"MEASUREMENT OF SERUM CHOLINESTERASE LEVELS IN TYPE 2 DIABETES AND ITS POSSIBLE ROLE AS A MARKER FOR CARDIOVASCULAR RISK ASSESSMENT IN RELATION TO LIPID PROFILE- ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

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This is to certify that the dissertation entitled **"MEASUREMENT OF SERUM CHOLINESTERASE LEVELS IN TYPE 2 DIABETES AND ITS POSSIBLE ROLE AS A MARKER FOR CARDIOVASCULAR RISK ASSESSMENT IN RELATION TO LIPID PROFILE- ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY." (REG NO. BG0117004).**

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ABBREVIATIONS

Ach	-	Acetyl Choline
AChE	-	Acetyl Choline Esterase
AHA	-	American Heart Association
BMI	-	Body Mass Index
BuChE	-	Butyryl Choline Esterase
CAD	-	Coronary Artery Disease
CCF	-	Congestive Cardiac Failure
CHD	-	Coronary Heart Disease
CHF	-	Congestive Heart Failure
CI	-	Class Interval
CV	-	Cardiovascular
DM	-	Diabetes Mellitus
FBS	-	Fasting Blood Sugar
FHS	-	Framingham Heart Study
GDM	-	Gestational Diabetes Mellitus
HbA1C	-	Hemoglobin A1c
HDL	-	High Density Lipoproteins
HLA	-	Human Leucocyte Antigen
Hr	-	hour
IQR	-	Interquartile Range
kg/m^2	-	Kilogram per square metre
LDL	-	Low Density Lipoproteins
LPL	-	Lipoprotein Lipase
mg/dl	-	Milligram per decilitre

MI	-	Myocardial Infarction
mm/hg	-	Millimetres of mercury
mRNA	-	Messenger Ribo Nucleic Acid
PAD	-	Peripheral Artery Disease
PPBS	-	Post Prandial Blood Sugar
RBC	-	Red Blood Cells
RNA	-	Ribonucleic Acid
SD	-	Standard Deviation
T2DM	-	Type 2 Diabetes Mellitus
U/ml	-	Units per millilitre
VLDL	-	Very Low Density Lipoproteins
WBC	-	White Blood Cells
WHO	-	World Health Organisation

ABSTRACT

Background and Objectives:

Type 2 Diabetes Mellitus is a disease that affects nearly 8.7 percent of the Indian population.[2] T2DM related complications affect many organ systems and are responsible for the majority of the morbidity and mortality associated with the disease including cardiovascular diseases which are responsible for 30-50 percent mortality in DM patients past the age of forty years.[1] The incidence and increase of deaths and disability due to cardiovascular diseases in T2DM patients can be attributed to the coexistence of hyperglycaemia with factors such as dyslipidaemia and obesity.[3] Serum pseudocholiesterase levels are known to be raised in patients with obesity/ patients with normal body weight but having dyslipidaemia.[6] Studies have also been done to show that Serum pseudocholinesterase levels have been raised in case of diabetes but the exact mechanism is not known as the biological function of this enzyme remains an enigma.[5] There is a need to screen diabetic patients for cardiovascular risk in order to prevent further mortality and morbidity and further scope for studies to discover newer ways to screen for cardiovascular risk in T2DM patients with reference to dyslipidaemias and one such method may be through the use of serum cholinesterases. Thus, further studies are needed into identifying cause of raised cholinesterase levels in T2DM and whether this enzyme's levels can be used as a screening test for cardiovascular risk in diabetics. The objectives of the present study is to study the relation of raised pseudocholinesterase levels with increased risk for cardiovascular complications with reference to raised lipid indices in type 2 diabetes mellitus patients. With a secondary objective to identify the association

between variations of Serum Cholinesterase in T2DM patients with Hypertension or changes in BMI.

Methods:

The present cross sectional study was conducted on diabetic patients admitted in KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi from Jan 2018 to Dec 2018. All known Type Two Diabetic patients were screened by the following tests after physical examination: HbA1c, FBS, PPBS, Serum Cholinesterase, Lipid Profile and Serum creatinine. All the patients fulfilling the inclusion criteria and willing to participate were included in the study after obtaining Informed consent. The relevant investigations were done and the data was collected using a proforma meeting the objectives of the study. The data collected was coded and entered into Microsoft Excel Worksheet. For the continuous quantitative variables, mean and standard deviation were calculated. For the categorical variables, frequency and proportion were calculated. Percentages were used to determine the categorical data. Suitable graphs and tables were used to depict the data. Independent sample t-test/ ANOVA/Paired t- test was used to assess statistical significance.

Result

A total of 100 subjects of T2DM were involved in the analysis. Higher levels of Serum cholinesterase were observed in T2DM where mean duration of diabetes was 98.22 ± 99.33 months. There was a weak positive relation between cholinesterase and total cholesterol (r: 0.047, p: 0.643). There was a weak negative correlation between cholinesterase and HDL (r: -0.108, p: 0.287). There was a weak positive correlation between cholinesterase and LDL (r: 0.036, p: 0.723). There was a weak positive correlation between cholinesterase and Triglycerides (rs: -0.123, p: 0.223).

There was a weak positive correlation between cholinesterase and VLDL (rs: 0.147, p: 0.145). There was a weak positive correlation between cholinesterase and BMI (r: 0.289, p: 0.004). The mean of Cholinesterase (U/ml) was 5.61 ± 0.37 in people with hypertension and it was 5.52 ± 0.32 in people without hypertension, which was not significant. (p value 0.284).

Conclusion

While there was a positive relation between dyslipidemia and pseudocholinesterase in Type 2 Diabetics it is not possible to declare conclusively that the main cause of raised pseudocholinesterase levels in Type 2 Diabetics is because of Dyslipidemia. Further studies are needed to determine the cause. Thus, raised serum pseudocholinesterase levels cannot be recommended to be used as a tool for cardiovascular risk assessment in T2DM patients.

There is also a need to further research the genetic aspects for cause of raised serum pseudocholinesterase in T2DM which was beyond the scope of the current study.

Key Words : Pseudocholinesterase, Diabetes, Lipid Profile, Cardiovascular Risk, Dyslipidemia

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INTRODUCTION

Diabetes Mellitus (DM) is an iceberg disease with the current estimate being that the global prevalence is 10% in adults aged over 25 years. This does not even include patients with pre diabetes.[1] The prevalence of the disease has drastically increased over the past two decades. While it was only estimated that there were 3 crore cases in 1985 now we have 425 million in 2017. So based on current trends, it is estimated that there will be approximately 63 crore cases of Diabetes Mellitus by the year 2045[10]. Closer home, India is a country with a population of 1.3 billion people and counting[9]. The population in India has an increased susceptibility to Diabetes Mellitus[1] with nearly 8.7 percent of this gigantic population suffering from type 2 diabetes (T2DM).[2].

DM comprises of metabolic disorders that can cause hyperglycemia. DM is diagnosed by any one of the following criteria:

1. Symptoms of diabetes plus random blood glucose concentrations of more than or equal to 200mg/dl
2. Fasting Plasma glucose more than or equal to 126mg/dl
3. HbA1c more than 6.5%
4. 2hr plasma glucose more than or equal to 200mg/dl[14]

T2DM related complications affect many organ systems and are responsible for the majority of the morbidity and mortality associated with the disease. They can be microvascular complications or macrovascular complications. Cardiovascular diseases are increased in individuals with T2DM. According to the FHS, there is a

marked increase in PAD, CAD, MI and CHF (1-5 fold) in T2DM[3]. In view of this, T2DM patients have been considered to be a "CHD risk equivalent" by the "The American Heart Association (AHA)". It has been found that T2DM patients have not had a previous episode of Myocardial Infarction, now have been considered to be equally susceptible for CAD as non-diabetic individuals who have had a prior Myocardial infarction [11]. CHD is responsible for 30-50 percent mortality in DM patients, past the age of forty years [1]

The incidence and increase of deaths and disability due to cardiovascular diseases in T2DM patients can be attributed to the coexistence of hyperglycaemia with factors such as dyslipidemia and obesity[3]. Wherein disorders of lipoprotein metabolism are collectively referred to as dyslipidaemias[15]. These factors are associated with macrovascular complications.

Thus there is a need to screen diabetic patients for cardiovascular risk in order to prevent further mortality and morbidity in T2DM patients and further scope for studies to discover newer ways to screen for cardiovascular risk in T2DM patients with reference to dyslipidemias.

The enzyme Cholineesterase is comprised of a specific or true cholinesterase known as acetyl choline esterase (AChE) and nonspecific pseudo cholinesterase, butyryl cholinesterase (BuChE)[4] . While the enzyme AChE is a specific esterase that predominantly hydrolyzes acetylcholine (ACh),[12] the enzyme BuChe is non-specific type of cholinesterase enzyme that hydrolyses choline esters as well as other esters and this pseudocholinesterase enzyme, present in the serum has a role in lipoprotein metabolism[5]. Serum pseudocholiesterase levels are known to be raised in patients with obesity/ patients with normal body weight but having dyslipidaemia[6]

Studies have also been done to show that Serum pseudocholinesterase levels have been raised in case of diabetes[4] but the exact mechanism is not known as the biological function of this enzyme remains an enigma[5].

