EVALUATION OF SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS

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This to certify that the dissertation entitled **"EVALUATION OF SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS"- A CROSS SECTIONAL STUDY** is the bonafide original work done by **DR.C.GUNASUNDARI,** Post graduate in **Biochemistry** under overall supervision and guidance in the Department of Biochemistry, Govt. Kilpauk Medical College, Chennai, in partial fulfillment of the regulations of **The Tamilnadu Dr. M.G.R. Medical University** for the award of M.D.Degree in Biochemistry (Branch XIII)

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CONTENTS

ABBREVIATIONS

eNOS	-	Endothelial nitric oxide synthase
CAD	-	Coronary artery disease
CVD	-	Cardiovascular disease
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
GLP-1	-	Glucagon like peptide
GLUT	-	Glucose transporter
VDCC	-	Voltage dependent calcium channel
VAMP	-	Vesicle associated membrane protein
SNAP	-	Soluble N-ethylmaleimide sensitive factor attachment protein
SNARE	-	Soluble N - ethylmaleimide sensitive factor attachment protein receptor
PI3K	-	Phosphatidylinositol 3 kinase
MAPK	-	Mitogen activated protein kinase
ERK	-	Extracellular signal regulated kinase
PDK	-	Phosphoinositide dependent protein kinase
PIP3	-	Phosphatidyl inositol 3,4,5-triphosphate
mTOR	-	Mammalian target of rapamycin
GSK3	-	Glycogen synthase kinase 3
FoxO	-	Forkhead box containing protein O
PEPCK	-	Phosphoenol pyruvate carboxy kinase

PTEN	-	Phosphatase and tensin homologue
SOCS	-	Suppressor of cytokine signaling protein
ENPP	-	Ectonucleotide pyrophosphatase/phosphodiesterase
PPARG	-	Peroxisome proliferator-activated receptor gamma
TCF2	-	Transcription Factor 2
MCP-1	-	Monocyte chemoattractant protein-1
TLR-4	-	Toll like receptor 4
IKK/NF k	-	IkappaB kinase/nuclear factor kappa
PLTP	-	Phospholipid transfer protein
AGE	-	Advanced glycosylated end product
VEGF	-	Vascular endothelial growth factor
SREBP	-	Sterol regulatory element binding protein
NEFA	-	Non-esterified fatty acid
VCAM 1	-	Vascular cell adhesion molecule 1
ICAM	-	Intracellular adhesion molecule
CETP	-	cholesterylester transfer protein
ChREBP	-	Carbohydrate responsiveness element-binding protein
MTP	-	Microsomal triglyceride transfer protein

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia associated with impairment in the metabolism of carbohydrates, lipids and proteins. It was first reported in Egyptian manuscript about 3000 years ago[1]. In 1936, the distinction between type 1 and type 2 DM was clearly made [2]. Type2 DM was first described as a component of metabolic syndrome in 1988 [3].

The origin and etiology of DM may vary greatly but always it include defects in either insulin secretion or insulin response or both at some point in the course of disease. Mostly patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or Type 2 DM (formerly known as non-insulin dependent DM). Type 2 DM is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [4].

The worldwide prevalence of diabetes has continued to increase dramatically. Globally, as of 2011, an estimated 366 million people had DM, with type 2 making up about 90% of the cases [5,6]. The number of patients with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. Among the

top ten countries with the largest number of diabetic patients, five are in Asia.[1].China tops the list with 90.0 million followed by India which has 61.3 million people affected by diabetes. The numbers are expected to rise to 129.7 million and 101.2 million, respectively by 2030. These estimates are likely to be underestimations as the prevalence data are mostly available for urban areas and reports from rural areas are very few. India is a large rural nation and the recent available studies indicate rising prevalence of the diabetes in the rural areas also [7-9].

The prevalence of diabetes is reaching a pandemic proportion which is mostly due to rapid lifestyle transitions and by a narrowing in the urban-rural divide in living conditions. Although there are disparities in the sample selection and screening criteria, the prevalence estimates are increasing both in the urban and rural regions of India. A recent study in Kerala, concluded that the rural population has a higher prevalence of diabetes than the urban population [10].

In India, prevalence of Diabetes mellitus ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas. Diabetes causes dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels. Age adjusted mortality rates among diabetics is 1.5 to 2.5 times greater than general population. Most of this excessive mortality is

mainly attributed to cardiovascular disease [11].The hyperglycemia observed in diabetes mellitus if not controlled may lead to various life threatening complications such as micro and macro vascular diseases [12].

Uric acid is the end product of purine catabolism. Excessive serum uric acid accumulation can cause various diseases. For more than 50 years, increased serum levels of uric acid have been implicated in cardiovascular disease. Different mechanisms have been suggested through which uric acid may be involved in the atherosclerotic process and its clinical complications. Uric acid may act as a prooxidant, particularly at increased concentrations, and may be a marker of oxidative stress [13, 14].

Uric acid promotes vascular smooth muscle proliferation and also upregulates the expression of platelet-derived growth factor and monocyte derived chemotactic protein1[15- 17]. This would enhance the atherogenesis and its progression. As a result of insulin resistance, there is a decrease in excretion of uric acid due to reduced effect of insulin, [18,19].

The prevalence of dyslipidemia in type 2 diabetes is double with respect to the general population. Dyslipidemia is an important risk factor for cardiovascular disease (CVD) and plays a major role in the progress

of atherosclerosis[20]. These are more complex abnormalities that are caused by interrelationship among obesity, insulin resistance and hyperinsulinism [21].

According to *Freedman et al (1999)*, when the overweight subjects were compared with their respective thinner counterparts, they presented 2.4 to 7.1 times higher probability to have an elevated total cholesterol, LDL cholesterol, triglycerides[22] and blood pressure as well as 12.6 times higher probability to have hyperinsulinemia. It is worth to emphasize that the fatty tissue is exclusively related to risk factors, such as the altered insulin and lipid profile, which can contribute to the development of the insulin resistance syndrome, which comprises several risk factors for the emergence of cardiovascular complications [23]. In patients with type 2 diabetes, which is equivalent to CHD [4], it is most commonly characterized by elevated TG and reduced HDL-C [25].

These abnormalities can be present alone or in combination with other metabolic disorders. The prevalence of dyslipidaemia varies depending on the population studies, geographic location, socioeconomic development and the definition used [26,27].

In patients with type 2 diabetes mellitus, the risk of cardiovascular disease and cardiovascular mortality is significantly increased relative to healthy individuals[28, 29].

Dyslipidemia is a major causative factor for the increased cardiovascular risk associated with type 2 diabetes, which includes abnormalities in all lipoproteins [30–32].

Type 2 DM is associated with various plasma lipid and lipoprotein (LP) abnormalities that are recognized as predictors for coronary heart disease [33]. Hypertriglyceridemia and reduced HDL cholesterol is the most common dyslipidemia in patients with noninsulin-dependent diabetes mellitus, but essentially any pattern of dyslipidemia may be present [34].

Dyslipidemia is a major risk factor for coronary heart disease (CHD). Cardiovascular disease is a cause of morbidity and mortality in patients with type 2 diabetes mellitus due to associated abnormalities in lipids such as serum triglycerides (TC) 69%, serum cholesterol 56. 6%, low-density lipoprotein cholesterol (LDL) 77% and high density lipoprotein cholesterol (HDL) 71% [35,36]. Early detection and treatment of hyperlipidemia in Patients with type-2 diabetes can prevent the

progression of cardiovascular disease associated with atherogenic abnormalities and minimize the risk for Coronary artery disease.

Hyperuricemia and hyperlipidemia are the metabolic abnormalities frequently associated with type 2 diabetic patients. In present study the levels of biochemical parameters like serum uric acid and serum lipid profile were evaluated and correlated for the risk of cardiovascular disease in type 2 diabetes mellitus.

AIM AND OBJECTIVE

To evaluate serum uric acid and lipid profile in type 2 Diabetes mellitus.

OBJECTIVE

1) To assess the risk factors like serum uric acid & lipid profile for cardiovascular disease in type 2 Diabetes mellitus.

2) To compare the level of serum uric acid and lipid profile in type 2 Diabetes mellitus patients with non diabetic healthy individuals.

REVIEW OF LITERATURE

Diabetes mellitus is a disorder of multiple aetiologies, which is characterized by chronic hyperglycemia with impairment of carbohydrate, fat and protein metabolism due to deficiency of insulin, deficiency of insulin action or both. Type-2 DM is the most common form of diabetes accounting for 90% of the cases [37]. The chronic hyperglycemia of diabetes leads to significant long-term effects, especially dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels [38].

PREVALENCE

It has been estimated that the global burden of type 2 diabetes mellitus in 2010 was 285 million people which is expected to increase to 438 million in 2030. The World Health Organisation estimated that 9% of the world's population had diabetes in 2014, and more than 90% of these suffered from type 2 diabetes. Moreover, type 2 diabetes already causes 5 million deaths per year, commonly due to cardiovascular diseases. Type 2 diabetes is expected to become the 7th cause of death globally by 2030. [39]

Currently in India, 40.9 million people are affected with diabetes and the projected estimate for the year 2025 is 69.9 million[40]. The prevalence in the southern part of India is higher-13.5% in Chennai, 12.4 % in Bangalore, and 16.6% in Hyderabad, compared to Eastern India (Kolkatta)- 11.7 %,North India (New Delhi)-11.6 %, and Western India (Mumbai)- 9.3%. [41]

In Chennai, the prevalence in 2000 was 13.5%,which increased to 14.3% in 2004 and is further raised to 18.6% in 2006. [42]Although Type 2 is widely diagnosed in adults, it is markedly increased in the paediatric age group for the past two decades. Depending on the population studied, T2DM now contributes 8-45% of all new cases of diabetes reported among children and adolescent[43].

UNDIAGNOSED DIABETES-THE HIDDEN THREAT

Currently as many as 50% of people with diabetes are undiagnosed. Since therapeutic intervention can reduce complications of the disease, there is a need to detect diabetes early. Its incidence is increasing rapidly. [44,45]. The Kashmir valley study showed that the prevalence of undiagnosed diabetes was 4.25 percent, which was more than double to that of the known diabetes (1.9%) [46]. The individuals who are unaware of their disease status are left untreated and they are

more prone to microvascular as well as macrovascular complications. Hence, it is necessary to detect the undiagnosed diabetic subjects in India and offer early therapy to these individuals.

Causes for rise in prevalence of diabetes

The dramatic rise in the prevalence of type 2 diabetes and related disorders like obesity, hypertension and the metabolic syndrome could be related to the rapid changes in life style that has occurred during the last 50 yr. Although this “epidemiological transition”, which includes improved nutrition, better hygiene, control of many communicable diseases and improved access to quality healthcare have resulted in increased survival rate, it has also led to the rapid rise of the new-age diseases like obesity, diabetes and heart disease.

The intrusion of western culture into the lives of traditional indigenous communities has also had devastating results in terms of the rise in diabetes and related metabolic disorders. In virtually all populations, higher fat diets and decreased physical activity and sedentary occupational habits have accompanied the process of modernization which has resulted in the increased prevalence of obesity and type 2 diabetes .

Moreover, the ‘fast food culture’ which has increased in our cities and towns is also a major cause of the diabetes epidemic. The ‘fast-foods’ that are fat and calorie rich are easily available in the numerous food outlets. Majority of the people in Indian cities depend on these unhealthy ‘junk’ foods, this may be a major factor in the rising prevalence of diabetes and cardiovascular diseases in urban slums. One point worth emphasizing is that diabetes can no longer be considered as a disease of the rich. The prevalence of diabetes is now rapidly increasing among the poor in the urban slum dwellers, the middle class and even in the rural areas. This is due to rapid changes in physical activity and dietary habits even among the poorer sections of the society. [47].

The next factor driving the epidemic is what has been referred to as ‘sedentarinism’ or the adoption of sedentary behaviour. Over the past few decades, a huge number of the working population has shifted from manual labour associated with the agriculture sector to physically less demanding office jobs.

With the advent of computer and video games, sedentarinism is now affecting the children and youth as they tend to spend more time in front of televisions or computers than playing outdoors.[48,49].

Etiologic Classification of Diabetes Mellitus. Adapted from WHO and ADA [50,51]

I. Type 1Diabetes mellitus

A. Autoimmune

B. Idiopathic

II. Type 2 Diabetes mellitus

Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance

III. Other types of diabetes mellitus

A. Genetic defects in β-cell function

B. Genetic defects in insulin action

C. Disease of the exocrine pancreas

D. Endocrinopathies

E. Pharmacologically or chemically induced

F. Infections

G. Infrequent forms of autoimmune diabetes

H. Other syndromes occasionally associated with diabetes

IV. Gestational diabetes mellitus

Occurs in women during gestation

RISK FACTORS

NON MODIFIABLE RISK FACTORS

1. Positive family history of type 2 DM: seen in 75% of patients and the prevalence increases to 62% when both father and mother are affected.

2. Genetic factors: 20 different genes like CDKAL1, FTO, HHEX, SLC30A8, TCF7L2 etc have been detected to be strongly associated with type 2 diabetes

3. Age, race and ethnicity[52,53]

MODIFIABLE RISK FACTORS

1. Body mass index(BMI), Waist/hip ratio (WHR), Waist circumference(WC) are the obesity indicators playing an important role in the development of type 2 diabetes.

2. Hypercholesterolemia –increased total cholesterol, VLDL, LDL, triglyceride and decreased levels of HDL are commonly associated with type 2 diabetes.

3. Hypertensive patients are at increased risk than normotensive patients.

4. Dietary habits-people taking diet low in whole grains, decreased fiber, vitamins, minerals, antioxidants are at greater risk of developing type 2 diabetes. [52,53]

TYPE 2 DIABETES

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder. The interaction between several genetic and environmental factors results in a heterogeneous and progressive disorder with variable levels of insulin resistance progresses to type-2 diabetes, when β cells are no longer able to secrete sufficient insulin to overcome insulin resistance. Abnormalities in other hormones such as reduced secretion of the incretin, glucagon-like peptide 1 (GLP-1), hyperglucagonemia, and raised concentrations of other counter-regulatory hormones also contribute to insulin resistance, reduced insulin secretion, and hyperglycemia in type 2 diabetes[54-60].

Obesity contribute to insulin resistance through several pathways. These include

* an imbalance in the concentrations of hormones (eg, increased leptin, reduced adiponectin, and increased glucagon)

* increased concentrations of cytokines (eg,tumour necrosis factor α, interleukin 6)
* suppressors of cytokine signalling
* other inflammatory signals and possibly retinol-binding protein [61 64].

Concurrent alterations in β-cell function often include a period of compensatory hyperinsulinemia with abnormal secretory dynamics. When insulin secretion is no longer sufficient to overcome insulin resistance, glucose intolerance progresses to type 2 diabetes. The decline in β-cell function seems to cause chronic hyperglycemia (glucotoxicity), chronic exposure to non-esterified fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation[65–67]. Patients with type 2 diabetes usually have pancreatic α-cell dysfunction that results in increased or nonsuppressed glucagon secretion in the presence of hyperglycemia and probably reduced prandial GLP-1 secretion[68].

