic
48	M	172	64	21.63332	110	70	94	107	5.4	17	0.8	209	116	128	49	2.2	1.7	1.9	non diabetic