Thus, further studies are needed into identifying cause of raised cholinesterase levels in T2DM and whether this enzyme's levels can be used as a screening test for cardiovascular risk in diabetics.

OBJECTIVES

1. To study the relation of raised pseudocholinesterase levels with increased risk for cardiovascular complications with reference to raised lipid indices in type 2 diabetes mellitus patients.

2. To identify the association between variations of Serum Cholinesterase in T2DM patients with Hypertension or changes in BMI

REVIEW OF LITERATURE

Diabetes Mellitus:

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia.

Mechanism of Glucose regulation

Insulin plays the major role in glucose homeostasis. However, integrated control of glucose utilisation is done in association with various neurological and other hormonal signals. The other major hormone being, glucagon. Glucagon is secreted by pancreatic α-cells.

In fasting state, glucagon stimulates gluconeogenesis and glycogenolysis by stimulating liver and kidney. Low insulin levels promote gluconeogenesis and glycogenolysis from liver. There is also decreased uptake in insulin-sensitive tissues such as muscles and fat. All these machanisms are used to increase blood glucose levels.

In post-prandial state, due to high blood glucose insulin is more and glucagon is less. So, the body attempts to reduce blood glucose by storing carbohydrates and fats and increasing production of proteins. . There is also increased uptake in insulin-sensitive tissues such as muscles and fat

Some tissues, however, such as the brain use glucose in an insulin independent fashion.

Action of Insulin:

Half the insulin that enters into portal circulation, is metabolised by the liver. The remaining insulin through systemic blood vessels, reaches and binds to the insulin receptors at various cites. Insulin binding to it's receptors, stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and recruitment of intracellular signalling molecules such as insulin receptor substrates. This results in the wide spread metabolic and mitogenic effect of insulin and activation of other insulin receptors signalling pathways induces glycogen synthesis, protein synthesis, lipogenesis and regulation of various genes in insulin responsive cells.

Classification:[14]

Diabetes Mellitus is classified on the basis of the pathogenic process that leads to hyperglycaemia and can be classified as follows based on etiology:

1. Type 1 diabetes: caused by Beta cell destruction and usually can lead to insulin defficiency which is absolute. It can be either Immune Mediated or Idiopathic

2. Type 2 diabetes: maybe insulin resistance with relative insulin deficiency or with a primary defect in insulin secretion with resistance.

3. Other specific types of Diabetes:

I. Genetic defects of beta cell development or function.
II. Genetic defects in insulin action such as: Type A insulin resistance, leprechaunism or Rabson-Mendhall syndrome

III. Pancreatic causes:

1. Pancreatitis
2. Pancreatectomy
3. Neoplasia
4. Cystic Fibrosis
5. Hemochromatosis
6. Fibrocalculous pacreatopathy

IV. Other endocrine causes: Acromegaly, Glucagonoma Cushing's syndrome, Pheochromocytoma, Somatostatinoma and Aldosteronoma and Hyperthyroidism

V. Secondary to Drugs:

1. Glucocorticoids
2. Vacor
3. Pentamidine
4. Nicotinic Acid
5. Diazoxide
6. Beta- adrenergic agonists
7. Thiazides
8. Calcineurin
9. mTOR inhibitors
10. Hydantoins
11. Asparginase
12. Alpa-interferons
13. Protease Inhibitors

14. Antipsychotics
15. Epinephrine

VI. Infections:

1. Congenital Rubella
2. Cytomegalovirus
3. Coxsackie Virus

VII. Diabetes secondary to immune mechanisms:

1. "Stiff Person syndrome"
2. Anti-Insulin receptor abs

VIII. Diabetes may occasionally occur in patients with other genetic diseases:

1. Wolfram's Syndrome
2. Downs Syndrome
3. Klinefelter's syndrome
4. Turner's Syndrome
5. Friedreich's Ataxia
6. Huntington's Chorea
7. Lawrence-Moon-Biedl Syndrome
8. Myotonic Dystrophy
9. Porphyria
10. Prader-Willi'Syndrome

4. GDM

Criteria for Diagnosis of Diabetes Mellitus:

1. Symptoms of diabetes plus random blood glucose concentrations of more than or equal to 200mg/dl
2. Fasting Plasma glucose more than or equal to 126mg/dl
3. HbA1c more than 6.5%
4. 2hr plasma glucose more than or equal to 200mg/dl[14]

Risk Factors for Diabetes Mellitus: [1]

Host Factors:

1. Age: Prevalence rises with age mainly manifesting in middle age.
2. Sex: Preponderance of diabetes is seen in males more commonly in parts of Asia.[17]
3. Race/Ethnicity[14]
4. Genetic Factors: The concordance of T2DM in identical twins is between 70% and 90%
5. Genetic markers: Type 1 diabetes is HLA associated while Type 2 DM is not[18]
6. Immune Mechanism[1]
7. Obesity: Obesity is a risk factor, central obesity is associated more with the incidence T2DM. Risk can be affected by both severity and duration. Although the waist circumferenceis more specific than BMI[19], BMI more than 25kg/m2 is considered a risk factor for T2DM.[14]

8. Maternal Diabetes: Offspring's of diabetic pregnancy including gestational Diabetes are more at risk for childhood obesity and so are at risk for T2DM at an early age.
9. History of Cardiovascular disease
10. HDL cholesterol level <35mg/dl and/or triglyceride level >250mg/dl[14]

Environmental Factors:[1]

1. Sedentary Lifestyle disrupts the functioning of insulin by decreasing receptor sensitivity to it, thereby leading to increased risk of T2DM
2. Diet: Fat rich diet is associated with increased risk of T2DM
3. Alcohol damages the pancreas and liver and also contributes to obesity.[18]
4. Infections
5. Chemical Agents
6. Stress

Type 2 Diabetes Mellitus (T2DM):

Of the above, the underlying causes of insulin resistance and abnormal insulin secretion are central to the development of Type 2 diabetes mellitus.

Although there is controversy regarding the primary defect, most studies support the view that there is insulin resistance first which is then followed by insulin secretory defect. However, diabetes develops only when insulin secretion becomes inadequate. [14]

Pathophysiology:

Type 2 Diabetes Mellitus is characterised by impaired glucose tolerance, insulin resistance, excessive hepatic glucose production and abnormal fat metabolism. In the early stages of the disorder, despite the prescence of insulin resistance, glucose tolerance remains near-normal because of the compensatory increase in insulin output by pancreatic beta cells.

However, as insulin resistance and the subsequent compensatory hyperinsulinemia progress, there is damage to the pancreatic islets and individuals will be unable to sustain the hyperinsulinemic state.

First there will be impaired glucose tolerance which is characterised by elevated post-prandial glucose, following which, due to further decline in insulin secretion and increased hepatic glucose production, overt diabetes will develop and ultimately result in beta cell failure. [14]

Complications of Type 2 Diabetes Mellitus:

Diabetes related complications effect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease.

Diabetes related complications can be divided into vascular and non-vascular complications.

The vascular complications of T2DM are further subdivided into microvascular and macrovascular.

1. Vascular complications:

   A. Microvascular complications:

   1. Eye disease:

   a. Retinopathy:

   i. Proliferatiive

   ii. Non-prolifereative

   b. Macular edema

2. Neuropathy:

   a. Sensory

   i. Mononeuropathy

   ii. Polyneuropathy

   b. Motor

   i. Mononeuropathy

   ii. Polyneuropathy

   c. Autonomic

3. Nephropathy: Albuminurea and declining renal function

   B. Macrovascular Complications:

   1. Coronary Heart Disease

   2. Peripheral Arterial Disease

   3. Cerebro-Vascular Disease

   C. Non Vascular Complications:

   1. Gastrointestinal:

   a. Gastroparesis

   b. Diarrhoea

2. Genitourinary:

a. Uropathy

b. Sexual Dysfunction

3. Dermatological

4. Infectious

5. Eye Diseases:

a. Cataracts

b. Glaucoma

6. Chiroarthropathy

7. Periodontal Disease

8. Auditory defects

D. Others:

1. Depression

2 Obstructive Sleep Apnoea

3. Fatty liver disease

4. Hip fracture

5. Cognitive Impairments

6. Dementia

7. Low testosterone in men

Mechanism of Complications of type 2 Diabetes Mellitus:

The mechanisms by which T2DM leads to complications is secondary to chronic hyperglycaemic state, however the mechanisms by which chronic hyperglycaemia causes complications is not known.

It is possible that hyperglycaemia alters gene expression in cells by altering the inheritable phenotype of genes.