The insulin secretion signaling pathway

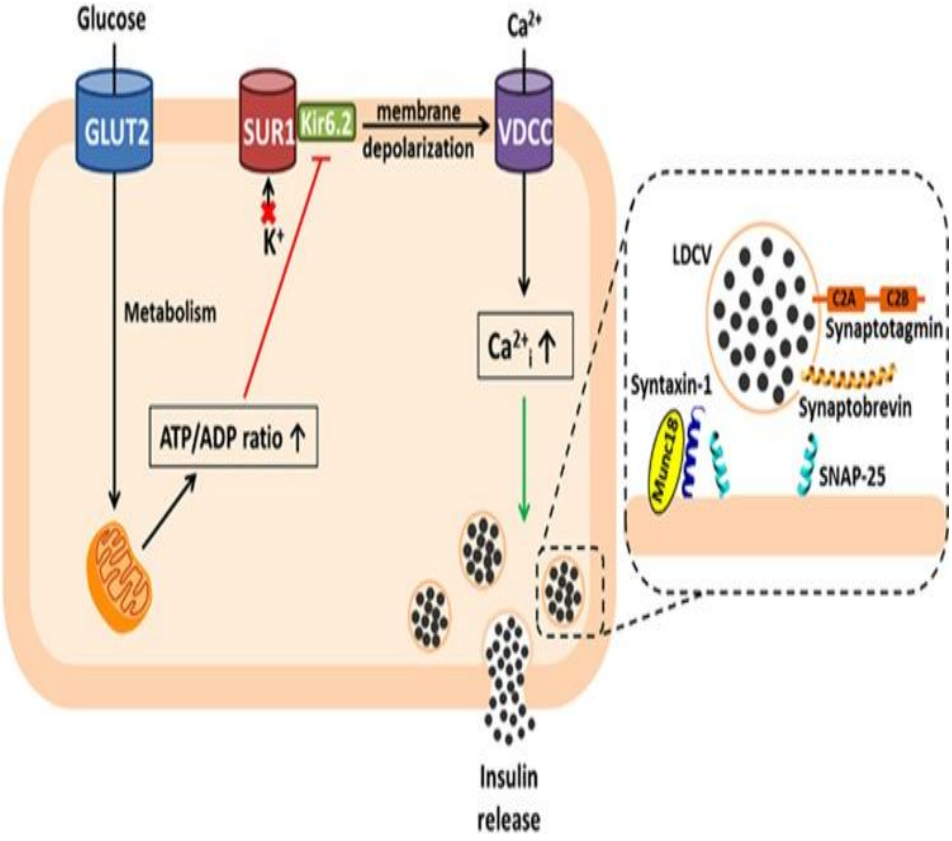
The main stimulus for insulin release from β-cells are elevated blood glucose levels following food intake.[69] The circulating blood glucose is taken up by the facilitative glucose transporter GLUT2 (SLC2A2), which is present on the surface of the β-cells. Glucose

undergoes glycolysis inside the cell, generating adenosine triphosphate (ATP),which results in an increased ATP/ADP ratio. This altered ratio then leads to the closure of ATP-sensitive K^+-channels (K_{ATP}-channels) leading to subsequent decrease in the magnitude of the outwardly directed K^+-current which elicits the depolarization of the membrane, followed by the opening of voltage-dependent Ca^+-channels (VDCCs). The increase in intracellular calcium concentration eventually triggers the fusion of insulin-containing granules with the membrane and the subsequent release of their content.[70]

The whole secretory process is biphasic. The first phase peaking around 5 minutes after the glucose stimulus with the majority of insulin being released during this first phase. The second phase which is somewhat slower and the remaining insulin is secreted.[71-73] The key molecules that mediate the fusion of the insulin-containing large dense-core vesicles are the synaptosomal-associated protein of 25kDa (SNAP-25), syntaxin-1 and synaptobrevin 2 (or vesicle-associated membrane protein VAMP2), all of which belong to the superfamily of the soluble *N*-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor proteins (SNAREs).

Together with the Sec1/Munc18-like (SM) proteins they form the so-called SNARE complex.[74] To initiate fusion, synaptobrevin 2, a *vesicle (v*-SNARE) that is integrated into the vesicle's membrane, fuses with the *target (t*-SNAREs) syntaxin-1 and SNAP-25, which are located in the target cell membrane,[75,76] with mammalian uncoordinated (Munc)-18 playing a key regulatory role.[77,78]

The insulin secretion signaling pathway



MECHANISM OF INSULIN ACTION

SIGNAL TRANSDUCTION IN INSULIN ACTION

The two main pathways of insulin signaling emanating from the insulin receptor-IRS node are the

* phosphatidylinositol 3-kinase (PI3K, a lipid kinase)/AKT (also known as PKB or protein kinase B) pathway [79,80]
* Raf/Ras/MEK/ MAPK (mitogen activated protein kinase, also known as ERK or extracellular signal regulated kinase) pathway[81].

The PI3K pathway is responsible for most metabolic effects of insulin, and is connected exclusively through IRS, while the MAPK pathway emanates from both IRS and Shc and is involved in the regulation of gene expression and, in cooperation with the PI3K pathway, in the control of cell growth ("mitogenesis") and differentiation [82].Most insulin effects appear to be mediated through the interaction of IRS-1 and -2, and Shc, with the insulin receptor [82-,84]. Other docking proteins like CBL, APS, SH2B, GAB1 and-2 and DOCK1 and-2 have been less extensively studied [84].

The PI3K Signaling Pathway

Activation of the PI3K pathway is triggered by the binding of the p85 or p55 regulatory subunit of PI3K (an adapter which has 8 isoforms) to IRS1 and-2, resulting in activation of the p110 catalytic subunit (which has three isoforms) and generation of phosphatidylinositol-3,4,5-triphosphate (PIP3), which leads to activation of the three isoforms of AKT/PKB by PDK (phosphoinositide-dependent protein kinase) 1 and -2. PDKs bind to PIP3 in the cell membrane and become thereby activated[82,79,80].

Four of the critical downstream substrates of AKT/PKB are mTOR, mammalian target of rapamycin, involved in the regulation of protein synthesis[85]; GSK3 (glycogen synthase kinase 3), involved in the regulation of glycogen synthesis[86]; FoxO (forkhead box-containing protein, O subfamily) transcription factors, especially FoxO1, involved in the regulation of gluconeogenic and adipogenic genes[87] and AS160 (AKT substrate of 160kDa), involved in glucose transport [88] .

mTOR is a serine/threonine kinase that acts as a nutrient sensor; it is the catalytic subunit of two structurally distinct complexes,mTORC1 and mTORC2. It stimulates protein synthesis by phosphorylating

eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and p70 ribosomal protein S6 kinase (p70S6K).

GSK3 is a serine/ threonine protein kinase that inhibits glycogen synthase (but is also involved in other cellular processes); it is inhibited when phosphorylated by AKT/PKB.

FoxO1 is a transcription factor that translocates to the nucleus in the absence of insulin signal, and stimulates the expression of genes such as PEPCK (phosphoenolpyruvate carboxykinase), the key enzyme in gluconeogenesis [82], as well as cyclin G2, an atypical cyclin that blocks the cell cycle and is inhibited by insulin [89], and appears to play a key role in insulin (and IGF-I)-induced mitogenesis.

AS 160 is a 160-kD AKT substrate that plays a key role in insulin-stimulated glucose transport [90, 88].

The MAPK-ERK Signaling Pathway

Grb2 is an adapter protein that binds to IRS and Shc, and exists in a complex with SOS (son of sevenless), a guanyl nucleotide exchange factor that promotes GDP/GTP exchange on the small G protein p21 ras [91]. This in turn activates the cascade of serine/threonine kinases Raf/MEK/ ERK1-2. Phosphorylated ERK 1-2 translocate to the nucleus if

the signal is of sufficient duration and phosphorylates there an array of transcription factors and mitogen-and stress-activated protein kinases [90,81].

INSULIN REGULATION OF GLUT4 TRANSLOCATION

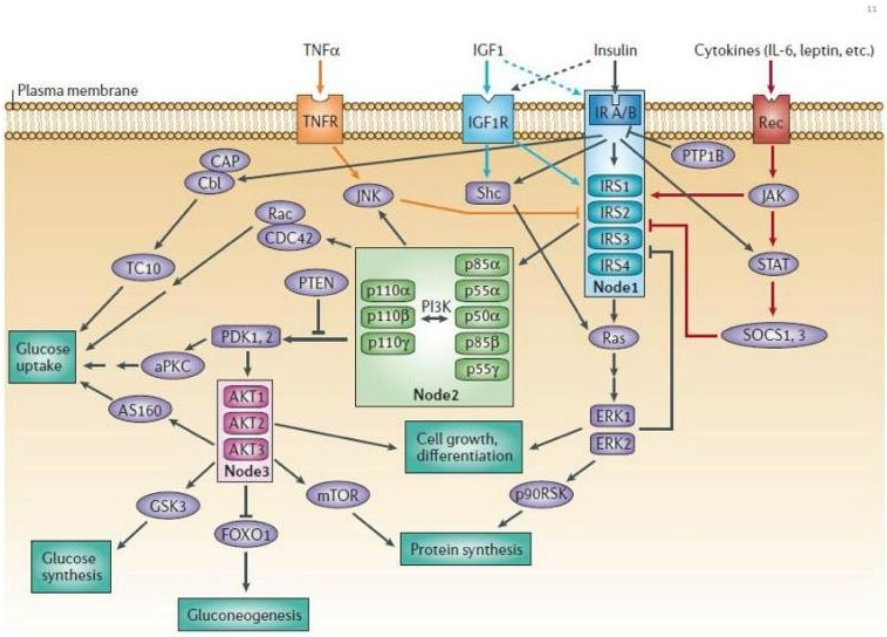
The prototypical metabolic effect of insulin is the stimulation of glucose transport in adipose tissue and skeletal and cardiac muscle[90,92,93]. Glucose disposal into muscle is the major component of insulin action that prevents postprandial hyperglycemia. This is accomplished through the translocation by exocytosis of the insulin-sensitive glucose transporter GLUT4 from intracellular vesicles to the plasma membrane, by a mechanism that is still far from completely understood [94,95].

GLUT4 has the unique characteristic of a mostly intracellular disposition in the unstimulated state, in storage vesicles called GSVs that are acutely redistributed in the plasma membrane in response to insulin and other stimuli like exercise [95].

The major insulin signaling pathway involved in GSVs translocation is the PI3K/PDK1/AKT2 pathway, through phosphorylation of the AS160 substrate. Atypical Protein kinases C (aPKCs) isoforms appear to be also involved downstream of PDK1 but not through AKT.

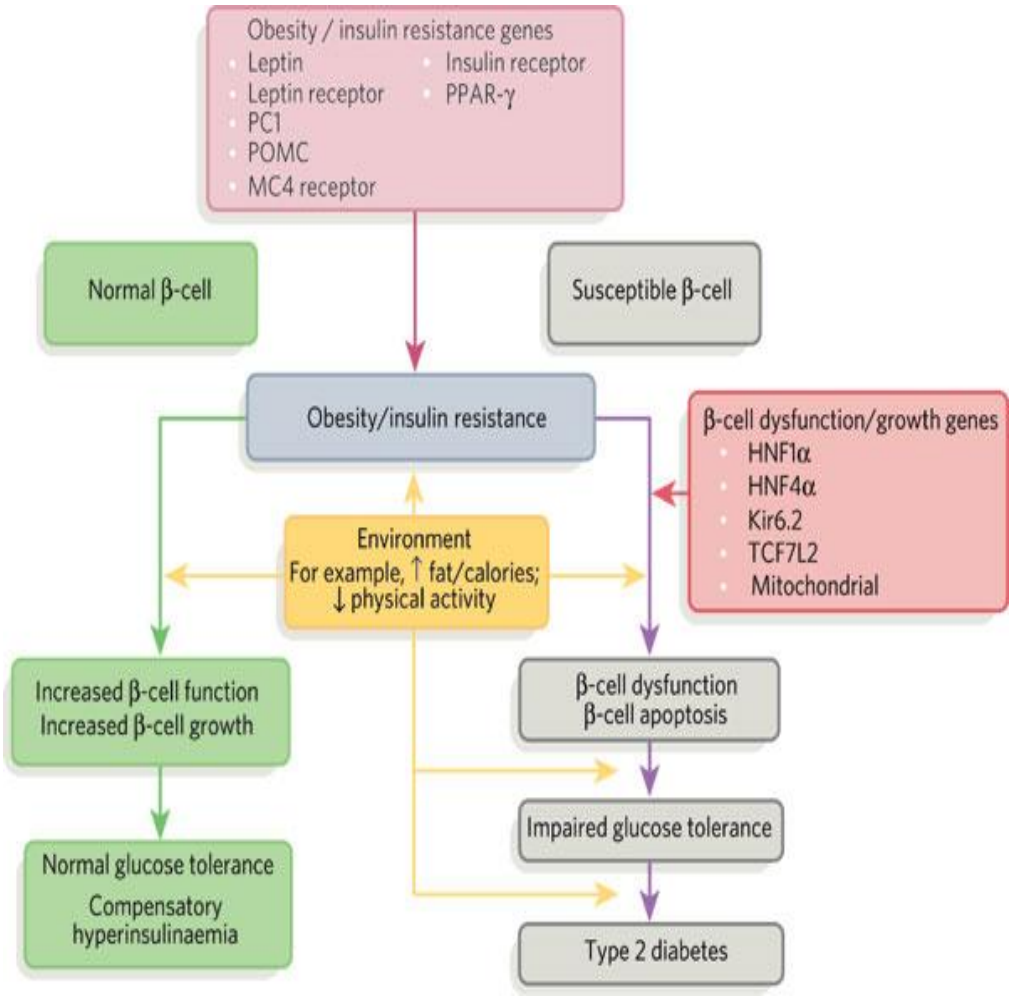
A parallel signaling pathway [94] in adipocytes, emanating from caveolae and lipid rafts has been proposed, that involves the phosphorylation of the adaptor protein Cbl by the insulin receptor, and results in the activation of a small G protein, TC10, a member of the Rho family which modulates actin structure. [95].

INSULIN RECEPTOR SIGNAL TRANSDUCTION NETWORK



The canonical insulin receptor signal transduction network. The two major canonical insulin receptor signaling cascades (PI3K and ERK) are shown. The critical nodes (IR/IRS, PI3K, AKT) are boxed. Crosstalk from IGF-I receptor, cytokine receptors and TNFα is indicated. Negative regulation by PTP1B and PTEN is shown.

PATHOPHYSIOLOGY OF TYPE 2 DM [96-99]



Role of Genetics

A weak association between type 2 diabetes and the calpain 10 gene had been demonstrated, and the rare known type 2 diabetes susceptibility variants (PPARG and E23K in KCNJ11) increased the risk slightly only. Recently, a major type 2 diabetes susceptibility gene, accounting for 20% of cases, TCF7L2, has been identified [100]. Studies conducted in European Caucasian, Asian Indian and Afro-Caribbean populations [101] have confirmed the ubiquitous distribution of the association. TCFL2 is associated with alterations in insulin secretion. Genotype–phenotype relationship studies disclosed severely impaired insulin secretion in carriers of susceptibility variants [102].

Role of environmental factors

Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc. are independent risk factors of pathogenesis. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass,induces insulin resistance. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars,and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. [103]

ROLE OF INSULIN RESISTANCE

A central feature of type-2 diabetes is insulin resistance, a condition in which cells cannot respond properly to insulin.

This occurs primarily at the level of so-called insulin-sensitive tissues, such as liver, muscle, and fat, and can be caused by multiple mechanisms.

MECHANISM OF INSULIN RESISTANCE

Several factors have been proposed to explain the mechanisms of insulin resistance. These include: (a) obesity; (b) inflammation; (c) mitochondrial dysfunction; (d) hyperinsulinemia; (e) lipotoxicity / hyperlipidemia; (f) genetic background;(g) endoplasmic reticulum (ER) stress; (h) aging; (i) oxidative stress; (j) fatty liver; (k) hypoxia; (l) lipodystrophy.

Inflammation and insulin resistance

Inflammation inhibits the insulin signaling activity in adipocytes and hepatocytes through several mechanisms.

- inhibition of IRS-1 (insulin receptor substrate 1) and insulin receptor in the insulin signaling pathway [104,105].

- inhibition of PPAR γ function [106,105]. Reduction of PPARγ activity contributes to insulin resistance.
- increase in plasma free fatty acid (FFA) through stimulation of lipolysis and blocking TG synthesis [107].

These effects are primarily observed in adipose tissue and liver. Muscle insulin action is not sensitive to inflammation. The cytokines include TNF- α, IL-1, IL-6, MCP-1 and PAI-1,[108 –110] play a major role.

Mitochondrial dysfunction and insulin resistance

Mitochondrial dysfunction is defined as reduction in mitochondrial number, density or function. As oxidation and metabolism of fatty acid and glucose occurs in mitochondria, a reduction in mitochondrial function may contribute to FFA and lipid accumulation which enhances insulin resistance [111]

Hyperinsulinemia and insulin resistance

Hyperinsulinemia denotes a constant high level of plasma insulin in the fasting condition. Studies consistently support that over production or supply of insulin leads to hyperinsulinemia, and causes insulin resistance in human and animal models. Inhibition of IRS-1/2 function

after activation of the negative feedback loop in the insulin signaling pathway is the mechanism[90].

Lipotoxicity

The plasma level of FFA is tightly controlled by insulin. When FFAs is persistently maintained at a high level, it leads to systemic insulin resistance and type 2 diabetes.

This condition is often observed in patients with a high risk of type 2 diabetes [112]. Lipodystrophy and adipose tissue dysfunction contribute to the FFA elevation [113,114]. In the mechanism, FFAs may suppress IRS-1 through activation of the negative feedback loop of the insulin receptor pathway [90].

FFA elevation is often associated with hyperlipidemia, which is a risk factor of insulin resistance. Hyperlipidemia includes an increase in cholesterol, FFA, and TG in the plasma. These lipid indicators are normally down regulated by insulin. These parameters will increase in the blood when insulin resistance occurs. Insulin stimulates uptake of FFA by liver and adipose tissue and conversion of FFA into TG. Insulin also induce uptake of TG in lipid protein by adipocytes. When adipose tissue response to insulin is lost, the levels of FFA and TG will increase in the

blood. FFA was considered to induce insulin resistance through induction of inflammation. FFA, such as palmitate (saturated FFA) and linoleic acids, were reported to induce activation of IKK/NF- κB pathway through an interaction with Toll-like receptor 4 (TLR4)[115-117]

Oxidative stress

Oxidative stress occurs as a result of imbalance between production and disposal of reactive oxygen species (ROS). ROS is mainly generated in mitochondria during oxidation of fatty acid or glucose for ATP or heat production. ROS is required for normal signal transduction in cells [118]. But, ROS over production will induce oxidative stress. ROS has been reported to inhibit insulin signal transduction by activation of PKC, JNK and NF- κB [119]. ROS also mediates TNF- α and glucocorticoid signal in insulin resistance [120].

Microvascular and Macrovascular Complications of Diabetes

Microvascular Complications of Diabetes

Diabetic retinopathy

The most common microvascular complication of diabetes is Diabetic retinopathy. Aldose reductase is the initial enzyme in the intracellular polyol pathway which involves the conversion of glucose

into alcohol (sorbitol). Excess glucose levels will increase the flux of sugar molecules through the polyol pathway, which leads to accumulation of sorbitol in cells. Sorbitol accumulation leads to osmotic stress which has been suggested as an underlying mechanism in the development of diabetic retinopathy.[121]

Increased glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGE). In animal models, these substances have also been associated with formation of microaneurysms and pericyte loss.[121,122] Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been involved in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia.[121,123]

Diabetic nephropathy

It is defined as proteinuria > 500 mg in 24 hours in patients with diabetes. This is preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30-300 mg/24 hours. Diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy, if not managed in time. This progression occurs in both type 1 and type 2 diabetes.[124]

The underlying mechanism of injury may involve the same mechanisms for diabetic retinopathy. The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies), and other changes..[125,126]

Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes."[127]

The precise nature of injury to the peripheral nerves from hyperglycemia is not known but may be is related to mechanisms such as polyol accumulation, injury from AGE, and oxidative stress. Peripheral neuropathy in diabetes may manifest in different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy.[128]

Macrovascular Complications of Diabetes

The chief pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis occurs as a result of chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce collagen accumulation and smooth muscle proliferation in the arterial walls. The final result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Acute vascular infarction occurs due to rupture of this lesion.[129]

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide production and increased free radical formation in platelets, as well as altered calcium regulation, may enhance platelet

aggregation. Increased levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. Increased coagulability and impaired fibrinolysis further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes.[130] Diabetes mellitus increases the risk of cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the major cause of death in patients with either type 1 or type 2 diabetes.[131,132] In fact, CVD accounts for the greatest part of health care expenditures in people with diabetes.[132,133]

Among macrovascular diabetes complications, coronary artery disease has been associated with diabetes in numerous studies beginning with the Framingham study.[134] More recent studies have observed that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in nondiabetic patients with a history of previous MI.[135]These reports have lead to new recommendations by the ADA and American Heart Association that diabetes be considered a coronary artery disease risk equivalent rather than a risk factor.[136]

Diabetes mellitus is also a strong independent risk factor of stroke and cerebrovascular disease, as in coronary artery disease.[137]Patients with type 2 diabetes have a much higher risk of 150-400% for stroke. Risk of stroke-related dementia as well as stroke-related mortality, is increased in patients with diabetes.[130]

Diagnosis of Type 2diabetes

American Diabetes Association (ADA) 2016 Guidelines[138]

Diabetes Mellitus

- HbA1c ≥ 6.5 % (≥ 48 mmol/mol)
- Random plasma glucose ≥ 200mg/dl (≥ 11.1 mmol/l)
- Fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl)
- OGTT 2 hour glucose in venous plasma ≥ 200mg/dl (≥ 11.1 mmol/l)

Impaired Fasting Glucose

IFG means fasting glucose levels from 100-125 mg/dl (5.6 mmol-6.9 mmol/l) in venous plasma.

Impaired Glucose Tolerance

IGT is 2 hour plasma glucose in the OGTT in the range of 140-199 mg/dl (7.8-11.0 mmol/l) with fasting glucose < 126 mg/ dl (< 7.0 mmol/l).

ABNORMALITIES OF LIPID METABOLISM IN TYPE 2 DIABETES

In type 2 diabetes, lipid abnormalities are the major factors leading to an increased cardiovascular risk. Diabetic dyslipidaemia includes not only quantitative lipoprotein abnormalities, but also qualitative and kinetic abnormalities, together resulting in a shift towards a more atherogenic lipid profile. The quantitative lipoprotein abnormalities are raised triacylglycerol levels and lowered HDL-cholesterol levels. Qualitative lipoprotein abnormalities include an increase in large, very low-density lipoprotein subfraction 1 (VLDL1) and small, dense LDLs, as well as increased triacylglycerol content of LDL and HDL, glycation of apolipoproteins and increased susceptibility of LDL to oxidation.The main kinetic abnormalities are increased VLDL1 production, decreased VLDL catabolism and increased HDL catabolism. Although the pathophysiology of diabetic dyslipidaemia is not clear,the insulin

resistance and relative insulin deficiency seen in patients with type 2 diabetes are likely to contribute to these lipid changes.

Dyslipidemia is very common in patients with type 2 diabetes mellitus, with a prevalence of 72–85% [139,140]. Lipid abnormalities seen in patients with type 2 diabetes play a major role in the development of atherosclerosis. Raised triacylglycerols and decreased HDL-cholesterol are the main quantitative lipid abnormalities of diabetic dyslipidemia.[141-143,144]. These abnormalities are well known risk factors for the development of atherosclerosis [145].

Cholesterol absorption and synthesis

Patients with type 2 diabetes have a decreased plasma level of campesterol, a marker of cholesterol absorption, and higher plasma levels of lathosterol, a marker of cholesterol synthesis[146]. Using peroral administration of isotopes, decreased cholesterol absorption and increased cholesterol synthesis have been observed in patients with type 2 diabetes [147]. The mechanisms responsible for these changes in cholesterol homeostasis are not yet clarified.

In a study performed in 263 patients with type 2 diabetes, liver fat content was independently associated with plasma lathosterol [148]. It has

been suggested that this could be due to increased expression of *SREBP*2, encoding sterol regulatory element-binding protein, a factor regulating cholesterol uptake and synthesis, noticed in conditions of increased liver fat content [149].

Postprandial hyperlipidemia and chylomicrons

In patients with type 2 diabetes and insulin resistance, an increase in chylomicron production is seen, leading to the postprandial hyperlipidemia observed in this population [150]. Indeed, patients with type 2 diabetes have an increased rate of intestinal ApoB-48 secretion [151] and augmented expression of microsomal triglyceride transfer protein-*MTP* (responsible for the addition of triacylglycerols to ApoB-48) within the intestine [152]. Insulin resistance seems to be involved in increased chylomicron production, since the normal acute suppression of postprandial chylomicron secretion, by insulin, is absent in patients with type 2 diabetes [153]. In addition, increased plasma NEFA concentrations (as a result of reduced inhibition of hormone-sensitive lipase in type 2 diabetes [154] may further drive ApoB-48 secretion [155]. The clearance of chylomicrons is also impaired in type 2 diabetes [156].

The activity of LPL, the enzyme responsible for chylomicron hydrolysis, is significantly lowered in patients with type 2 diabetes

mellitus[157,158]. Insulin resistance is also associated with raised plasma levels of ApoC-III, an inhibitor of LPL [159]. The final result of all these changes is a large pool of chylomicrons (hypertriglyceridemia). Also, patients with type 2 diabetes show increased levels of atherogenic remnant particles, including chylomicron remnants and VLDL remnants[160].

Postprandial hyperlipidemia promotes atherosclerosis and cardiovascular events in patients with type 2 diabetes. The increase in postprandial triacylglycerols is shown to be correlated with the increase in TNFα, IL-6 and vascular cell adhesion molecule 1

Increased (VCAM-1) values, in patients with type 2 diabetes, indicating a proinflammatory effect[161]. The magnitude of postprandial hypertriglyceridemia is strongly correlated with the reduction in flow mediated dilatation, in patients with type 2 diabetes, indicating a role in endothelial dysfunction [162].

VLDL and IDL

Increased plasma triacylglycerol levels in patients with type 2 diabetes are largely due to an increased number of VLDLs, particularly large $VLDL_1$ particles. Both increased production and delayed catabolism

of VLDL are responsible for the increased VLDL pool. In vivo kinetic studies in patients with type 2 diabetes have shown an augmented production of both VLDL-ApoB and VLDL-triacylglycerols [163–165]. More precisely, it has been demonstrated that type 2 diabetes is associated with increased production of large $VLDL_1$ particles [166,167].

Insulin resistance is associated with decreased inhibition of hormone-sensitive lipase in adipose tissue by insulin, leading to increased lipolysis and, thereby, augmented NEFA portal flux to the liver. This has been shown to stimulate synthesis of triacylglycerols in hepatocytes [168]. First, data from animal studies have shown that insulin resistance is associated with a reduction in ApoB degradation in hepatocytes, leading to an increase in the ApoB pool available for VLDL assembly [169,170]. Second, *MTP* expression is increased in insulin-resistant states and type 2 diabetes [171]. In insulin resistance, the reduced activation of PI3K leads to increased forkhead box protein O1 (FOXO1) activation, which is normally inhibited by activated PI3K.

This increased activation of FOXO1 is responsible for augmented transcription of the *MTP*gene [172]. Third, it has been suggested that insulin resistance could be responsible for the increased activity of two

factors such as phospholipase D1 and ARF-1involved in the formation of $VLDL_1$ [173].

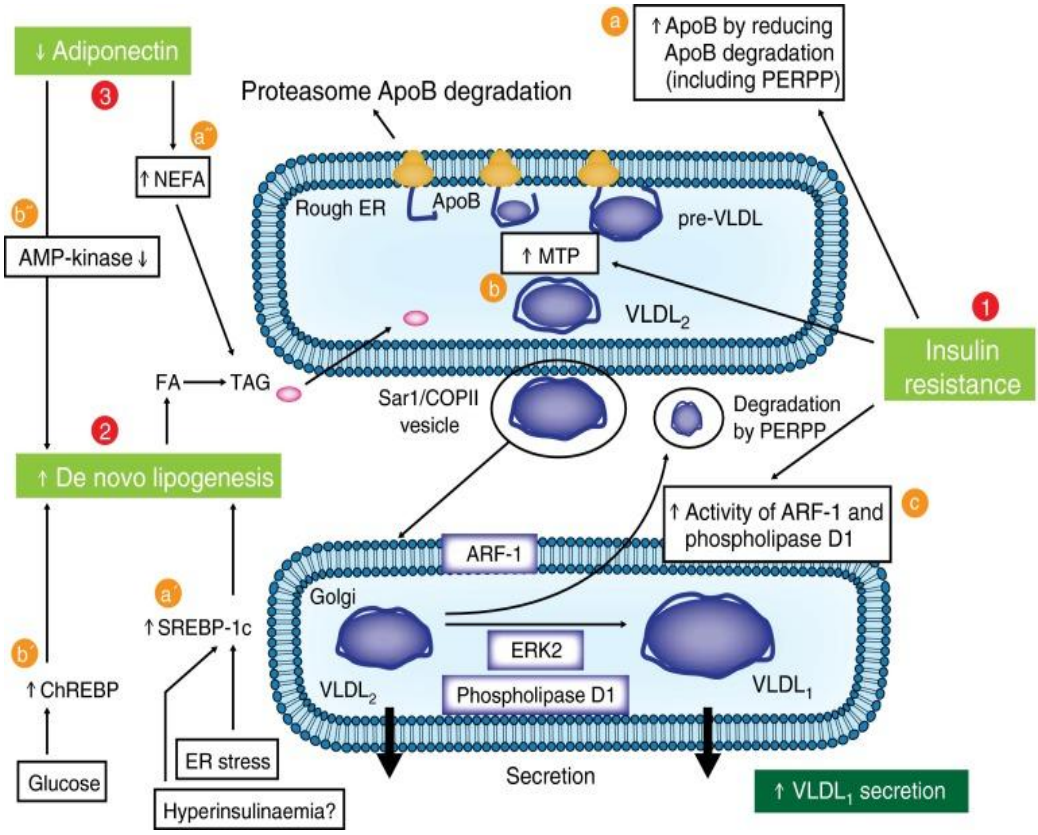
In addition, de novo lipogenesis is increased in individuals with insulin resistance [174]. This increased de novo lipogenesis is secondary to augmented expression of both carbohydrate responsiveness element-binding protein (ChREBP) and sterol regulatory element-binding protein (SREBP)-1c in insulin resistance and type 2 diabetes[168]. It is suspected that, in patients with type 2 diabetes, hyperglycemia directly activates ChREBP [175]. The increase in SREBP-1c expression could be related to the augmented ER stress observed in insulin resistance and type 2 diabetes [176]. Moreover, decreased plasma adiponectin levels in type 2 diabetes may promote VLDL production by increasing plasma NEFA levels, as a consequence of reduced muscle NEFA oxidation, and by inducing a decrease in AMP-kinase activation in the liver, which promotes de novo lipogenesis [168].

As assessed by kinetic studies using radioisotopes[164] and stable isotopes [163], catabolism of VLDLs is decreased in patients with type 2 diabetes, which also causes hypertriglyceridemia. This defect in VLDL catabolism mainly reflects the reduced activity of LPL in type 2 diabetes, particularly in adipose tissue [158]. Since insulin is an activator of LPL, it

has been suggested that the decrease in LPL activity may be due to a relative insulin deficiency and/or insulin resistance. In addition, increased plasma levels of ApoC-III (an inhibitor of LPL) could also contribute to the decreased catabolism of VLDL in patients with type 2 diabetes, since increased plasma levels of ApoC-III were associated with impaired VLDL clearance in obese insulin-resistant men [177].

The type of VLDL particles produced in type 2 diabetes is also altered, with a shift towards a greater proportion of larger particle size ($VLDL_1$)[144,178]. These are enriched with cholesterol esters and phospholipids relative to smaller VLDL particles. Larger triacylglycerol-enriched VLDL particles are more atherogenic, as indicated by their significant association with endothelial dysfunction [162], and their preferential uptake by macrophages, leading to the formation of foam cells in vessel walls [179].

Pathophysiology of increased hepatic VLDL production in type 2 diabetes



LDL

In patients with type 2 diabetes, the mean LDL-cholesterol level is comparable or slightly elevated relative to that in individuals without diabetes[141,143,144]. However, the catabolism of LDL is substantially reduced[163,180], inducing a longer duration of LDL in plasma that may enhance lipid deposition within artery walls. In patients with type 2 diabetes, the number of LDL B/E cell-surface receptors is significantly decreased, which may be due to reduced insulin-mediated expression and could be responsible for observed impairments in LDL catabolism [181]. It has also been suggested that reduced LDL catabolism could be partly due to a decreased affinity of LDL for its receptor following ApoB glycation[182].

Increased glycation of LDL is observed in patients with type 2 diabetes mellitus as a consequence of hyperglycemia [183]. Glycated LDL has decreased affinity for LDL B/E receptors [184] and is preferentially taken up by macrophages, leading to the formation of foam cells [185].

Another lipoprotein modification observed in type 2 diabetes is increased LDL oxidation which has marked atherogenic potential. Patients with type 2 diabetes show increased oxidation of LDLs and have an increased number of oxidised LDL particles in their plasma [143].

Oxidised LDLs demonstrate a decreased affinity for the LDL receptor, and are preferentially taken into macrophages via specific oxidised LDL receptors prior to foam cell development[86]. In addition, they have chemoattractant effects on monocytes by increasing the formation of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), by endothelial cells, and by stimulating the formation of cytokines, such as TNFα or IL-1, by macrophages, which amplifies the inflammatory atherosclerotic process [186].