There are four theories postulated for the mechanism of complications

1. Increased intracellular glucose leads to the formation of advanced glycosylation end products which binding of glycosylation products to a cell surface receptor, leading to cross linking of proteins and altered extra cellular matrix composition causing vascular complications like atherosclerosis and abnormal functioning of endothelium.

2. Hyperglycaemia increase in glucose metabolism.

3. Hyperglycaemia activates protein kinase- C, which alters the transcription of genes.

4. Hyperglycaemia alters functions of protein glycosylation and changes in gene expression of transforming growth factor or plasminogen activator inhibitor-1. [3]

T2DM and Cardiovascular Diseases:

Risk:

Cardiovascular diseases are increased in individuals with T2DM.

The Framingham Heart Study showed a significantly high incidence of CV diseases such as PAD, CAD, MI and CCF in diabetics.

There was twice the risk of heart diseases in men and 4 fold increase in heart diseases in women even while accounting for other cardiovascular risks. This is even higher in diabetic patients who are young adults.[11] The prognosis for Coronary artery disease patients/ for patients with myocardial infarction with T2DM is much worse than for non-diabetic patients with the same disease.[3]

The AHA has considered T2DM patients to be a "CHD risk equivalent" and T2DM patients who have never had an episode of MI have been deemed to have the same amount of incidence of CV events as non-diabetic individuals who have had a prior Myocardial infarction [11]. CHD is responsible for 30-50 percent of deaths in diabetics who are middle aged or passed the forty years [1]

Etiopathogenesis:

The most common cause of heart disease in T2DM is structural heart disease by myocardial ischaemia or by myocardial infarction.[20] Myocardial ischaemia occurs when the myocardium, due to hypo-perfusion and ischaemia does not receive the amount of blood it requires to function. This can occur to the entire myocardium or only a part. Thus, there is decrease in the oxygen supply to the heart causing an imbalance between supply and demand to the heart muscles.

The most common etiology for ischemia is secondary to atherosclerosis.[22]

T2DM accelerates atherosclerosis via vascular smooth muscle proliferation and inflammation [20]. There is an increase in cardiovascular complications in T2DM patients due to the co-existence of hyperglycaemia with other common etilogies for macrovascular diseases such as dyslipidemia, obesity, hypertension, reduced physical activity and cigarette smoking [3]

The above major risk factors disturb the normal functioning of the vessel walls thus there is loss of vascular tone, loss an anti-thrombotic endothelium and loss of suppression/activation of inflammatory cells. The loss of these defences causes vasoconstriction, intraluminal thrombus production and abnormal interactions between various cellular components of blood such as RBC's and WBC's and Thrombocytes with the vascular endothelium.

Atherosclerosis also alters the nature of circulating blood.

The combination of a vulnerable vessel in a patient with vulnerable blood promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.[22]

Imaging studies have also shown that left ventricular hypertrophy is an important characteristic of a diabetic heart.[21]

Significance:

Evidence of atherosclerotic vascular disease should be sought in individuals with DM, as there will invariably the presence of underlying cardiovascular diseases.

T2DM patients tend to present with silent ischaemia, with no symptoms, thus in such patients it is advisable to thoroughly evaluate for cardiac diseases, especially before any surgeries.[3]

T2DM and Dyslipidemia:

Individuals with T2DM may have several forms of dyslipidemia. The most common patterns of Dyslipidemia in T2DM are hypertriglyceridemia and HDL levels.[3]

Disorders of lipoprotein metabolism are collectively referred to as dyslipidemias.

Lipoproteins are large macromolecular complexes composed of lipids and proteins that transport poorly soluble lipids, vitamins, cholesterol, etc. to and from tissues.

There are 100's of proteins which influence lipoprotein metabolism and may interact to produce dyslipidemia in an individual but, there are a few discrete nodes that regulate lipoprotein metabolism. These include:

1. Assembly and secretion of triglyceride rich very low density lipoproteins by the liver.
2. Lipolysis of triglyceride rich lipoproteins by LPL
3. Receptor mediated uptake of apoB-containing lipoproteins by the liver
4. Cellular cholesterol metabolism in hepatocytes and enterocytes
5. Neutral lipid transfer and phospholipid hydrolysis in the plasma.

Dyslipidemias are generally characterised by increased plasma levels of cholesterol, triglycerides or both, and invariably accompanied by reduced levels of high density lipoprotein (HDL) cholesterol levels.

The majority who have some form of dyslipidemia are prone to it because of their genetic predisposition and their surroundings and risk factors such as lifestyle, medical conditions or drugs. Many of them are at increased risk for atherosclerotic cardiovascular diseases, making it important to diagnose and treat dyslipidemia which further becomes a form of primary prevention for atherosclerotic cardiovascular diseases.[15]

Thus, comprehensive diabetes care must contain aggressive investigation and management of not only hyperglycemia but also hyperlipidaemia to prevent increased cardiovascular risk.[3]

Thus, there is a need to screen diabetic patients for cardiovascular risk in order to prevent further mortality and morbidity in T2DM patients and further scope for studies to discover newer ways to screen for cardiovascular risk in T2DM patients with reference to dyslipidemias.

T2DM and Serum Pseudocholinesterase :

History of Serum Pseudocholinesterase:

The term cholinesterase was coined to describe the group of enzymes that were able to hydrolyse ACh and other choline esters. This was done in the year 1932 by Stedman.

Eight years later, it was shown by Alles and Hawes, that there were two types of cholinesterases found. One in plasma which varied from the one found on RBCs. A Serum cholinesterase and a true cholinesterase[6]

Biochemistry of Serum Pseudocholinesterase:

Thus the enzyme Cholinesterase is comprised of two separate components, a specific or true cholinesterase known as acetyl choline esterase(AChE) and nonspecific pseudo cholinesterase, butyryl cholinesterase(BuChE)[4] . These two enzymes share a structural homology of 65%[12]

While the enzyme AchE is a specific esterase that predominantly hydrolyses acetylcholine (Ach)[12], the enzyme BuChe is non-specific type of cholinesterase enzyme that hydrolyses choline esters as well as other esters.

Both AChE and BuChe are reduced in case of organo-phosphorous poisoning.

Plasma pseudocholinesterase is produced in the liver, comprises of four identical subunits, each of which consists of a polypeptide chain. Each chain is further made up of 574 amino acids and 9 carbohydrate chains. Each sub unit weighs over 80,000. There are two active sites in plasma pseudocholinesterase known as the

anionic site and the esteratic site. The esteratic site combines with the carbonyl group of the ester linkage and is responsible for hydrolysis.[6]

Pseudocholinesterase levels are also altered in patients with chronic liver disease and in patients with abnormal renal function. [6]

Functions of Serum Pseudocholinesterase:

Pseudocholinesterase enzyme, present in the serum has a role in lipoprotein metabolism [5]. Davis et al [6] mention that serum cholinesterase could play a part in the metabolising of lipids or help in the regulation of choline. Serum pseudocholinesterase levels are known to be raised in patients with obesity/ patients with normal body weight but having dyslipidaemia [7]

Studies have also been done to show that Serum pseudocholinesterase levels have been raised in case of diabetes[4], when the activity of serum pseudo cholinesterase levels was measured in diabetics and non diabetics, it was noticed there was a significant raise in pseudocholinesterase activity in diabetics. [24]

However, the exact mechanism is not known as the biological function of this enzyme remains an enigma[5].

Significance:

Thus it is possible that since Pseudocholinesterase levels are increased in T2DM and also in patients with dyslipidemia and also since it is established that dyslipidaemia also occurs in case of T2DM, there may exist a possible association between the presence of raised pseudocholinesterase levels and dyslipidemia in diabetic patients.

This association if proved can further be used to detect cardiovascular risk in diabetes since it has already been established that dyslipidemia in T2DM patients is a major risk for cardiovascular diseases.

Further studies and analysis are required in this field to look for ways to screen for cardiovascular diseases in Diabetics as, it has already been stated that cardiovascular diseases are one of the major causes of morbidity and mortality in Type diabetes patients.

METHODOLOGY

Study Design:

A One Year Hospital Based Cross Sectional Study

Study source:

Patients admitted in the wards of Department of General Medicine at KLES Dr.Prabhakar Kore Hospital, Belgaum fulfilling the inclusion criteria were selected consecutively.

Study duration: 1 Year

The study was conducted from January 2018 to December 2018.

Ethical clearance:

Ethical clearance was granted by the JNMC Institutional Ethics Committee on Human Subjects Research, J.N.Medical College, Belagavi. (Ref: MDC/DOME/42 dated 22/11/2017)

Sample size:

All consecutive patients who were diagnosed as T2DM and not having any of the exclusion criteria were included in the research.

Sample size: 100

As this is a cross- sectional study,

Sample size was calculated by the following formula:

$N= 4PQ/D^2$, Where,

N=Sample size

P = Prevalence of the disease

Q= 100- P

D = Absolute error taken as 10%

(P = 50 (assumed prevalence as similar study not done to estimate prevalence of raised cholinesterase levels in T2DM); Q = 50; D=10)

Inclusion Criteria:

All patients diagnosed with Type 2 Diabetes Mellitus not having any of the exclusion criteria mentioned below.

Exclusion Criteria:

Patients, diagnosed with Type 2 Diabetes Mellitus with the following:

1. Renal Diseases,
2. Acute/Chronic Liver Diseases,
3. Malnutrition
4. Organophosphorus poisoning.

Data collection:

All patients previously diagnosed with Type 2 Diabetes Mellitus were subjected to detailed history and examination and through necessary investigations diagnosis of Type 2 Diabetes was confirmed.

All known Type Two Diabetic patients were screened by the following tests after examination.

- HbA1c,
- FBS,

- PPBS
- Serum Cholinesterase,
- Lipid Profile
- Serum creatinine

All the patients fulfilling the inclusion criteria and willing to participate were included in the study after taking institutional ethical clearance and obtaining Informed consent. The relevant investigations were done and the data was collected using a proforma meeting the objectives of the study.

Statistical Method for Data Analysis:

The data collected was coded and entered into Microsoft Excel Worksheet. For the continuous quantitative variables mean and standard deviation were calculated. For the categorical variables, frequency and proportion were calculated. Percentages were used to determine the categorical data. Suitable graphs and tables were used to depict the data. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). The association between the variables and outcome were done by comparing the mean values. Independent sample t-test/ ANOVA/Paired t- test was used to assess statistical significance.

Cholinesterase was the primary outcome variable. Lipid profile, BMI and Hypertension were the primary variables. A P-value <0.05 was taken for statistical significance.

"IBM-SPSS version 22" was used for statistics.[31]

RESULTS:

A total of 100 subjects were involved in the analysis.

Table-1: Age distribution in patients (N=100)

	Mean±SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Age	61.16 ± 11.18	60.00	30.00	85.00	58.94	63.38

The mean Age was 61.16 ± 11.18, with min age, 30 and max age, 85

Table-2: Gender distribution in patients (N=100)

Gender	**Frequency**	**Percentages**
Male	75	75.0%
Female	25	25.0%

Among the study population, 75 (75.0%) participants were male and remaining 25 (25.0%) participants were female. (Figure 1).

Figure 1: Pie chart of gender in the study population (N=100)

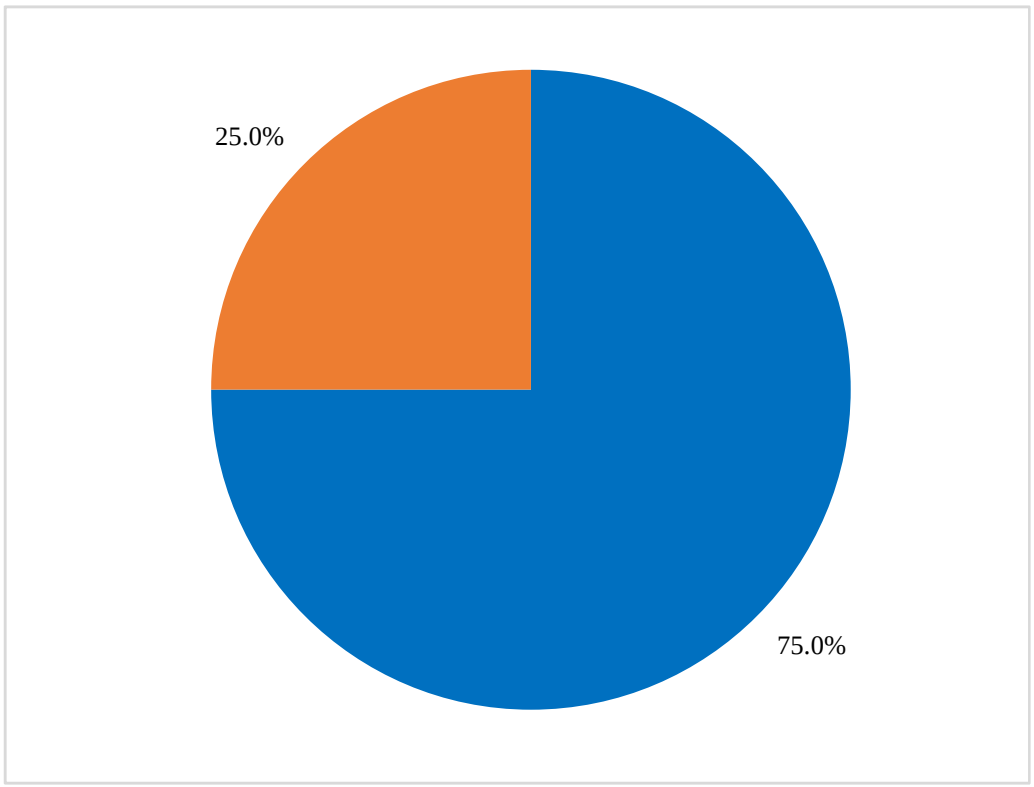

Table-3: Incidence of hypertension in patients (N=100)

Hypertension	Frequency	Percentages
Yes	77	77.0%
No	23	23.0%

Among the study population, 77 (77%) people had Hypertension. (Figure 2).

Figure 2: Pie chart of hypertension in the study population (N=100)

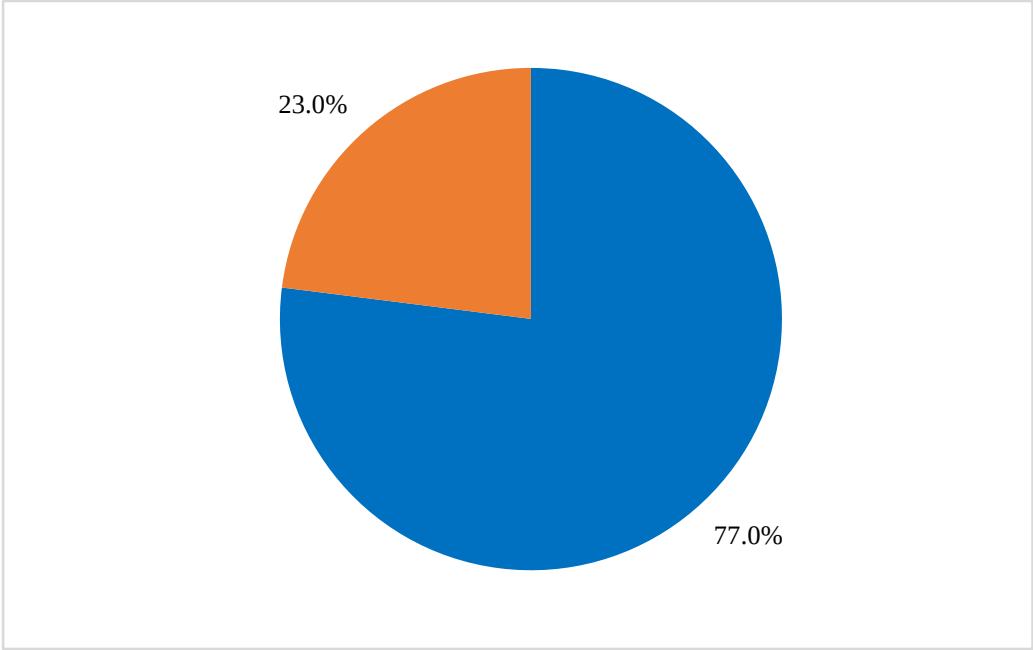

Table 4: Descriptive analysis of duration of diabetes in the patients (N=100)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Duration in Months	98.22 ± 99.33	60.00	0.00	480.00	78.51	117.93

The mean duration was 98.22 ± 99.33 months in the study population, ranging between 0 month to 480 months (95% CI 78.51 to 117.93).

Table 5: Presence of family history of diabetes in the patients (N=100)

Family History of Diabetes	Frequency	Percentages
Yes	53	53.0%
No	47	47.0%

Among the study population, 53 (53%) people had family history of diabetes (Figure 3).