Small, dense, triacylglycerol-rich LDL particles (known as subclass B particles) are more common in type 2 diabetes [187]. This is mainly related to hypertriglyceridemia, and $VLDL_{1.}$ Triacylglycerol is the major predictor of LDL size in patients with type 2 diabetes and in non-diabetic individuals [141]. The characteristic hypertriglyceridemia seen in patients with type 2 diabetes stimulates CETP, leading to the preferential formation of triacylglycerol-rich small, dense LDL particles than the larger ones[178]. The presence of small, dense LDL particles has been reported to be associated with increased cardiovascular risk and progression of atherosclerosis [188].

Small, dense LDL particles are more atherogenic. They are more likely to undergo glycation and oxidation than larger LDL particles,

which promotes the generation of foam cells [143,189]. In addition, they show increased affinity for intimal proteoglycans, which may favour the penetration of LDL into the arterial wall [190].

HDL

Plasma levels of HDL-cholesterol and ApoA-I are decreased in patients with type 2 diabetes [141-143].The proportion of circulating smaller HDL particles (HDL_3) is raised particularly while there are fewer large HDL particles (HDL_2). Hence, the overall number of HDL particles is reduced [178]. Reduced levels of HDL_2 in patients with type 2 diabetes have been reported to be associated with both hypertriglyceridemia and obesity [191].

Kinetic studies using radioisotopes [192] and stable isotopes [193] have reported that the decrease in HDL-cholesterol in patients with type 2 diabetes is due to increased catabolism of HDL. The activity of hepatic lipase, the enzyme controlling HDL catabolism, is enhanced in insulin-resistant states, which seems to be responsible for the observed increase in HDL catabolism [194]. Hypertriglyceridemia is a major contributing factor to the accelerated HDL catabolism seen in type 2 diabetes. It has been recently observed that both raised $VLDL_1$ production and decreased $VLDL_1$ catabolism are independent factors associated with increased

HDL catabolism in insulin-resistant states [195]. It is suggested that the increased pool of triacylglycerol-rich lipoproteins (mainly $VLDL_1$), observed in type 2 diabetes, promotes CETP-mediated triacylglycerol enrichment of HDL particles and, as a consequence, enhances HDL catabolism, since HDL-rich particles are very good substrates for hepatic lipase.

The reduction in phospholipids in large HDL particles in patients with type 2 diabetes is associated with increased arterial stiffness. Patients with type 2 diabetes also have reduced ApoE content in large HDL particles, which may have an atherogenic effect, since large, ApoE-rich HDL usually prevents LDL binding to proteoglycans in the vessel wall [196]. ApoM, which is mainly associated with HDL, is decreased in patients with type 2 diabetes due to diabetes-associated obesity [196,197]. ApoM mediates the enrichment in sphingosine-1-phosphate in HDL, which promotes arterial vasodilation by stimulating endothelial nitric oxide formation [198].

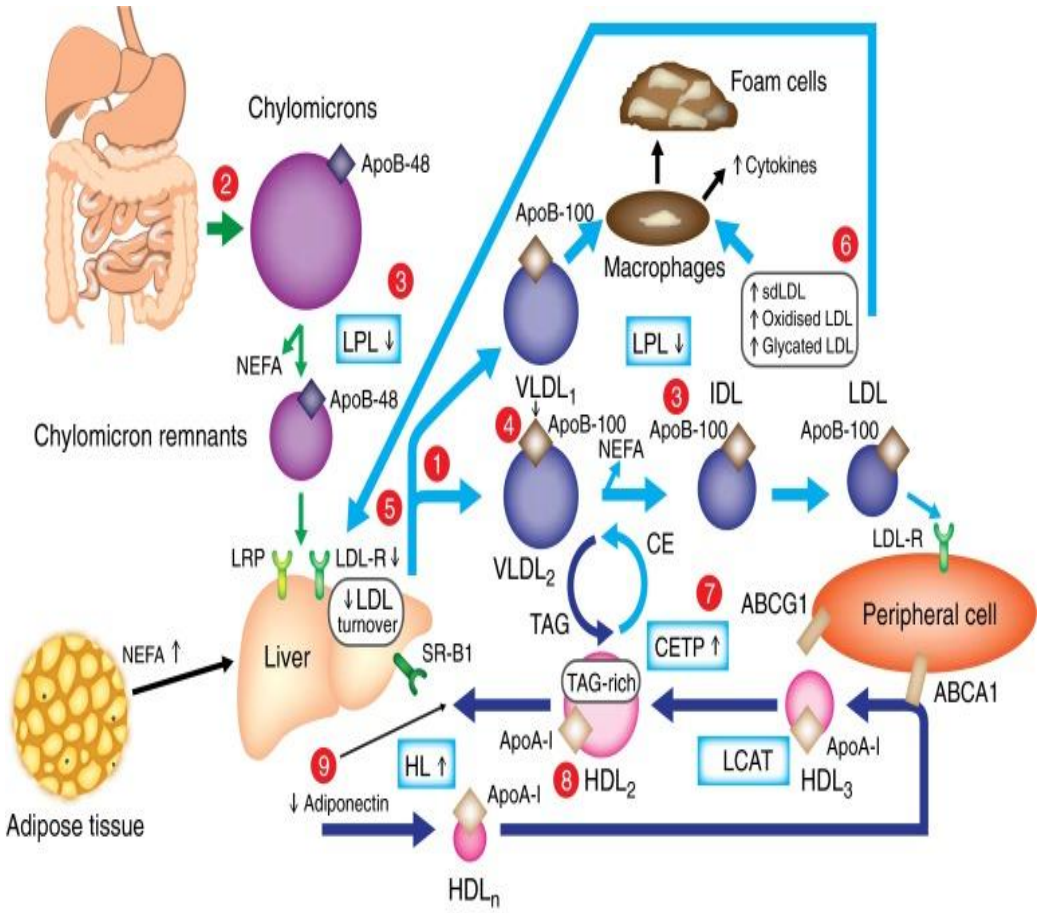
In patients with type 2 diabetes, HDL has a reduced capacity to promote ex vivo cholesterol efflux from cells. This may be due to decreased expression of ABCA1, which is the membrane transporter responsible for the first step of cholesterol transfer from cell membranes

to HDL [199]. Furthermore, glycation of ABCA1 has been shown to reduce its activity [200].

The ability of HDL to counteract the inhibition of endothelium-dependent vasorelaxation induced by oxidised LDL is impaired in type 2 diabetes. This reduction in HDL vasorelaxant effect is inversely correlated with HDL triacylglycerol content [201].

As a result, HDL in patients with type 2 diabetes has a weaker stimulatory effect on endothelial nitric oxide synthesis [202].

MAIN LIPID ABNORMALITIES IN TYPE 2 DIABETES



CE-cholesterol esters; CETP - cholesteryl ester transfer protein; sdLDL - small, dense LDL; HDLn - nascent HDL; HL- hepatic lipase; HSL - hormone-sensitive lipase; LPL-lipoprotein lipase; LDL-R- LDL receptor; SR-B1-scavenger receptor B1; TAG- triacylglycerol.

Main lipid abnormalities in type 2 diabetes.

Triacylglycerols (hypertriglyceridemia, qualitative and kinetic abnormalities):

(1) raised VLDL production (mostly VLDL1)

(2) increased chylomicron production

(3) decreased catabolism of both chylomicrons and VLDL (diminished LPL activity)

(4) increased production of large VLDL (VLDL1), preferentially taken up by macrophages;

LDL (qualitative and kinetic abnormalities):

(5) reduced LDL turnover (decreased LDL B/E receptor)

(6) increased number of glycated LDL, small, dense LDL (TAG-rich) and oxidised LDL, which are preferentially taken up by macrophages**;**

Low HDL-cholesterol (qualitative and kinetic abnormalities):

(7) raised CETP activity (increased transfer of triacylglycerols from TAG-rich lipoproteins to LDLs and HDLs),

(8) higher TAG content of HDLs, promoting HL activity and HDL catabolism,

(9) decreased plasma adiponectin favouring the increase in HDL catabolism.

Lipid transfer proteins

The qualitative lipoprotein abnormalities observed in patients with type 2 diabetes, such as increased triacylglycerol content of LDL and HDL particles, indicate increased CETP activity [203]. The main factor responsible for the increased CETP activity in type 2 diabetes is the augmented pool of triacylglycerol-rich lipoproteins (mainly VLDL), which directly stimulate CETP. However, hyperglycemia per se could also activate CETP, since glycation of lipoproteins increases CETP activity [204]. In addition, a recent study in patients with diabetes mellitus reported that glycation of ApoC-I decreases its inhibitory effect on CETP [205]. Increased PLTP mass and PLTP activity have also been observed in patients with type 2 diabetes [206], and this is associated with increased intima–media thickness [207].

DYSLIPIDEMIA AS CARDIOVASCULAR RISK FACTOR IN TYPE 2 DM

Dyslipidemia is a disorder which arises as a result of abnormalities in the plasma lipoproteins. The lipid abnormalities in diabetes include quantitative changes such as increase in very low density lipoprotein (VLDL) synthesis and increase in low density lipoprotein-C (LDL-C) levels and decrease in high density lipoprotein C (HDL-C) level.

Qualitative changes consists of increase in triglyceride (TG), LDL-C and decrease in HDL-C, non-enzymatic glycation of LDL and non-enzymatic glycation of high density lipoprotein (HDL)[208]. Due to the abnormalities in lipoproteins, diabetes mellitus is associated with cardiovascular and cerebrovascular morbidity and mortality [209].

In type 2 diabetes mellitus, enhanced lipolysis leads to high free fatty acid levels in plasma and consequent accumulation of fat in liver. Due to this, more Acetyl-COA is now available which cannot be efficiently oxidized by TCA cycle because the availability of oxaloacetate is limited. The stimulation of gluconeogensis is responsible for the depletion of oxaloacetate. The excess of Acetyl-COA therefore is diverted to cholesterol leading to hypercholesterolemia.

There is hyperlipidemia, especially an increase in non-esterified free fatty acids,triglycerides and cholesterol. Other factors which are responsible for hypercholesterolemia are low fibre diet, lack of exercise, sedentary and inactive life style, high energy intake tends to obesity, stress etc. Lipid abnormalities that occurs in these situations are hypertriglyceridemia, low levels of HDL and increased of LDLcholesterol and oxidative damage. Glucose can undergo autoxidation and produce free radicals which can damage vascular function. [209,210]

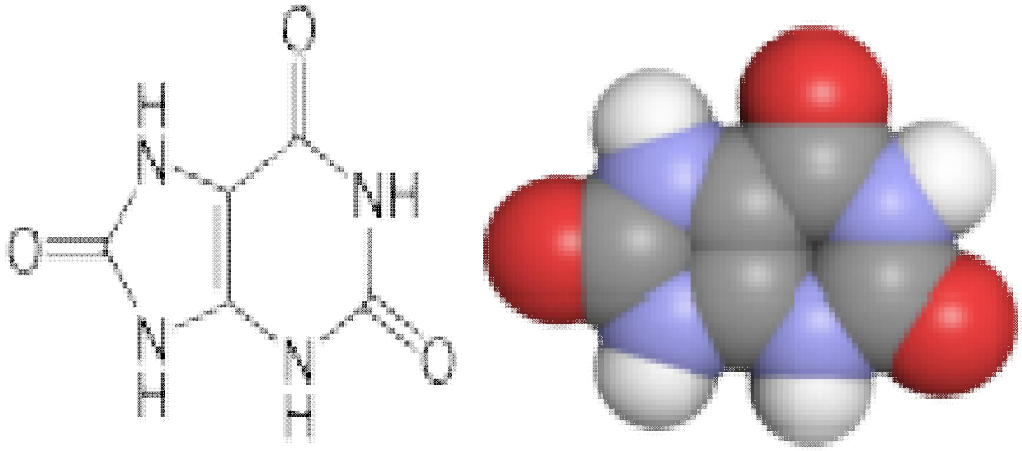
Patients with type 2 diabetes mellitus are at greater risk of developing vascular diseases because of lipid changes.It has been well observed that controlling diabetes and lipid levels provide great benefit to diabetic patients. Lipid abnormalities in type 2 diabetic patients are increased serum triglycerides, very low density lipoproteins, low density lipoproteins and lowered high density lipoproteins.

Insulin resistance syndrome has been widely found that it is associated with type 2 diabetes mellitus in which high density lipoprotein is quite reduced leading to cardiovascular complication.[211-213]

URIC ACID

It is a product of the metabolic breakdown of purine nucleotides. Serum uric acid is one of the important contributors of antioxidant capacity and acts as antioxidant in the early stages of atherosclerosis [214]. However, during later stages of atherosclerosis when the uric acid level is elevated, it functions as pro-oxidant rather than antioxidant. The antioxidant and oxidant function of uric acid mainly depends on various factors such as depletion of antioxidants, surrounding oxidant environment, acidity etc. All these factors which make uric acid act as a pro-oxidant is found in the accelerated atherosclerotic-vulnerable plaque of the intima of the arteries [214].

STRUCTURE OF URIC ACID (2,6,8,TRI OXO PURINE)



HYPERURICEMIA IN TYPE 2 DM

Hyperuricemia is a metabolic consequence originating with a wide range of etiology concerned with increased production or decreased excretion of uric acid and also as a combination of both[215]

Hyperuricemia is probably associated with glucose intolerance due to various mechanisms, however, the most important is the association between insulin and renal resistance to absorption of urates[216-218] .

Hyperinsulinemia as a consequence of insulin resistance causes an increase in serum uric acid concentration by both reducing renal uric acid secretion and accumulating substrates for uric acid production. [219] Biologically uric acid plays an important role in worsening of insulin

resistance by inhibiting the bioavailability of nitric oxide, which is essential for insulin stimulated glucose uptake.

Hyperuricemia is caused by muscle wasting and weight loss in diabetes mellitus. Chronic high glucose concentration causes tissue injury, which in turn leads to increased nonprotein nitrogen substances. This phenomenon may account for increased uric acid levels. [219]

Hyperinsulinemia due to insulin resistance modify handling of uric acid by kidney. Increased activity of HMP shunt linked to insulin resistance cause increase in uric acid level [220].Various epidemiological studies with different study designs had been used to examine the relation between the serum uric acid and coronary artery disease. The positive association with a high risk for coronary artery disease was demonstrated in type 2 DM [221]

For 1mg/dl increase in uric acid level, the CVD risk in type2 diabetes increases by 15-20%**.** It Inhibits NO production by inducing endothelial dysfunction. Hyperuricemia has been presumed to be a consequence of insulin resistance rather than its precursor and has been presumed to be associated with oxidative stress which is related to the development of complications in diabetes[222]

A cohort Study involving 2,726 type 2 diabetic patients, who were followed for a mean period of 4.7 years in Italy, showed that higher Serum Uric acid levels are associated with increased risk of Cardiovascular mortality in type 2 diabetes patients[223].

An Epidemiologic Follow-up Study from 1971 to 1992 conducted in America involving 5926 subjects suggests that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality.[224]

Chronic hyperuricemia has been suggested as independent risk factor for hypertension, metabolic syndrome, chronic kidney disease and cardiovascular disease [225]. So hyperuricemia should be a red flag indicating the overall approach for reducing the risk by global risk reduction program [226]

Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease. Population based studies have shown that hyperuricemia is an independent risk factor for cardiovascular disease (CVD). This association has been found to be particularly robust among

individuals high risk for CVD, including those with obesity, hypertension, diabetes and renal disease.

Hyperuricemia has been reported to be associated with obesity and insulin resistance, and consequently with type2 diabetes. Further, important biological effects of uric acid are related to endothelial dysfunction by inducing anti proliferative effects on endothelium and impairing nitric oxide production and inflammation, through raised C-reactive protein expression. [235]

There are strong evidences that hyperuricemia has been linked with Cardiovascular disease.[236-238]. Hyperuricemia predispose to the development of hypertension and is also thought to result in increased oxidative stress and production of free radicals, which eventually can be the nidus of future cardiovascular disease [239]. Animal model study have proved that uric acid causes dramatic increase in the expression and release of MCP-1,infiltration of macrophages and expression of proinflammatory cytokine TNF-α in the vascular smooth muscles, and thus can eventually lead to atherosclerosis [239].

ASSOCIATION OF HYPERURICEMIA WITH DYSLIPIDEMIA FOR CARDIOVASCULAR RISK IN TYPE 2 DM

A close relationship between hyperuricemia and cardiovascular diseases has been reported in several epidemiological studies [227-230] and correlations between hyperuricemia, dyslipidemia, and diabetes have also been recently reported.[231-233]

Hyperuricemia and Dyslipidemia are metabolic abnormalities frequently associated with type 2 diabetes mellitus patients. Its prevalence depends on the severity of diabetes,glycemic control, nutrition status and other factors. [234]

A cross-sectional Study carried out over a period of 3 months from November 2008 to January 2009 in 601 patients with Type 2 DM at Lagos, Nigeria, concluded that SUA is positively and significantly associated with serum TGL and total cholesterol.[240]

Li Qin et al have reported that raised serum uric acid levels has a strong positive correlation with increased levels of triglyceride, total cholesterol, LDL cholesterol. They have also shown that higher uric acid levels were associated with lower HDL cholesterol level, indicating a negative correlation between them [241,242].

In concurrence with previous reports, the study observed significant positive correlation of serum uric acid with serum triglycerides, total cholesterol, LDL cholesterol, and a significant negative correlation with HDL cholesterol levels.[243,244]

MATERIALS AND METHODS

This study was conducted during the period of July 2016 - December 2016 as a cross sectional study in the department of Diabetology and Department of Biochemistry in Government Kilpauk Medical College, Chennai.

STUDY POPULATION

- **CASES:**

65 patients with type 2 diabetes mellitus on oral hypoglycemic drugs less than five years duration in the age group of 40 years-60 years cases are selected from OPD of department of diabetology, Government Kilpauk Medical College, Chennai.

- **CONTROLS:**

65 healthy non diabetic individuals in the age group of 40 years-60 years, age and sex matched.

INCLUSION CRITERIA:

- Patients with type 2 diabetes mellitus in the age group of 40-60 years.
- Both genders(male & female) are included

- Those who are on treatment with oral hypoglycemic drugs are included.

EXCLUSION CRITERIA:

- Type 1 diabetes mellitus
- Pregnant women with GDM
- Patients on treatment with statins, insulin, uricosuric drugs
- Patients with hypertension
- Individuals with history of alcoholism
- Patients with malignancy (leukemia, lymphoma, myeloma)
- Patients with arthritis, cardiac and renal disease

SAMPLE COLLECTION:

5ml of fasting venous blood was drawn from antecubital vein of patients in a plain vacutainer tube under sterile conditions after fulfilling the selection criteria.

Serum was separated by centrifugation at 3000 rpm for 15minutes and the separated serum was stored at -20^0c for further analysis.

ESTIMATION OF GLUCOSE:

Method : Glucose oxidase- peroxidase method. (GOD/POD) (END POINT METHOD)

Kit used: Erba.

Principle:

In serum, glucose is oxidized to yield gluconic acid and hydrogen peroxide in the presence of glucose oxidase. The enzyme peroxidase catalyzes the oxidative coupling of 4-aminoantipyrine with phenol to yield a colored quinoneimine complex. The intensity of pink colored quinoneimine complex is proportionate to glucose concentration and was measured at 505nm.

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GLUCOSE OXIDASE}} \text{Gluconic Acid} + H_2O_2$$

$$H_2O_2 + \text{Phenol} + \text{4AAP} \xrightarrow{\text{PEROXIDASE}} \text{Quinoneimine complex} + H_2O$$

Reagent composition:

Enzyme reagents and standard:

Ingredients	Concentrations
Glucose oxidase	≥ 20,000 U/L
Peroxidase	≥ 2,000 U/L
Phenol	10 mmol/L
Phosphate buffer	200 mmol/L
Glucose standard	100 mg/dl

Assay procedure: (Semi automated analyzer)

	Blank	Standard	Test
Sample	---	---	10µl
Standard	---	10µl	---
Enzyme reagent	1.0ml	1.0ml	1.0ml

Mixed well after each addition and incubated at 37˚C for 5 minutes and the absorbance was read at 505nm.

Reference range:

Fasting : 70-100 mg/dl

Post prandial : 90-140 mg/dl

ESTIMATION OF BLOOD UREA

Method: UV - GLDH

Kit: Accucare

Principle:

The test is performed as a kinetic assay in which the initial rate of the reaction is linear for a limited period of time. Urea is hydrolysed by urease to NH_3 and CO_2. The NH_3 produced combines with alpha-oxoglutarate and NADH in the presence of glutamate dehydrogenase to produce glutamate and NAD.

$$\text{Urea} + H_2O \xrightarrow{\text{Urease}} 2NH4 + CO2$$

$$NH_4^+ + NADH + H^+ + \text{2-oxoglutarate} \xrightarrow{\text{GLDH}} \text{Glutamate} + NAD^+$$

The initial rate of decrease in absorbance is directly proportional to the urea concentration in the sample. Absorbance is measured at 340nm.

Reagent composition:

Reagent I: buffer reagent

Reagent II: enzyme reagent

Urea standard: 50 mg/dl

4 parts (4 ml) of buffer reagent mixed with one part (1 ml) of enzyme reagent.

Assay Procedure : (Semi auto analyzer)

	Blank	Standard	Test
Sample	---	---	10µl
Standard	---	10µl	---
Enzyme reagent	1.0ml	1.0ml	1.0ml

Mixed well and absorbance measured immediately at 340 nm.

Reference Range:

Serum/ plasmaUrea →15- 40 mg/dl

ESTIMATION OF SERUM CREATININE

Method : Jaffe's Method , Initial rate method

Kit used : Erba

Principle :

Creatinine in alkaline solution reacts with picrate to form an orange-yellow compound. The color is proportional to the concentration of creatinine in the sample when measured at 505nm.

Reagent composition:

Reagent I: Picric acid reagent.

Picric acid – 25.8 mmol/L

Reagent II: Sodium hydroxide reagent.

Sodium hydroxide – 95 mmol/L

Creatinine standard: 2 mg/dl

Reagents were allowed to attain room temperature. Equal volumes of reagent 1 and reagent 2 were mixed, waited for 15 minutes before use .

Procedure:

	Blank	Standard	Test
Sample	---	---	100µl
Standard	---	100µl	---
Enzyme reagent	1.0ml	1.0ml	1.0ml

To 1 ml of the reconstituted reagent 100µl of the serum was added and absorbance (A1) taken at 20 seconds after mixing was noted & final absorbance (A2) at 80 seconds were measured.

Reference Range:

Males**:** 0.7 - 1.4 mg/dl

Females**:** 0.6 - 1.3mg/dl

TOTAL CHOLESTEROL (CHOD-POD)

Method: Cholesterol Oxidase Peroxidase Method. End point assay

Kit: Accucare

Principle : Cholesterol esters are hydrolyzed to produce cholesterol. Hydrogen peroxide is then produced from oxidation of cholesterol by cholesterol oxidase. The indicator quinoneimine is formed

from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxide. The sorbance of the red quinoneimine dye is proportional to the concentration of cholesterol in the sample.

Cholesterol esters + H_2O ⟶ Cholesterol+ Free fatty acids

Cholesterol + O_2 ⟶ cholest-4-en-3-one + H_2O_2

$2H_2O_2$ + Phenol + 4-Aminoantipyrine ⟶ Quinoneimine dye+4H_2O

REAGENTS:

Reagent	**Composition**	**Concentration**
Cholesterol reagent	PIPES pH 6.9	90mmol/L
	Phenol	26mmol/L
	Cholesterol esterase	1000U/L
	Cholesterol oxidase	300U/L
	Peroxidase	650U/L
	4-aminophenazone	0.4mmol/L

System Parameters

Mode ---------- Endpoint

Reaction ---------- Ascending

Wavelength ---------- 505nm

Blank with ---------- Distilled water

Sample volume ---------- 10µl

Reagent volume ---------- 1000µl

Incubation time ----------10 minutes at 37°C

Concentration of standard ---------- 200 mg/dl

Sensitivity ---------- 0.113

Linearity ----------1000 mg/dl

Units----------mg/dl

Sample storage and stability: At 2-8°C for 7 days or freezing at -20^{0}C for 3 months

Manual assay procedure

	Blank	**STD**	**Sample**
Sample	-	-	10 µl
Standard	-	10 µl	-
Reagent	1000 µl	1000 µl	1000 µl

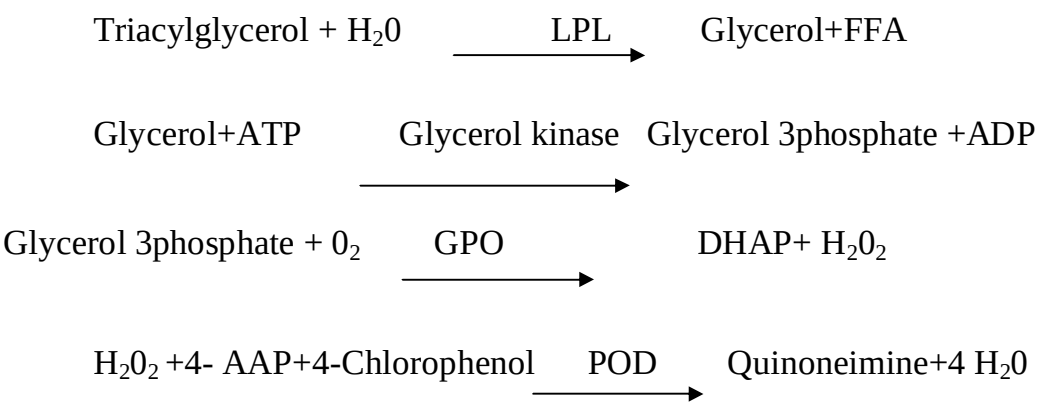
Mix and incubate for 5 minutes at 37°C.Measure absorbance of sample (AT) and standard (AS) against reagent blank at 505nm.The colour is stable for at least 30 minutes.

Linearity: The method is linear upto a concentration of 1000mg/dl. Dilute samples above this concentration 1:1 with 0.9% saline. Samples exceeding 1000mg/dl are diluted and re-assayed. The results were multiplied by dilution factor.

TRIACYLGLYCEROL

Method : Glycerol phosphate oxidase peroxidase method: End point assay

Principle: Determination of triglycerides after enzymatic splitting with lipoprotein lipase. Indicator is quinoeimine, which is generated from 4-chlorphenol by hydrogen peroxide under the catalytic action of peroxidase.



REAGENTS COMPOSITION:

Goods buffer pH 7.2	-	50nmol/l
4-Chlorphenol	-	4mmol/l
ATP	-	2mmol/l
Mg^{2+}	-	15 mmol/l
Glycerol Kinase	-	≥ 0.4 KU/l
Peroxidase	-	≥ 2kU/l
Lipoprotein lipase	-	≥ 2kU/l
4-Aminoantipyrine	-	0.5mmol/l
Glycerol -3-Phosphate oxidase	-	≥ 0.5U/l
Standard	-	200mg/dl

Specimen Stability: 2 days at 20-25^{0}C, 7 days at 4-8 ^{0}C, 3 months at -20^{0}C

ASSAY PARAMETERS:

Mode ----------Endpoint

Slope of reaction----------Increasing

Wave length----------505nm

Flow-cell temperature----------37^0C

Sample volume----------10µl

Reagent volume----------1000µl

Incubation time----------10 mins at 37^0C

Concentration of standard----------200 mg/dl

Linearity----------1000mg/dl

Units----------mg/ml

TEST PROCEDURE:

	Blank	**Standard**	**Test**
Serum			10µl
TAG Standard	-----	10µl	
TAG reagent	1000µl	1000µl	1000µl
Distilled water	10µl		

Mixed well and incubated at 37^0C for 10 minutes and measured the absorbance of standard (S) followed by test reagent (T) against reagent blank using 505 nm.

LINEARITY: The kit is linear upto 1000mg/dl. Samples exceeding 1000mg/dl were diluted and reassayed. The results were then multiplied by dilution factor.

REFERENCE RANGE:

Male : 60 -165 mg/dl

Female : 40 – 140 mg/dl

LDL CHOLESTEROL :

Using Friedwalds Equation :

LDL Cholesterol = Total Cholesterol – HDL Cholesterol – Triglyceride/5

Normal value : <100 mg/dl ---optimum

HDL-CHOLESTEROL

Method: Precipitation End Point Method

Principle: Chylomicrons, VLDL and LDL are precipitated by addition of phosphotungstic acid and magnesium chloride. After centrifugation, the high density lipoprotein (HDL) fraction recovered as clear supernatant. Its cholesterol content is estimated by enzymatic method.

Serum+ Phosphotungstic acid ⟶ Supernatant (HDL)+Precipitates

REAGENT COMPOSITION:

Reagent – 1	Enzyme chromogen
Reagent -2	Precipating reagent
HDL- Cholesterol standard	50mg/dl

Specimen Stability: Fresh fasting and nonhaemolysed serum samples were collected and stored at 2-8^{0}C

System parameters:

Reaction type-----Endpoint

Slope of reaction--Increasing

Wave length---------505nm

Flow-cell temperature----37^{0}C

Sample volume(for precipitation)----200µl

Precipitation Reagent 2----200µl

Sample volume(Supernatant)----50µl

Reagent 1 volume-----1.0ml

Incubation time-----10 mins at 37^{0}C

Concentration of standard----50 mg/dl

Dilution factor--2

Linearity---120mg/dl

Procedure: Step I- HDL cholesterol separation:

HDL cholesterol is precipated by addition of phosphotungstic acid. To 200µl of serum, 200 µl of HDL precipitating reagent added. Mixed well and kept at room temperature(15-30^{0}C) for 10 minutes and then centrifuged at 3000 rpm for 10 minutes and separated clear supernatant. The supernatant was used for HDL- cholesterol sestimation.

Step 2: HDL-Cholesterol estimation:

3 clean glass test tubes were taken, labeled as blank (B), standard(S) and Test (T).

Reagnet	**Blank**	**Standard**	**Test**
Enzyme reagent	1.0ml	1.0ml	1.0ml
HDL- Cholesterol standard	**--**	50µl	**---**
Supernatant from step 1	**---**	**--**	50µl
Distiled water	50µl		

Mixed well, incubated for 10 minutes at 37^0C and measured the absorbance of standard(S) followed by test(T) against reagent blank at 505nm

Reference Range:

Male : 30 - 55 mg/dl

Female : 45 - 65 mg/dl

URIC ACID

Method: URICASE/POD, End point assay

Principle: Uric acid is oxidized to Allantoin and hydrogen peroxide by the enzyme uricase. In the presence of peroxidase, released hydrogen peroxide is coupled with aniline derivative and 4-amino antipyrine to form coloured chromogen complex. Absorbance of coloured dye is measured at 550nm and is proportional to the concentration of uric acid in the sample.

$$\text{Uric acid} + 2H_2O \xrightarrow{\text{Uricase}} \text{Allantoin} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{Aniline derivative} + 4\text{ AAP} \xrightarrow{\text{POD}} \text{Chromogen complex} + H_2O$$

Reagents:

S.NO	REAGENT	COMPOSITION
1.	Uric acid mono Reagent	Triss buffer(pH 8.25) Uricase TBHB 4-Aminoantipyrine Peroxidase
2.	Uric acid standard	Uric acid Stabilizer Preservative

Reagent storage and stability: Reagents are stable at 2-8^0 C

Sample:

	Storage at	Stability
SERUM	Room temperature(15-30^{0}C)	3 Days
	2-8^{0}C	7 Days
	-20^{0}C	6 Months

Assay Parameters:

Mode ---------- End Point

Wave Length ---- 550 nm

Flow Cell temperature ---- 37^0C

Optical path length -------- 1 cm

Blanking ---------- Reagent Blank

Sample Volume ----- 20 µl

Reagent Volume ---- 1000 µl

Incubation time -------5 min

Concentration of standard ----- 6mg/dl

Stability of final colour ------- 15 min

Permissible Reagent Blank Absorbance ----- <0.4AU

Linearity ------ 25mg/dl

Units ---------- mg/dl

Procedure:

	Blank	**Standard**	**Test**
Serum	-	-	20 µl
Reagent 2	-	20 µl	-
Reagent 1	1000µl	1000 µl	1000 µl

Mixed well. Incubated at 37^0C for 5 minutes.

The analyzer was programmed as per assay parameters.

1. The analyzer was blanked with reagent blank.
2. Absorbance of standard followed by the test is measured.
3. Results were calculated as per given calculation formula

Reference range:

Males : 2.5 - 6.5 mg/dl.