Figure 3: Bar chart of family history of diabetes in the study population (N=100)

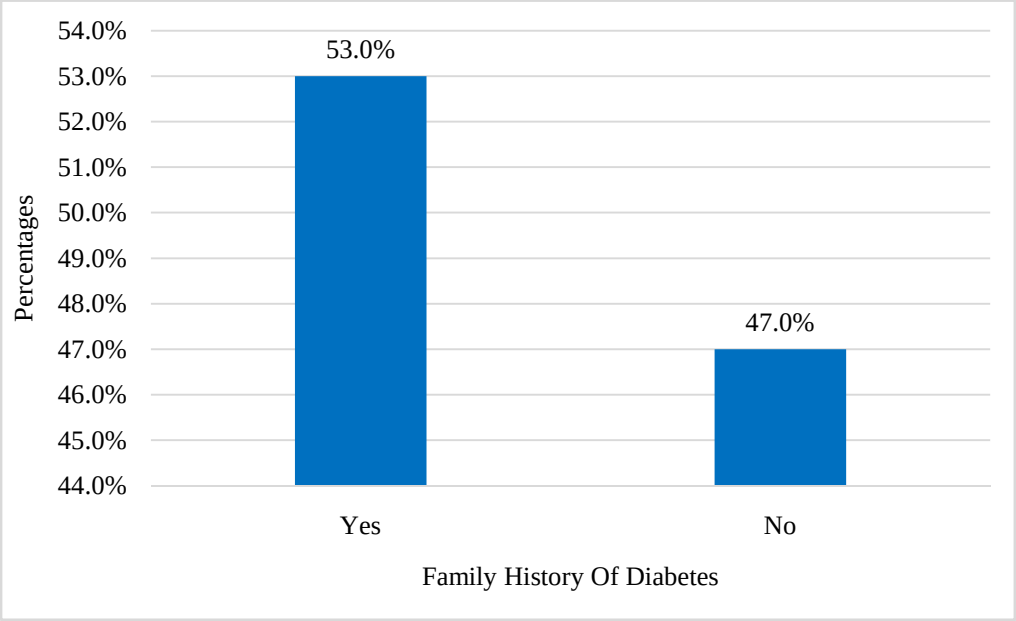

Table 6: Diabetic medication History (N=100)

Diabetic Medication	Number	Percentage
Insulin	11	11.0%
Insulin + Oral	3	3.0%
Oral	52	52.0%
Irregular	13	13.0%
No	21	21.0%

Among the diabetic medication in the study population, 11 (11%) people took Insulin, 3 (3%) people took Insulin + Oral medication, 52 (52%) people took Oral medication alone and 13 (13%) people took irregular medication. (Figure 4).

Figure 4: Bar chart of diabetic medication in the patients (N=100)

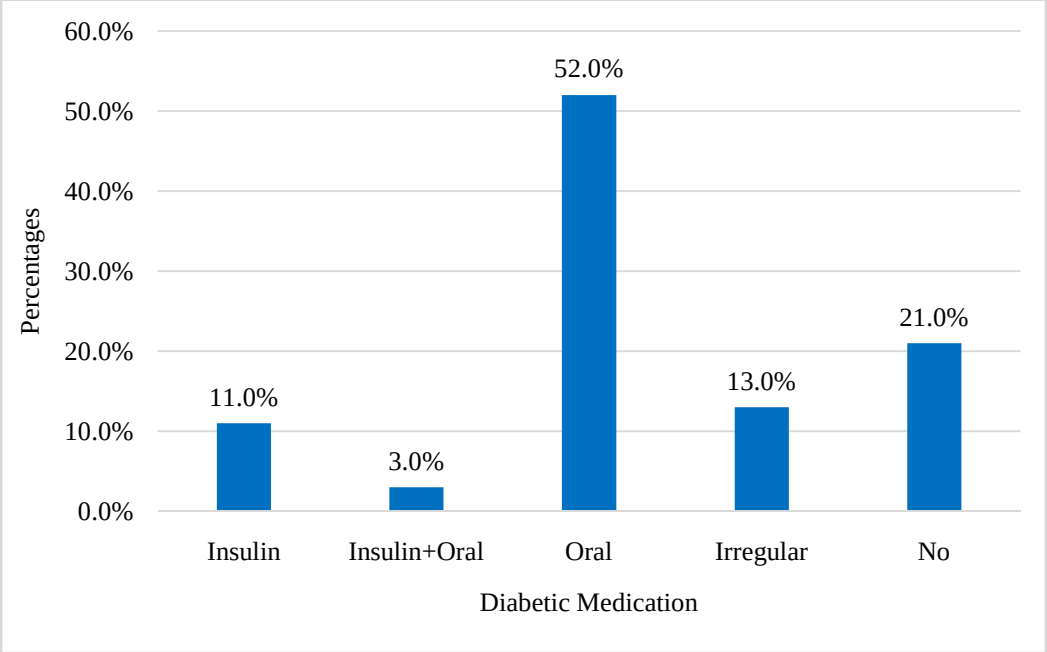

Table 7: History of cholesterol medication among patients (N=100)

Cholesterol Medication	Number	Percentage
Yes	38	38.0%
No	62	62.0%

Among the study population, 38 (38%) people had Cholesterol Medication. (Figure 5)

Figure 5: Pie chart of cholesterol medication in the study population (N=100)

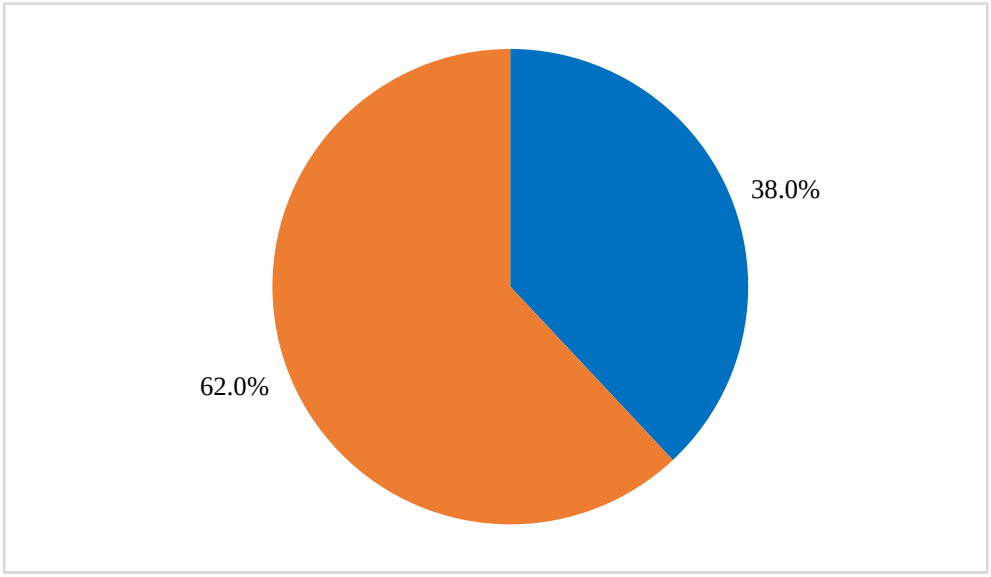

Table 8: Analysis of Blood Pressure in patients (N=100)

	Mean±SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Systolic Bp	140.76 ± 26.47	140.00	80.00	230.00	135.51	146.01
Diastolic Bp	84.18 ± 12.41	80.00	40.00	130.00	81.72	86.64

The mean systolic blood pressure was 140.76 ± 26.47mmHg in the study population, ranged between 80 to 230 (95% CI 135.51 to 146.01). The mean diastolic blood pressure was 84.18 ± 12.41 mmHg in the study population, ranged between 40 to 130 (95% CI 81.72 to 86.64). (Table 8)

Table 9: Description of BMI in patients (N=100)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
BMI (kg/m^2)	24.08 ± 2.98	23.89	18.42	32.34	23.49	24.67

The mean BMI was 24.08 ± 2.98 with, min BMI 18.42 kg/m^2 and max BMI 32.34 kg/m^2 in the study population (95% CI 23.49 to 24.67). (Table9)

Table-10: Analysis of Cholinesterase(U/Ml) in patients (N=100)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Cholinesterase(U/Ml)	5.59 ± 0.36	5.52	5.01	6.67	5.52	5.66

The mean Cholinesterase (U/Ml) was 5.59 ± 0.36 with minimum of 5.01 U/Ml and maximum of 6.67 (U/Ml). (Table10)

Table10a: Descriptive analysis of cholinesterase UML category in the study population (N=100)

Cholinesterase UML Category	**Frequency**	**Percentages**
5 to 5.50	48	48.0%
5.01 to 6	37	37.0%
>6	15	15.0%

Table 11: Descriptive analysis of Fasting Lipid Profile parameters in study population (N=100)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Total Cholesterol (mg/dl)	162.53 ± 51.27	153.50	66.00	270.00	152.36	172.70
HDL (mg/dl)	39.03 ± 12.37	37.00	15.00	79.00	36.58	41.48
LDL (mg/dl)	94.96 ± 46.96	88.50	6.00	200.00	85.64	104.28
Triglycerides (mg/dl)	139.83 ± 92.27	119.50	32.00	527.00	121.52	158.14
VLDL (mg/dl)	29.51 ± 21.21	25.00	2.00	130.00	25.30	33.72

The mean Total Cholesterol was 162.53 ± 51, minimum 66 mg/dl and maximum 270 mg/dl (95% CI 152.36 to 172.70). The mean HDL was 39.03 ± 12.37 minimum 15 mg/dl and maximum 79 mg/dl (95% CI 36.58 to 41.48). The mean LDL was 94.96 ± 46.96, minimum l 6 mg/dl and maximum 200 mg/dl (95% CI 85.64 to 104.28). The mean triglycerides was 139.83 ± 92.27, minimum 32 mg/dl and maximum 527 mg/dl (95% CI 121.52 to 158.14). The mean VLDL was 29.51 ± 21.21, minimum 2 mg/dl and maximum 130 mg/dl (95% CI 25.30 to 33.72), (Table 11)