Females : 3.5 – 7.0 mg/dl

RESULTS AND STATISTICAL ANALYSIS

This study done to evaluate serum Uric acid and Lipid profile in Type 2 Diabetes Mellitus patients was done in total of 130 subjects, of which 65 with known diabetes mellitus were taken as cases and 65 individuals without diabetes mellitus were taken as controls.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, Version 20.0

- If the P value is 0.000 to 0.010 then denoted by **,it imply significant at 1 level (Highly Significant)
- If the P value is 0.011 to 0.050 then denoted by *,it imply significant at 5 level (Significant)
- If the P value is 0.051 to 1.000 then no star, it imply Not Significant at 5 level (Not Significant)
- P value of <0.05 is considered significant
- Pearson's correlation was used

TABLE 1

AGE BETWEEN CASES AND CONTROLS

	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
Age in years	Control	65	48.55	5.403	.670	0.215
	Cases	65	49.74	5.441	.675	0.215

Age based distribution into cases and controls have showed no statistically significant difference.

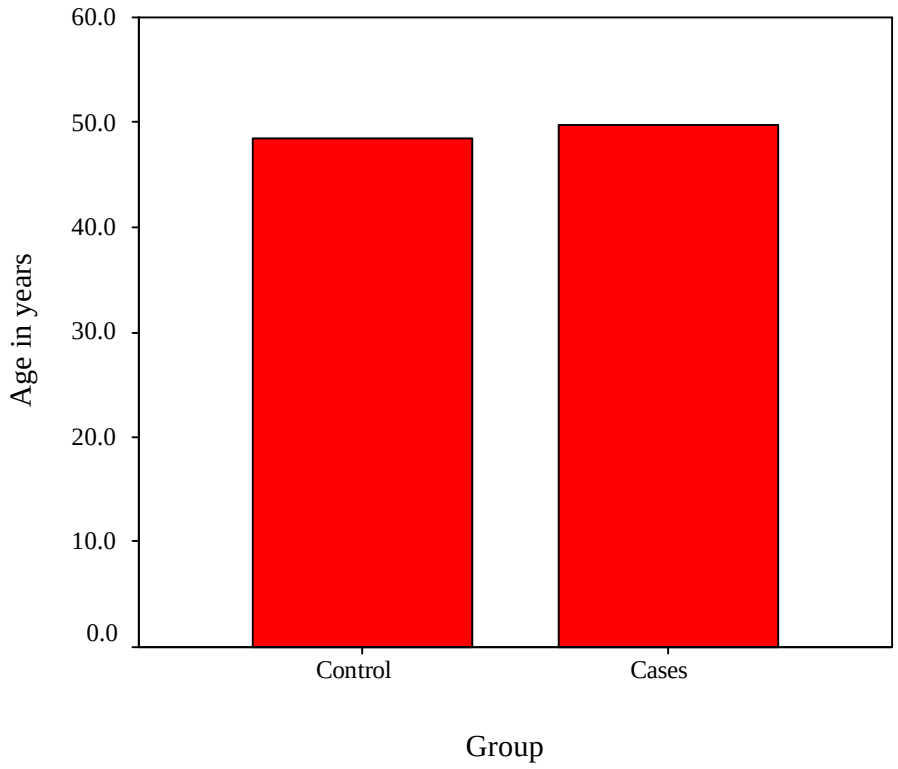


TABLE 2

COMPARISON OF FASTING BLOOD SUGAR BETWEEN CASES AND CONTROLS

	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
Glucose	Control	65	91.31	12.993	1.612	0.001**
	Cases	65	174.00	39.502	4.900	

The mean glucose value of cases is 174.00 and that of controls is 91.31 and the P value is 0.001 which is statically highly significant.

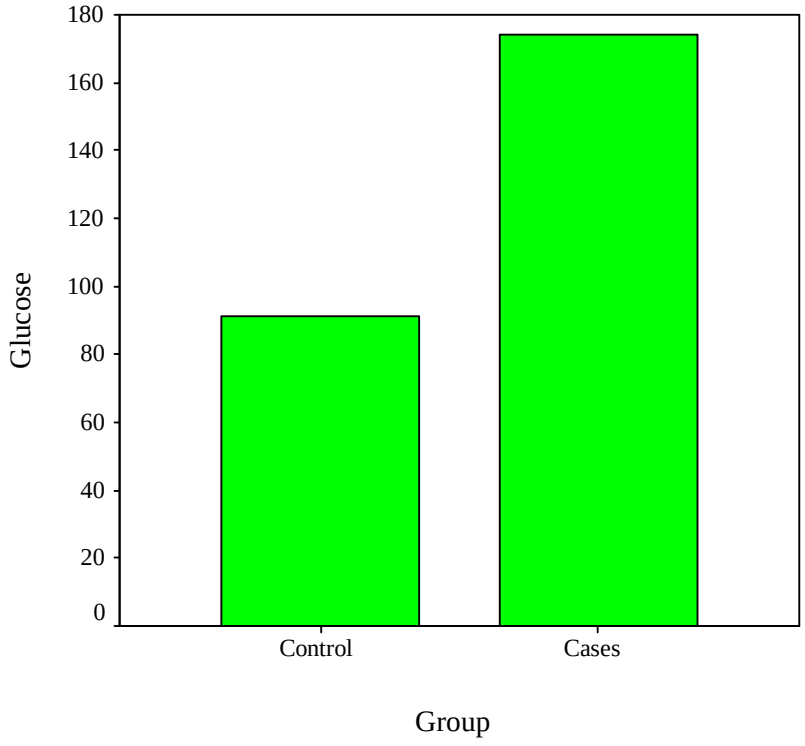


TABLE 3

COMPARISON OF UREA BETWEEN CASES AND CONTROLS

	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
Urea	Control	65	20.23	3.673	.456	0.001**
	Cases	65	24.54	5.951	.738	

The mean value of urea for control is 20.23 and for case is 24.54 and the P value is 0.001 which is statistically significant.

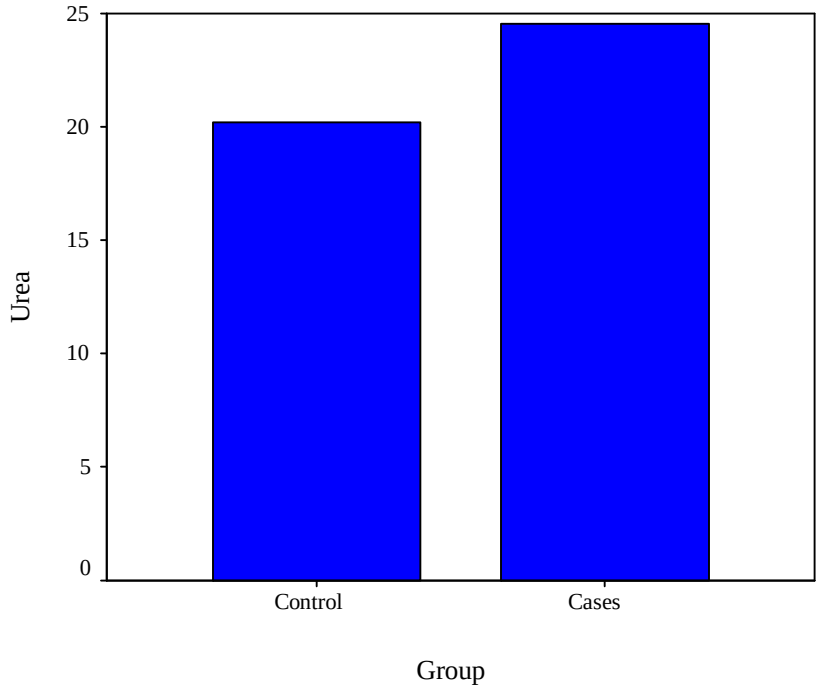


TABLE 4

COMPARISON OF CREATININE BETWEEN CASES AND CONTROLS

Creatinine	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
	Control	65	0.940	.1599	.0198	0.019*
	Cases	65	1.011	.1786	.0222	

The mean value of creatinine for control is 0.940 and that of case is 1.011 and the P value is 0.019 which is statistically significant.

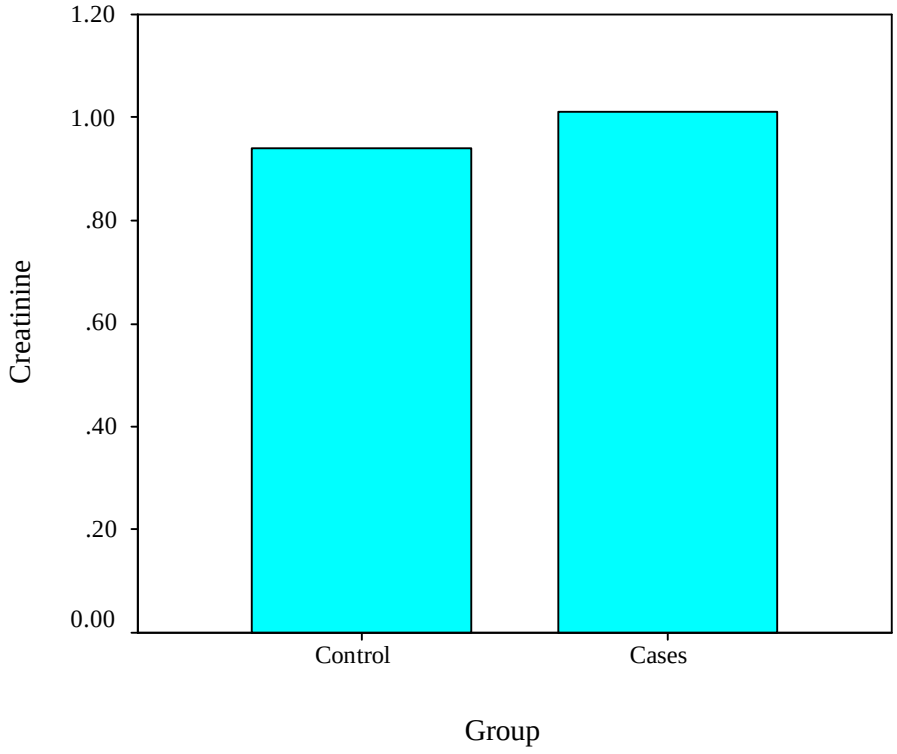


TABLE 5

COMPARISON OF TOTAL CHOLESTEROL BETWEEN CASES AND CONTROLS

	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
Total Cholesterol	Control	65	142.20	24.627	3.055	0.001**
	Cases	65	218.00	42.059	5.217	

Comparison between cases and control groups for total cholesterol shows highly significant difference in mean and the P value is 0.001 .

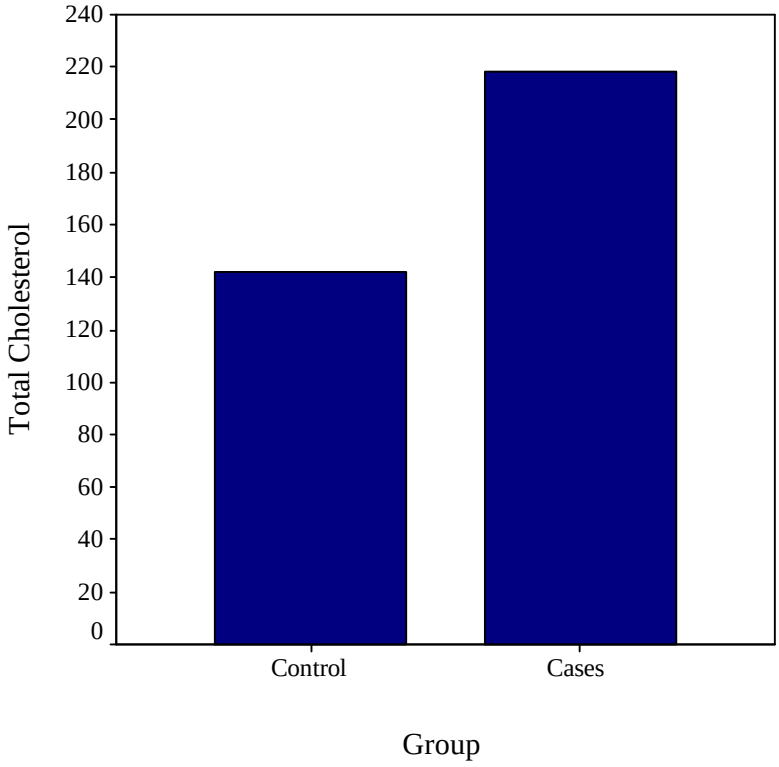


TABLE 6

COMPARISON OF TGL BETWEEN CASES AND CONTROLS

TGL	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
	Control	65	103.00	27.295	3.385	0.001**
	Cases	65	176.78	63.605	7.889	

The mean value of TGL for control is 103.0 and that of case is 176.7 and the P value is 0.001 which is statistically highly significant.

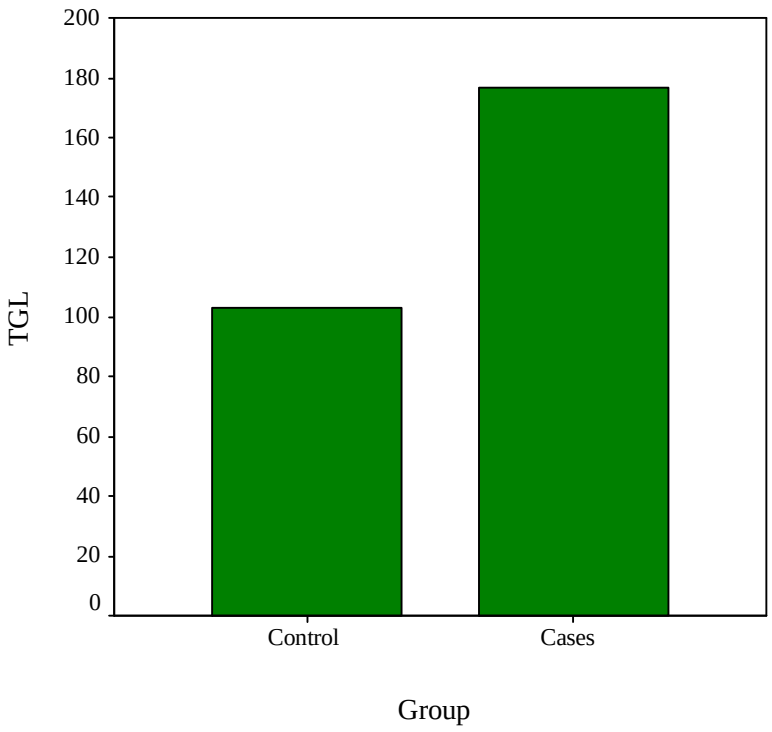


TABLE 7

COMPARISON OF HDL BETWEEN CASES AND CONTROLS

HDL	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
	Control	65	49.92	4.25	0.527	0.001**
	Cases	65	24.20	5.51	0.68	

Statistically significant difference was observed between the mean value of HDL for control and cases and the P value is 0.001 which is statistically highly significant.