Table 12: Correlation between Cholinesterase and fasting lipid profile parameters (N=100)

	(r)	P-value
Total cholesterol	0.047	0.643
HDL	-0.108	0.287
LDL	0.036	0.723

There was a weak positive correlation between cholinesterase and total. There was a weak negative correlation between cholinesterase and HDL. There was a weak positive correlation between cholinesterase and LDL (fig 6 to 8)

Figure 6: Scatter plot for Correlation between cholinesterase and Total cholesterol in the patients (N=100)

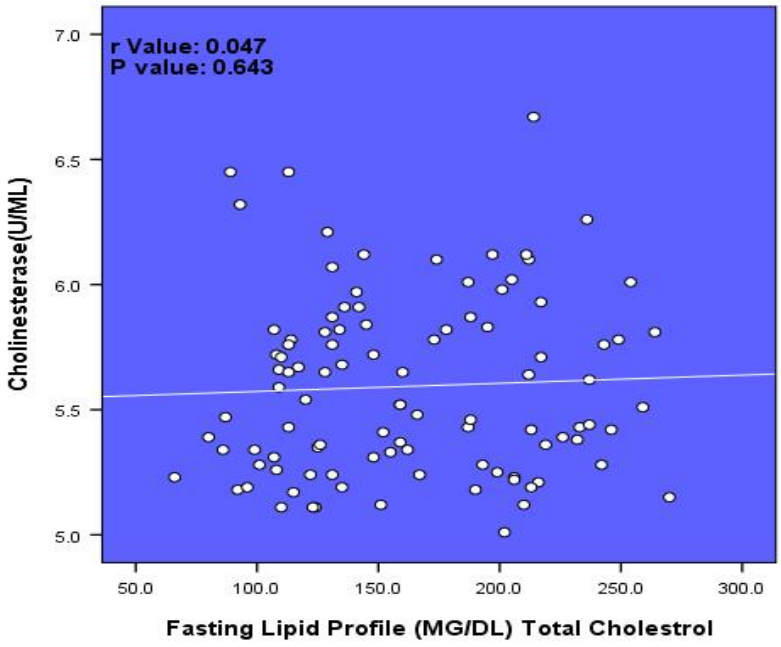

Figure 7: Scatter plot for Correlation between cholinesterase and HDL in the patients (N=100)

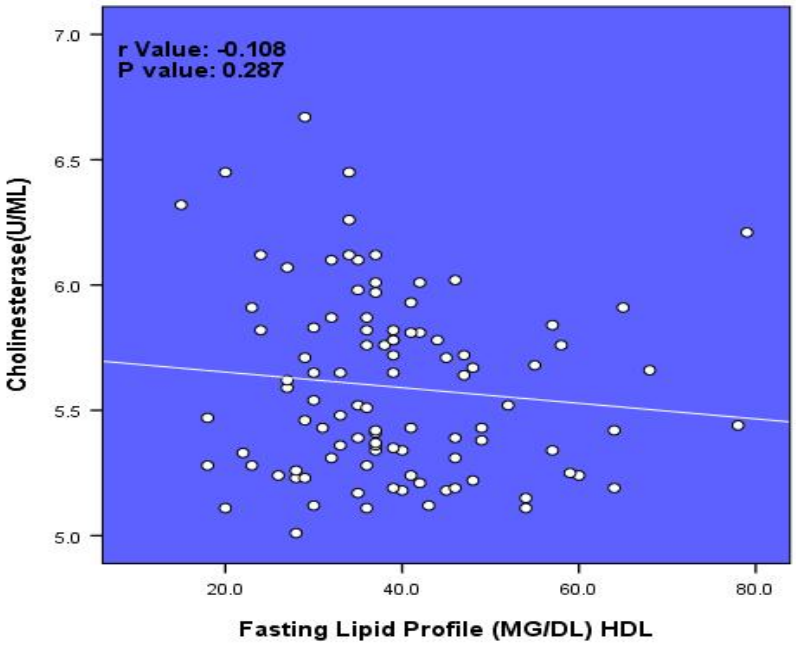

Figure 8: Scatter plot for Correlation between cholinesterase and LDL in the patients (N=100)

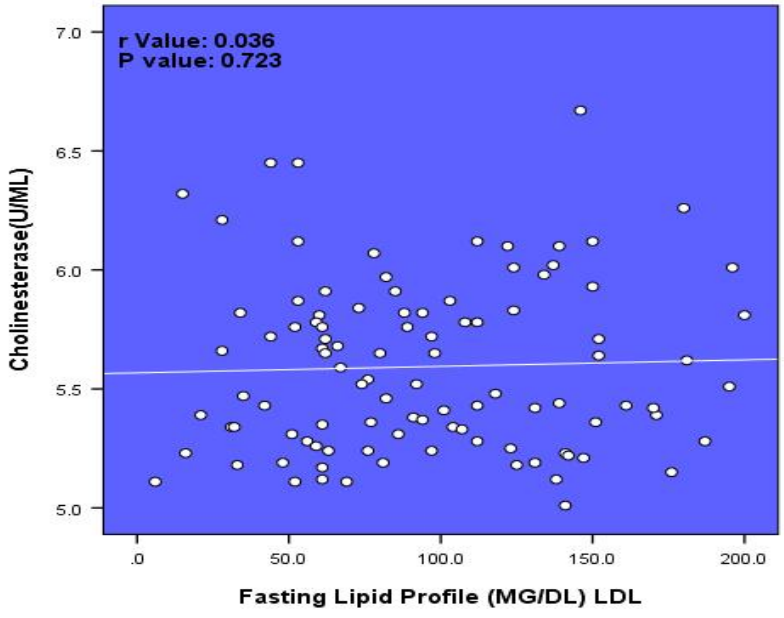

Table 13: Correlation between Cholinesterase and fasting lipid profile in the patients (N=100)

Parameter	Spearman's rho (rs)	P value
Triglycerides	0.123	0.223
VLDL	0.147	0.145

There was a weak positive correlation between cholinesterase and Triglycerides. There was a weak positive correlation between cholinesterase and VLDL (fig 9, 10)

Figure 9: Scatter plot for Correlation between cholinesterase and triglycerides in the patients (N=100)

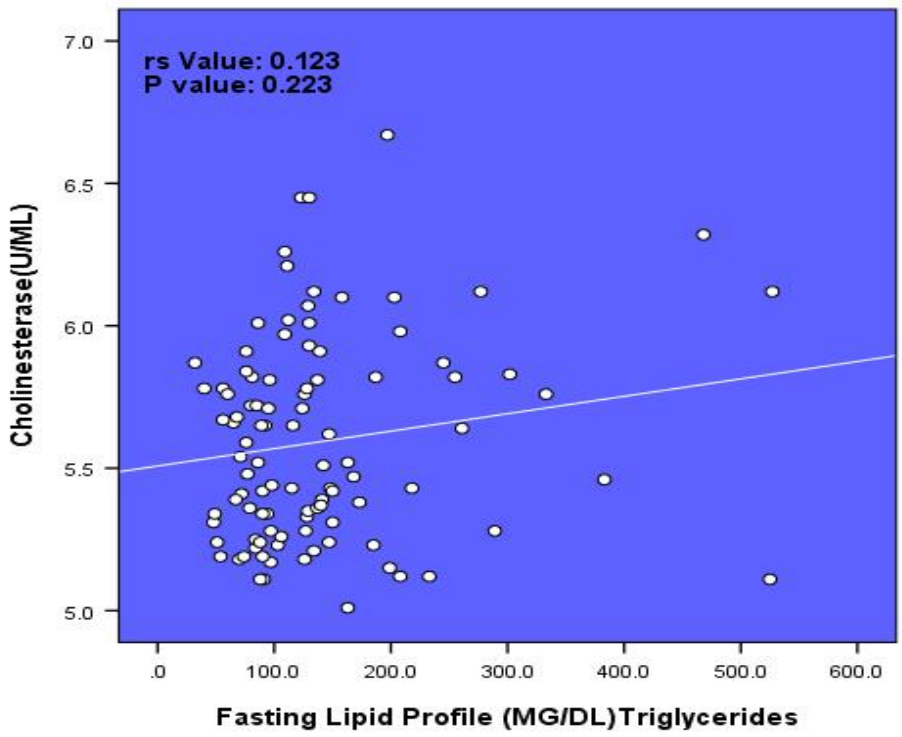

Figure 10: Scatter plot for Correlation between cholinesterase and VLDL in the patients (N=100)

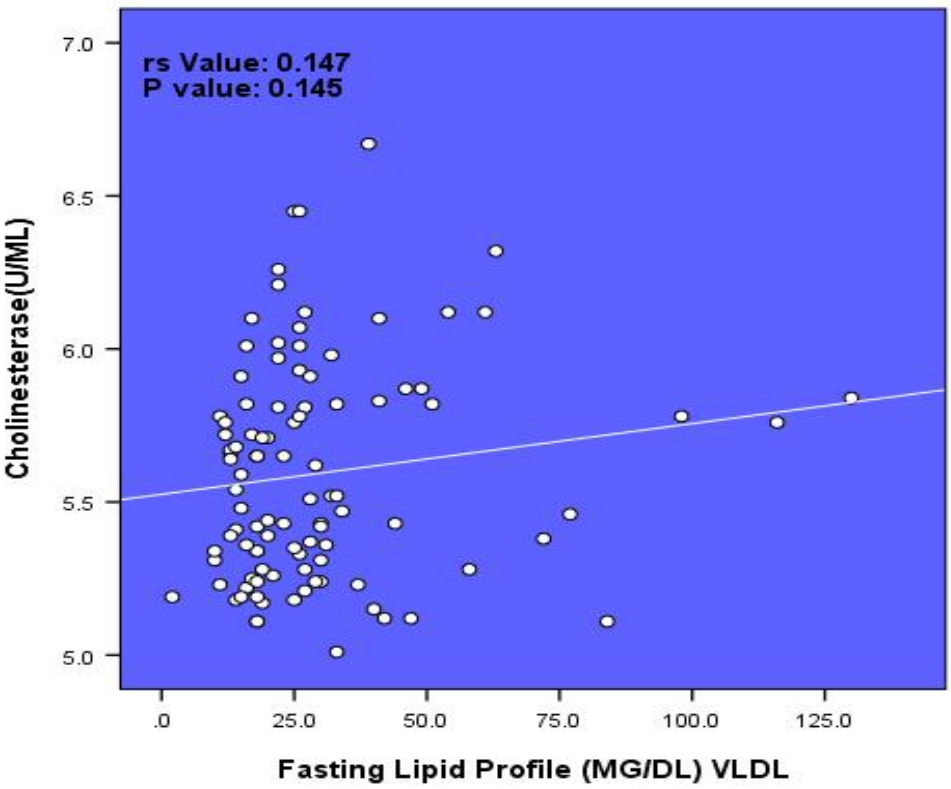

Table 14: Correlation between Cholinesterase and BMI (N=100)

	(r)	P value
BMI	0.289	0.004

There was a weak positive correlation between cholinesterase and BMI (fig 11)

Figure 11: Scatter plot for Correlation between cholinesterase and BMI in the patients (N=100)

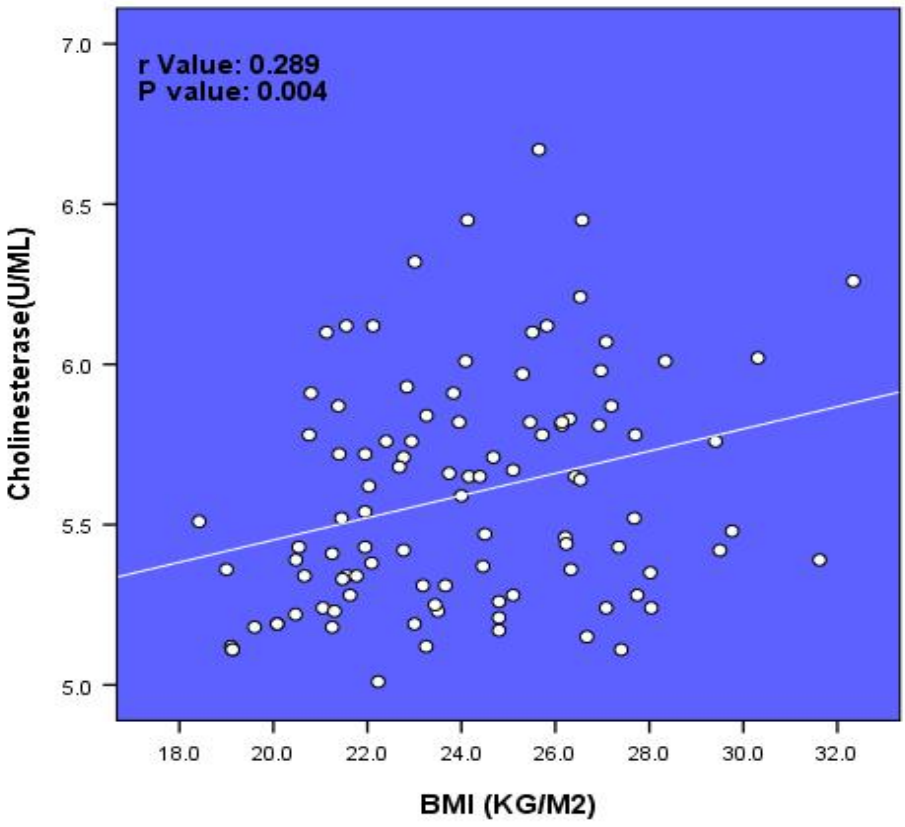

Table 15: Comparison of mean of Cholinesterase with hypertension (N=100)

Parameter	Hypertension (Mean± SD)		P value
	Yes (N=77)	No (N=23)	
Cholinesterase(U/ML)	5.61 ± 0.37	5.52 ± 0.32	0.284

The mean of Cholinesterase (U/ML) was 5.61 ± 0.37 in people with hypertension and it was 5.52 ± 0.32 in people without hypertension, which is not significant. (p value 0.284)

DISCUSSION

The present research was conducted in Department of General Medicine, JNMC, KAHER, Belagavi, among 100 patients of T2DM to study the relation of raised serum cholinesterase levels with increased risk for cardiovascular complications with reference to raised lipid indices and to study variations of Serum Cholinesterase with relation to comorbidities: Hypertension and Obesity.

Higher levels of Serum cholinesterase are observed in T2DM. According to Godfre et al, AChE activity has been found higher by an order of magnitude in islets of Langerhans than in the exocrine tissue from rat pancreas and this difference in activity was observed in healthy, control rats as well as rats made diabetic with streptozotocin. In addition, AChE activity in islets from diabetic rats was about 30–40% higher than in islets from control rats[25]. Likewise, according to Abbott et al, when the activity of serum BuChE was investigated in diabetic versus normal controls, it was found that BuChE was significantly elevated type 2 diabetes (7.22 ±1.95 units/mL) patients when compared with the controls. It was also found that serum activity of BuChE was correlated with insulin sensitivity particularly in T2DM patients[24].

Similarly, Roopa.R et al [4] observed that when a correlational analysis was made between the serum cholinesterase and lipid indices, there was a strong positive correlation with respect to total positive correlation with LDL-C and to C ratio and also negative correlation with HDL statistically significant ($p < 0.05$) and positive correlation for type 2 diabetic patients with increased BMI compared to normal BMI type patients.

When different risk factors were studied that are independently correlated with BuChE activity for coronary artery disease, it was found that BuChE activity was positively correlated with lipoprotein synthesis, hypertension and diabetes[27].

In the present study, the following observations were noted:

In present study majority of patients were male (75%).Female patients were only 25%. Mean age group of study population was 61.16 ± 11.18 years. Minimum age of patients was 30years and Maximum age was 60 years.

In present study 77% of patients were hypertensive. Mean systolic BP was 140.76 ± 26.47 mmhg and diastolic BP was 84.18 ± 12.41mmhg.

In present study Mean duration of diabetes 98.22 ± 99.33 months.

53% of study population family history showed diabetes.

38% of study population was using cholesterol medication (statins)

Mean BMI of study population was 24.08 ± 2.98 kg/m^2

Among 100 DM patients 52% of were on oral medication, 21% were not on any medication, 13% were on irregular medications, 11% were on insulin and 3% were on insulin+ oral medications.

Fasting lipid profile assessment was done in study population. Mean total cholesterol was 162.53 ± 51.27, mean HDL was 39.03 ± 12.37, mean LDL was 94.96 ± 46.96, mean triglycerides was 139.83 ± 92.27 and VLDL was 29.51 ± 21.21.

Mean cholinesterase levels were 5.59 ± 0.36 U/MI. Minimum cholinesterase was 5.01 U/MI and maximum cholinesterase was 6.67 U/MI.

In present study,

There was a weak positive relation between cholinesterase and total cholesterol (r: 0.047, p: 0.643).

There was a weak negative correlation between cholinesterase and HDL (r: -0.108, p: 0.287).

There was a weak positive correlation between cholinesterase and LDL (r: 0.036, p: 0.723).

There was a weak positive correlation between cholinesterase and Triglycerides (rs: -0.123, p: 0.223). There was a weak positive correlation between cholinesterase and VLDL (rs: 0.147, p: 0.145)

In present study there was a weak positive correlation between cholinesterase and BMI (r: 0.289, p: 0.004)

According to a study by Tomoyuki *et al*.[26] (2007), butyryl cholinesterase is strongly associated with adiposity, the serum lipid profile and insulin resistance with which the present study can be compared.