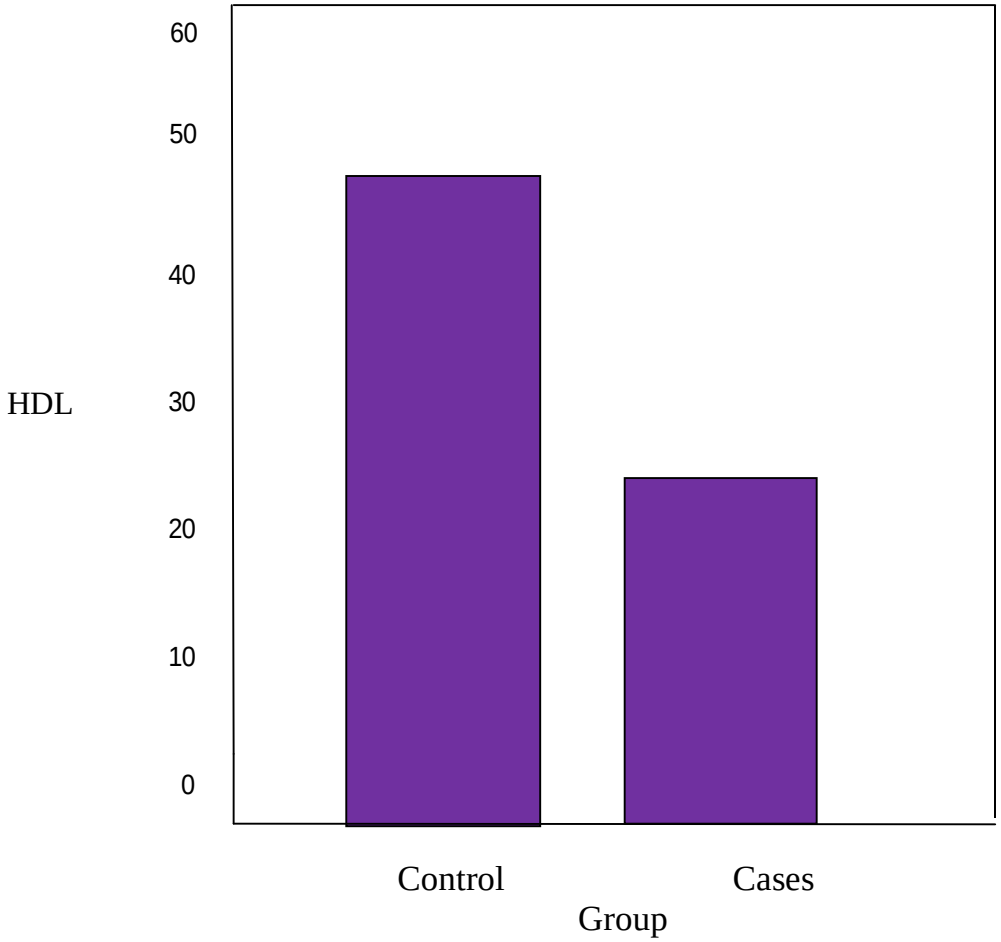


TABLE 8

COMPARISON OF LDL BETWEEN CASES AND CONTROLS

LDL	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
	Control	65	71.677	23.6155	2.9291	0.001**
	Cases	65	155.089	40.6039	5.0363	

The mean value of LDL for control is 71.67 and that of case is 155.08 and the P value is 0.001 which is statistically highly significant.

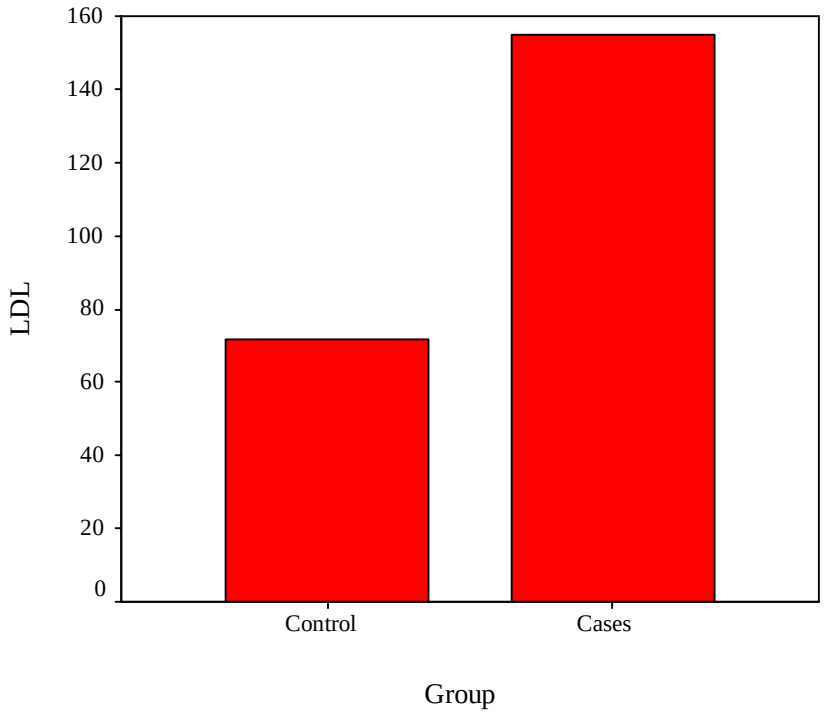
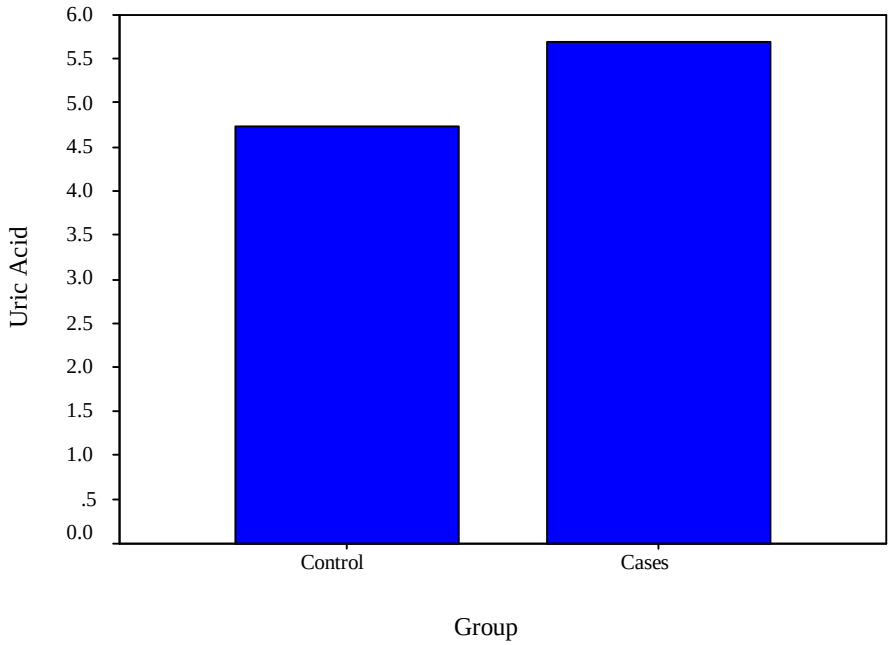


TABLE 9

COMPARISON OF URIC ACID BETWEEN CASES AND CONTROLS

	Group	N	Mean	Std. Deviation	Std. Error Mean	P Value
Uric Acid	Control	65	4.740	0.5249	0 .0651	0.001**
	Cases	65	5.689	1.6384	.2032	

Comparison of uric acid levels between cases and control groups showed statistically significant difference in the mean and the P value is 0.001 which is statistically highly significant.



PEARSON CORRELATION BETWEEN SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS

	R –VALUE	P -VALUE	SIGNIFICANCE
Uric acid vs.Total cholesterol	0.498	0.0001**	SIGNIFICANT
Uric acid vs.TGL	0.254	0.04*	SIGNIFICANT
Uric acid vs.LDL	0.448	0.0001**	SIGNIFICANT
Uric acid vs.HDL	-0.292	0.018*	SIGNIFICANT

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

This table shows correlation between serum uric acid and lipid profile in type 2 Diabetes mellitus. Total cholesterol, TGL and LDL were positively correlated with serum uric acid level and the correlation was statistically significant. High density lipoprotein cholesterol(HDL) was negatively correlated with serum uric acid and the correlation was statistically significant.

DISCUSSION

In this cross sectional study, 65 patients with type 2 diabetes mellitus were taken as cases and 65 healthy individuals were taken as controls. This study evaluated the levels of serum Uric acid and Lipid profile in type 2 diabetes and compared them with healthy controls. The serum uric acid level was correlated with lipid profile in type 2 DM.

The serum uric acid level was found to be increasd in diabetic patients than the healthy individuals and was statistically significant . The serum levels of total cholesterol, TGL, LDL were also raised in diabetic patients when compared with healthy controls and was statiscally significant. But the level of serum HDL was significantly decreased in type 2 diabetes than the healthy control group.

The study shows a normal renal profile in the patient and the control group, which signifies that the hyperuricemia under study is not due to decreased excretion of uric acid.

The study proves a statistically significant positive correlation ($p < 0.05$) between serum uric acid and Total Cholesterol, TGL and LDL and a significant negative correlation ($p < 0.05$) between serum uric acid and HDL. Therefore, it is inferred that hyperuricemia is associated with dyslipidemia in type 2 Diabetes Mellitus and these patients are at a high risk for developing CVD.

The increase in uric acid levels observed in the present study indicates a definite rise in uric acid levels in diabetic patients with a close relationship to cholesterol levels. The observed increase in uric acid levels in type-2 diabetic patients indicates a positive relationship of uric acid levels with cholesterol levels in type-2 DM subjects suggesting, the rise in uric acid parallels the increase in cholesterol levels [245].

Many life threatening complications of type-2 diabetes mellitus specifically micro angiopathy have been attributed to diabetes induced dyslipidemia. As there is a parallel rise in uric acid along with cholesterol levels in type-2diabetic subjects, an estimation of uric acid levels in serum may be an additional significant criteria to assess dyslipidemia as well as to control the dyslipidemia induced complications in type-2 diabetes mellitus [245].

The morbidity and mortality due to cardiovascular complications is higher in type 2 diabetes. Studies on the risk factors which increase the prognostic efficiency for cardiovascular risk in diabetic subjects are very few. In this study, there is increase in Total Cholesterol,LDL-Cholesterol, Triacylglycerol and decrease in HDL-Cholesterol in diabetic cases compared to healthy indicating atherosclerotic changes in

diabetics.Serum uric acid levels were found to be increased in diabetic subjects compared to non diabetic healthy individuals[246].

These results agree with the results obtained in a study done by Safi et al [247], who found the average level of serum uric acid in the diabetic patients was 6.07 mg/dl as compared to 5.01 mg/dl in the control group. It was observed that serum uric acid is positively associated with type 2 diabetes mellitus and the association was relatively more significant in patients with hyperlipidemia. Also these results were comparable to similar studies performed by different research workers.[248-251]

In the present study all lipid fractions with exception to HDL are significantly elevated in patients with type 2 diabetes, supporting the fact that high morbidity and mortality may be due to derangement in lipid profile leading to metabolic complications. Uric acid can promote LDL oxidation thereby triggering the progression of atherosclerosis by stimulating granulocyte adherence to the endothelium.

High range of glycaemia can promote non enzymatic glycosylation of LDL which in turn can be phagocytosed into the arterial wall independent of receptor mechanism [252,253] .Phagocytosed uric acid can transverse through dysfunctional endothelium, this in turn leads to plaque

formation. [254,255] Diabetics with elevated uric acid levels are at increased risk for developing coronary artery disease [256].

Strength of present study- simple cost effective biochemical test like uric acid is used, which can guide the deterioration in glucose metabolism instead of using complex tests for measurement of insulin resistance. Uric acid level can also guide as a marker of cardiovascular disease which is the commonest cause of mortality in diabetes mellitus[257].

Hyperglycemia is a well-known risk factor for hyperuricemia [259] and also hyperuricemia is a risk factor for the development of diabetes. Such counter influence leads to a vicious cycle, which may drive the development of co-morbidities such as Cardiovascular disease (CVD) in general and Coronary artery disease (CAD) in specific.

In our study, diabetic patients had higher total cholesterol, triglycerides, LDL cholesterol and lower HDL cholesterol than nondiabetic healthy individuals, which is consistent with published reports[258].We also observed higher serum uric acid levels among diabetics than nondiabetic healthy individuals with significant positive correlation between serum uric acid levels and hyperlipidemia.

CONCLUSION

In the present study, the levels of serum uric acid and serum lipid profile were evaluated in type 2 Diabetes mellitus patients and healthy individuals. The serum levels of Uric acid, Total cholesterol, TGL, LDL were raised and the High density lipoprotein cholesterol was decreased in type 2 diabetic cases when compared to healthy control group indicating atherosclerotic changes in type 2 diabetes mellitus patients.

Also there is a significant positive correlation between the levels of serum uric acid with total cholesterol, TGL, LDL and a significant negative correlation between serum uric acid with HDL in type 2 DM.

The present study proves that hyperuricemia is positively associated with dyslipidemia in type 2 DM. As there is a parallel rise in uric acid along with total cholesterol, TGL, LDL levels in type-2 diabetes patients, the estimation of serum uric acid along with serum lipid profile is highly beneficial in type-2 diabetes mellitus patients to assess the dyslipidemia induced cardiovascular complications.

Hyperuricemia and dyslipidemia are significant risk factors which can lead to possible cardiovascular disease and increase the morbidity and mortality in type 2 DM.So treatment of hyperuricemia and dyslipidemia

may prevent or decrease the development of cardiovascular disease in type2 DM. Further research is needed to determine the assessment and treatment of hyperuricemia and dyslipidemia for reducing the risk of cardiovascular disease in type 2 DM.

LIMITATIONS OF THE STUDY

- The sample size is relatively small, which was not enough to correlate serum uric acid with other parameters like fasting blood glucose,urea and creatinine
- Selection of individuals with prediabetic state like impaired fating glucose, impaired glucose tolerance also would have provided more information regarding the association of serum uric acid with progression of type 2 diabetes mellitus
- A large scale study taking into account of body mass index, impaired fasting glucose (IFG), impaired glucose tolerance(IGT),metabolic syndrome is however needed to avail a better understanding of this association between serum uric acid and dyslipidemia.

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INSTITUTIONAL ETHICS COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 19/2016 Dt: 20.06.2016
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval " EVALUATION OF SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS"- For Project Work submitted by Dr.C.Gunasundari, Post Graduate in MD (Bio-Chemistry), Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN 8/8/16
Govt.Kilpauk Medical College,
Chennai – 10.
3/8/16

ANNEXURE

PATIENT CONSENT FORM

STUDY TITLE: EVALUATION OF SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS

STUDY CENTRE: GOVT. KILPAUK MEDICAL COLLEGE HOSPITAL, CHENNAI-10

PATIENT'S NAME:

PATIENT'S AGE:

IDENTIFICATION NUMBER:

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask any questions and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the sponsor of clinical study, working on sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However I understand that my identity would not be revealed in any information released to third parties unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical and radiological tests.

Signature/thumb impression :

Patient's name and address:

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சி நிலையம் :

ஆராய்ச்சி [illegible]

[illegible] : பங்கேற்பவரின் வயது :

பதிவு எண் :

நோயாளி [illegible] கட்டங்களை (✓) செய்யவும்

1. மேலே குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுமையாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும் மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதனால் எவ்வித சட்ட விளைவுகள் இல்லை என்பதையும் அறிவேன். ☐

3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி மேலாளரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும், மேலும் இந்த நிபந்தனை நான் இவ்வாராய்ச்சியிலிருந்து விலகினாலும் தொடரும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் சட்டபூர்வமான தேவைகள் தவிர வெளியிடப்பட மாட்டாது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெரிவிக்கமாட்டேன் என்று உறுதியளிக்கிறேன். ☐

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் இந்த ஆராய்ச்சி காலம் முழுவதும் எனது உடல் நிலையில் ஏதேனும் மாற்றமோ அல்லது எதிர்பாராத வழக்கமில்லாத நோய் அறிகுறிகளோ ஏற்பட்டால் உடனடியாக ஆராய்ச்சி குழுவினரை அணுகுவேன் என்றும் உறுதியளிக்கிறேன். ☐

5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவ பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கிறேன். ☐

6. இந்த ஆராய்ச்சிக்கு உட்படுத்தப்படுவதற்கு எனது சொந்த விருப்பத்தின் பேரில் கையொப்பமிட்டு முழுமனதுடன் சம்மதிக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் ரேகை ஆராய்ச்சியாளரின் கையொப்பம்

இடம் [illegible]

PROFORMA

NAME: OP NO:

AGE/SEX:

ADDRESS: OCCUPATION:

DATE:

PRESENT HISORY: The duration of Diabetes

H/O treatment for diabetes,dyslipidemia

PAST HISTORY: History of cardiac/kidney disease.

History of any arthritis, malignancy

PERSONAL HOISORY:

H/O Smoking, Alcohol intake.

Bladder/Bowel Habits

FAMILY HISTORY:

H/O Diabetes

H/O Hypertension

ON EXAMINATION:

GENERAL EXAMINATION:

VITALS:

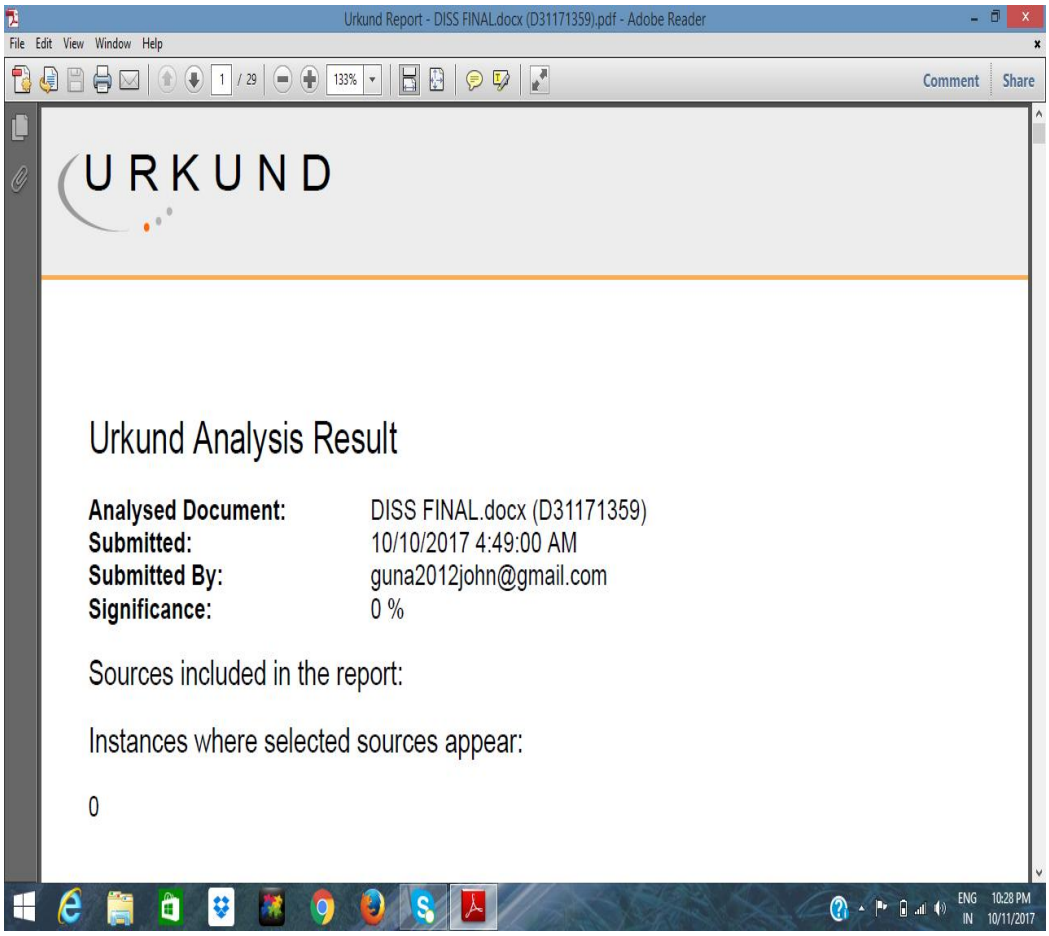
BP: PULSE RATE:

CVS: RS:

PER ABDOMEN: CNS:

INVESTIGATIONS:

1) Fasting blood sugar
2) Blood urea
3) Serum creatinine
4) Serum Uric acid
5) Total cholesterol
6) HDL cholesterol
7) LDL cholesterol
8) Triglyceride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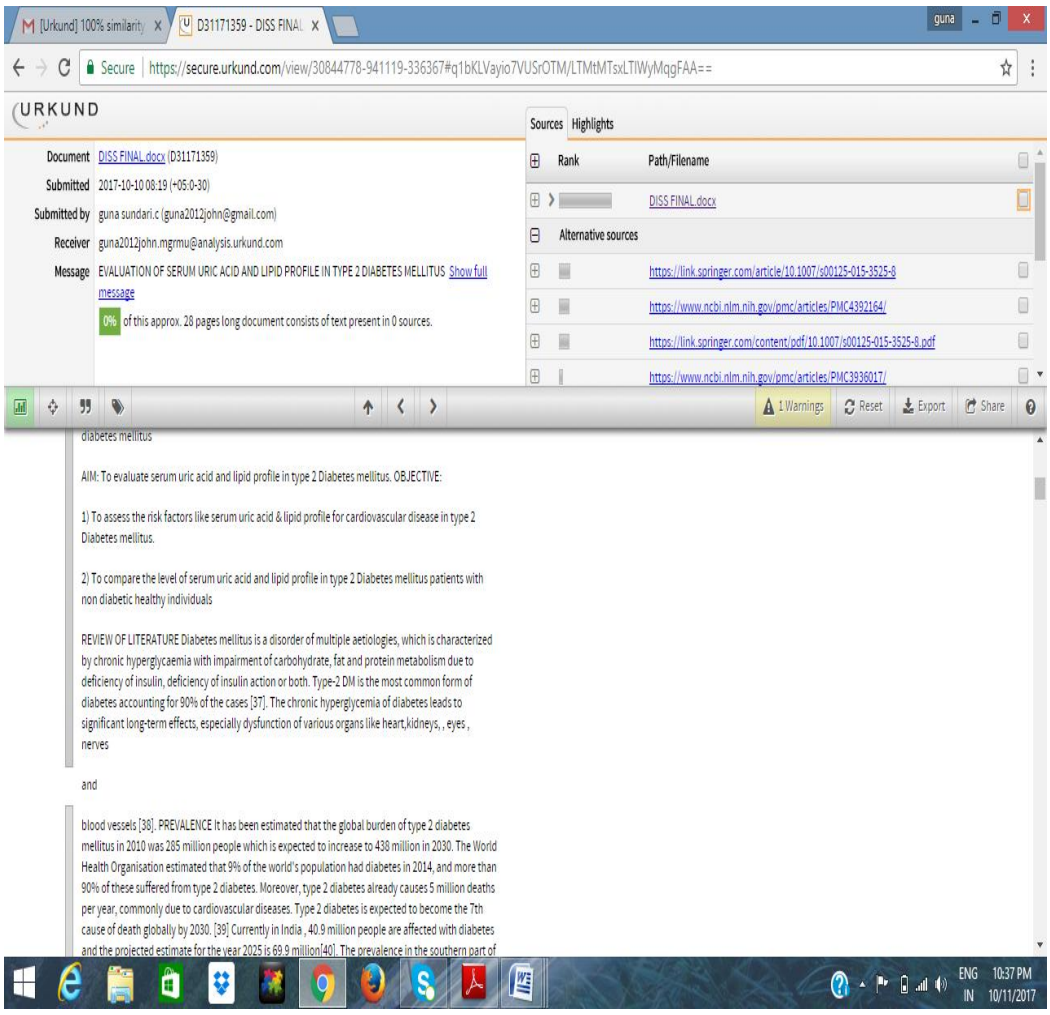
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Message EVALUATION OF SERUM URIC ACID AND LIPID PROFILE IN TYPE 2 DIABETES MELLITUS Show full message
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diabetes mellitus
AIM: To evaluate serum uric acid and lipid profile in type 2 Diabetes mellitus. OBJECTIVE:
1) To assess the risk factors like serum uric acid & lipid profile for cardiovascular disease in type 2 Diabetes mellitus.
2) To compare the level of serum uric acid and lipid profile in type 2 Diabetes mellitus patients with non diabetic healthy individuals
REVIEW OF LITERATURE Diabetes mellitus is a disorder of multiple aetiologies, which is characterized by chronic hyperglycaemia with impairment of carbohydrate, fat and protein metabolism due to deficiency of insulin, deficiency of insulin action or both. Type-2 DM is the most common form of diabetes accounting for 90% of the cases [37]. The chronic hyperglycemia of diabetes leads to significant long-term effects, especially dysfunction of various organs like heart,kidneys, , eyes , nerves
and
blood vessels [38]. PREVALENCE It has been estimated that the global burden of type 2 diabetes mellitus in 2010 was 285 million people which is expected to increase to 438 million in 2030. The World Health Organisation estimated that 9% of the world's population had diabetes in 2014, and more than 90% of these suffered from type 2 diabetes. Moreover, type 2 diabetes already causes 5 million deaths per year, commonly due to cardiovascular diseases. Type 2 diabetes is expected to become the 7th cause of death globally by 2030. [39] Currently in India , 40.9 million people are affected with diabetes and the projected estimate for the year 2025 is 69.9 million[40]. The prevalence in the southern part of
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MASTER CHART FOR CONTROLS

S.NO	AGE	SEX	GLUCOSE	UREA	CREATININE	TOTAL CHOLESTEROL	TGL	HDL	LDL	URIC ACID
1	48	F	118	20	1.1	120	143	46	45	4.6
2	54	F	99	20	1.2	164	111	45	97	4.1
3	46	M	66	19	1.2	145	102	52	73	4.5
4	44	M	78	22	0.9	124	130	50	48	4.8
5	48	M	88	16	1.2	179	91	48	113	4.6
6	45	M	68	15	0.8	138	148	46	62	5.1
7	43	F	71	18	0.9	131	140	54	49	4.9
8	57	M	82	18	0.9	125	79	50	59	4.5
9	59	M	83	21	0.9	128	147	53	46	4.1
10	58	F	78	16	0.8	140	118	54	62	5.1
11	56	F	65	14	0.9	144	129	53	65	4.9
12	43	F	94	18	0.8	191	136	59	105	4.8
13	47	F	86	23	1.1	151	97	55	77	4.7
14	43	F	70	18	0.8	131	102	59	52	4.8
15	57	M	84	19	0.9	117	89	45	54	4.4
16	44	F	86	21	1.2	150	117	53	74	4.6
17	45	M	120	19	0.9	173	135	50	96	4.4
18	46	F	94	23	0.8	135	150	53	52	4.6
19	56	M	101	21	1.1	147	101	50	77	4.2
20	53	F	88	23	1.2	170	91	48	104	4.9
21	41	M	97	20	1.1	139	87	56	66	5.2
22	48	F	92	23	1.2	127	104	47	59	5.6
23	46	F	99	19	0.7	164	72	54	96	4.7
24	43	F	91	20	0.9	133	114	48	62	5.1
25	45	F	89	24	1.1	132	147	54	49	5.3
26	54	M	94	16	0.8	162	69	52	96	4.6
27	58	M	83	18	0.7	136	147	54	53	5.6
28	43	M	103	18	0.9	144	101	53	71	4.5
29	51	M	86	22	0.9	159	49	50	99	4.6
30	57	M	79	21	1.2	135	102	52	63	5.2
31	43	F	88	20	1.1	178	65	46	119	5.1
32	54	F	96	29	1.2	183	53	54	118	4.7
33	55	F	103	23	1.2	181	123	44	112	5.1
34	57	F	92	16	0.9	154	145	46	79	5.3
35	49	M	105	18	0.8	163	99	44	99	4.6
36	41	M	114	16	0.7	156	72	47	95	5.8
37	47	F	112	21	1.1	131	90	54	59	5.3
38	48	F	116	26	1.2	186	120	49	113	5.4
39	46	M	108	17	0.8	184	97	54	111	4.8
40	42	F	66	22	0.9	163	125	49	89	4.9
41	48	F	93	16	0.8	124	132	54	44	5.6

42	45	F	104	15	0.9	156	73	54	87	4.5
43	46	F	98	17	0.7	132	131	52	54	5.2
44	43	F	94	19	0.8	123	99	54	49	5.6
45	56	M	98	22	1.1	192	136	54	111	5.3
46	53	M	98	18	0.8	165	145	50	86	5.1
47	44	M	80	28	1.1	110	119	53	33	4.6
48	49	M	110	19	0.8	157	88	51	88	5.2
49	48	M	113	18	0.9	198	143	55	114	4.7
50	43	F	105	20	0.9	116	78	49	51	4.8
51	42	M	98	15	0.8	112	76	42	55	3.8
52	53	F	78	24	0.9	101	76	45	41	5.1
53	47	M	86	26	0.8	118	74	48	55	4.8
54	52	M	97	21	0.9	132	84	54	61	4.2
55	56	M	98	24	0.8	123	82	42	65	3.6
56	58	F	89	27	1.1	124	81	45	63	3.7
57	54	M	95	30	0.9	108	73	44	49	3.4
58	46	M	87	19	0.8	118	88	43	57	4.2
59	47	M	88	16	0.8	114	89	46	50	4.6
60	42	M	78	18	0.8	112	81	47	49	3.7
61	48	M	84	16	0.8	125	72	49	62	3.8
62	46	F	86	23	1.1	118	78	43	59	4.1
63	42	F	76	20	0.9	115	75	52	48	4.5
64	45	F	83	23	1.1	113	91	43	52	4.9
65	43	F	87	28	0.8	124	94	46	59	5.1

MASTER CHART FOR CASES

S.NO	AGE	SEX	GLUCOSE	UREA	CREATININE	TOTAL CHOLESTEROL	TGL	HDL	LDL	URIC ACID
1	46	F	133	36	1.3	200	215	18	139	6.9
2	52	F	191	44	1.3	225	139	26	171	5.6
3	40	M	142	29	0.9	230	156	25	174	7.8
4	43	M	126	17	1.1	192	235	14	131	3.5
5	46	F	135	16	1.2	112	138	19	65	5.3
6	47	M	134	20	0.9	218	233	28	143	7.6
7	45	F	128	18	1.1	204	82	22	166	5.2
8	56	M	177	25	0.9	238	132	22	190	8.6
9	47	M	126	34	0.9	224	238	23	153	7.6
10	46	F	136	25	1.1	202	180	18	148	4.1
11	44	F	126	26	0.9	199	120	28	147	4.5
12	56	F	176	39	1.1	302	158	22	248	7.5
13	47	F	126	28	0.8	185	251	27	108	3.7
14	58	M	145	21	0.8	297	308	13	222	7.8
15	48	F	180	31	1.1	198	175	25	138	6.8
16	43	F	152	19	0.8	226	135	24	175	4.5
17	53	M	150	23	1.3	299	160	27	240	9.4
18	57	F	153	20	0.9	245	194	22	184	6.9
19	45	M	173	26	1.2	238	119	26	188	4.3
20	46	F	160	18	0.9	246	167	21	192	6.7
21	42	F	140	23	0.9	241	298	25	156	5.1
22	54	F	184	20	1.2	197	90	20	159	5.8
23	56	M	132	22	1.1	226	158	17	177	8.4
24	53	F	184	16	0.9	190	120	21	145	3.9
25	55	M	197	16	1.1	324	348	20	234	8.9
26	42	F	144	29	0.7	246	158	28	186	6.9
27	60	F	134	22	1.1	180	112	21	137	5.2
28	52	M	200	16	0.8	308	175	24	249	4.9
29	57	M	183	23	0.9	163	85	36	110	3.9
30	55	M	183	26	0.9	127	292	32	37	3.6
31	56	M	247	28	0.9	204	174	25	144	3.4
32	53	M	127	18	1.2	219	82	34	169	3.9
33	54	F	191	26	0.8	165	88	20	127	6.7
34	55	F	224	26	1.1	236	216	26	167	4.8
35	45	M	256	21	1.1	238	232	21	171	4.4
36	43	F	243	24	0.8	192	100	22	150	3.6
37	54	M	137	28	1.2	139	116	21	95	4.6
38	56	M	137	34	1.1	219	218	29	146	4.7
39	46	F	126	17	1.1	255	290	29	168	5.6

40	54	M	134	18	1.3	243	165	21	189	5.6
41	58	M	181	20	0.9	208	96	21	168	5.3
42	46	F	139	18	1.1	234	179	26	172	5.6
43	58	M	133	19	0.9	141	113	38	80	4.1
44	53	M	128	32	1.2	161	145	36	96	4.1
45	46	F	187	18	1.1	236	347	28	139	7.2
46	43	F	131	21	0.9	284	315	22	199	7.4
47	54	M	151	23	0.9	184	97	23	142	3.6
48	46	F	190	30	0.8	269	158	18	219	7.3
49	48	F	204	26	0.9	245	165	22	190	4.8
50	49	F	210	20	0.8	221	176	16	170	7.6
51	46	F	168	32	1.2	210	160	32	146	8.1
52	42	F	146	23	0.8	152	156	20	100.8	5.4
53	45	M	230	28	1.2	230	160	34	164	4.6
54	55	M	210	34	1.3	186	162	26	127.6	4.8
55	45	F	240	26	0.9	210	235	26	137	7.2
56	43	F	220	24	1.2	240	165	19	188	7.6
57	56	M	210	25	0.9	216	168	25	157.4	4.8
58	43	F	230	26	0.8	168	150	24	114	3.9
59	46	M	210	23	0.8	239	180	32	171	3.9
60	45	M	216	24	0.8	216	190	25	153	4.9
61	56	F	214	27	1.4	217	184	24	156.2	4.7
62	53	M	236	22	1.2	231	197	16	175.6	4.3
63	56	M	178	24	0.8	214	157	19	163.6	9.2
64	46	M	240	32	1.3	218	198	22	156.4	5.9
65	48	M	236	30	0.9	248	186	37	173.8	5.3