The results of the present study can also compared with study done by Alcantara *et al*.[27] (2002) butyryl cholinesterase activity was positively correlated with age, sex, body mass index, hypertension and diabetes, as well as with albumin, triglycerides, total cholesterol, low lipoprotein cholesterol and apoprotein measures of overweight, obesity traditional risk factors of coronary artery disease.

The mean of Cholinesterase (U/ml) was 5.61 ± 0.37 in people with hypertension and it was 5.52 ± 0.32 in people without hypertension, which was not significant. (p value 0.284). But in a study by Alcantara *et al*.[27] (2002) found positive correlation between butyryl cholinesterase activity and hypertension.

In a study conducted on 1,097 subjects from the Newfoundland adult population, evidence was found for the involvement of elevated levels of serum BuChE in the pathophysiological processes causing T2DM symptoms such as serum triglyceride levels, abdominal obesity, fasting blood glucose levels, and fasting insulin levels[29]. BuChE may be playing a role in causing T2DM through amyloid fibrils formation. It has been shown that the presence of amylin in pancreatic islet cells of T2DM patients causes apoptosis of beta cells by nitric oxide inactivation, lipid peroxidation and formation of excessive superoxide radicals[30].

There also exists evidence of a total of seventy five different expressions of the human BChE gene.

While a majority of mutations are single type and occur at sites placed away from the active site, they still can cause change in the butyryl cholinesterase activity.

It has been further postulated that, micro RNAs are involved in the process of gene expression regulation, thereby altering gene expression by making unique combinations with the mRNA, which could be the reason for raised serum cholinesterase in T2DM.[16]

Few studies like 'Serum butyrylch: a biochemical and bioinformatics approach' by Sridhar *et al*. [16](2005) showed but was inversely related to serum cholesterol and Mauro M. Cwiertnia *et al*.[28] (2010) suggested that the positive

correlation to the BChE activities to diabetes mellitus and to insulin resistance may depend on the CHE2.

Thus, while this study in accordance with multiple studies showed a relation between serum pseudocholinesterase and T2DM the raise of pseudocholinesterase in T2DM cannot be attributed directly to either dyslipidemia or raised BMI or hypertension.

Thus further studies are required to evaluate for cause of raise in cholinesterase levels in diabetic patients other than dyslipidemia which is beyond the scope of the current study.

CONCLUSION:

There was a weak positive correlation between cholinesterase and total cholesterol

There was a weak negative correlation between cholinesterase and HDL

There was a weak positive correlation between cholinesterase and LDL.

There was a weak positive correlation between cholinesterase and Triglycerides

There was a weak positive correlation between cholinesterase and VLDL

There was a weak positive correlation between cholinesterase and BMI

There was a weakly positive relation between raised pseudocholinesterase levels and dyslipidemia in type 2 diabetics

There was no significant relation between raised pseudocholinesterase levels and hypertension in type 2 diabetics.

There was relation between raised pseudocholinesterase levels and BMI in type 2 diabetics

In conclusion while there is a positive relation between dyslipidemia and pseudocholinesterase in Type 2 Diabetics it is not possible to declare conclusively that the main cause of raised pseudocholinesterase levels in Type 2 Diabetics is because of Dyslipidemia. Further studies are needed to determine the cause.

Thus, raised serum pseudocholinesterase levels cannot be recommended to be used as a tool for cardiovascular risk assessment in T2DM patients.

LIMITATIONS:

The study was limited to only one hospital so generalisation is limited.

There is a need to further research the genetic aspects for cause of raised serum pseudocholinesterase in T2DM which was beyond the scope of the current study.

SUMMARY

A cross-sectional study was conducted on 100 patients of T2DM to study the relation of raised serum cholinesterase levels with increased risk for cardiovascular complications with reference to raised lipid indices and to study variations of Serum Cholinesterase with relation to comorbidities: Hypertension and Obesity.

In present study majority of patients were male (75%).Female patients were only 25%. Mean age group of study population was 61.16 ± 11.18 years. Minimum age of patients was 30years and Maximum age was 60 years.

Mean cholinesterase levels were 5.59 ± 0.36 U/MI. Minimum cholinesterase was 5.01 U/MI and maximum cholinesterase was 6.67 U/MI.

According to the study, while there is a positive relation between dyslipidemia and pseudocholinesterase in Type 2 Diabetics it is not possible to declare conclusively that the main cause of raised pseudocholinesterase levels in Type 2 Diabetics is because of Dyslipidemia.

Thus, raised serum pseudocholinesterase levels cannot be recommended to be used as a tool for cardiovascular risk assessment in T2DM patients.

Further studies are needed to determine the cause for the same.

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ANNEXURE I – CONSENT FORM

Title Of Research Study: MEASUREMENT OF SERUM CHOLINESTERASE LEVELS IN TYPE 2 DIABETES AND IT'S POSSIBLE ROLE AS A MARKER FOR CARDIOVASCULAR RISK ASSESSMENT- ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE'S CHARITABLE HOSPITAL

Guide:- **Principal Investigator:-**

Introduction and Purpose:-

India has a high incidence of Type 2 Diabetes Mellitus and cardiovascular complications are very commonly associated with T2 Diabetes Mellitus.

There is a possibility of raised serum cholinesterases being associated with abnormal lipid profile and cardiovascular complications in type two diabetes

This study aims to find the association of type two diabetes mellitus with serum cholinesterase levels and identify the possibility for a simple single cheaper screening test for assessment of cardiovascular risk in diabetic patients.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study.

If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in

thisresearch record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

1. DR. ROOPA BELLAD MD Professor Dept. of PEDIATRICS, J.N. Medical College, K.L.E. University, Belgaum – 590010 Ph :9448113403

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has Been read to me, this consent form and have had all the questions answered

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's Name :……...

Signature / Left thumb impression:……...

of the participant

Name of the legally authorized :……...

representative / guardian

Signature / Left thumb impression :……...

Witness' name :……...

Signature / Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

ANNEXURE-II

PROFORMA

PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

PHONE NUMBER:

Duration of Diabetes:

Family history of Type 2 Diabetes: Yes/No

Personal history:

Diabetes:Yes/ No

Hypertension: Yes/ No

Treatment history:

1. Medications being used for Diabetes:

2. Taking Medications for Cholesterol: Yes/ No

PHYSICAL EXAMINATION:

VITALS:

Temperature

Pulse Rate

Blood Pressure

Icterus-Yes/No

Edema-Yes/No

Height: Weight: BMI: Waist Circumference:

Hepatomegaly: Yes/ No

INVESTIGATIONS

1. HbA1c:

2. Fasting Blood Sugar:

3. Post Prandial Blood Sugar:

4. Serum Cholinesterase:

5. Fasting Lipid Profile:

   Total Cholesterol:

   HDL Cholesterol:

   LDL Cholesterol:

   Triglycerides:

   VLDL Cholesterol:

6. Serum Creatinine:

ANNEXURE-III- ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91-(0)831 – 2470759

Ref: MDC/DOME/ 42

Date: 22/11/2017

To,

REG NO. BG 0117004

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"MEASUREMENT OF SERUM CHOLINESTERASE LEVELS IN TYPE 2 DIABETES AND IT'S POSSIBLE ROLE AS A MARKER FOR CARDIOVASCULAR RISK ASSESSMENT – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY IN KLE'S DR. PRABHAKAR KORE'S CHARITABLE HOSPITAL",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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ANNEXURES IV - MASTER CHART

Case No.	Name	Age	Sex	Diabetes	Hypertension	Duration of Diabetes	Family History Of Diabetes	Diabetic Medication	Choesterol Medication	Blood Pressure	BMI	HbA1c	Fasting Sugars	Post Prandial Sugars	Cholinesterase	Fasting Lipid Profile (MG/DL)				
										MM/HG	KG/M2	%	MG/DL	MG/DL	U/ML	Total Cholestrol	HDL	LDL	Triglycerides	VLDL
1	ALLABAKSH M TAMBALI	50	M	YES	YES	5 YR	NO	irregular	NO	160/90	23.5	14.9	145	224	5.23	206	28	141	185	37
2	AMEERKHAN R MOKASHI	69	M	YES	NO	NEWLY DIAGNOSED	NO	NO	NO	140/80	21.25	7.3	141		5.41	152	37	101	72	14
3	BALASAHEB K PATIL	63	M	YES	NO	NEWLY DIAGNOSED	YES	NO	NO	120/80	21.4	8.3	206	419	5.72	148	39	97	80	12
4	BHARATI S TIWADE	57	F	YES	YES	2 YR	YES	NO	NO	130/90	19.1	7.6	130	198	5.12	210	30	138	208	42
5	BHIMANGAUDA M PATIL	49	M	YES	YES	6 YR	YES	INSULIN	NO	130/80	28.34	9.3	140	217	6.01	254	42	196	86	16
6	BHUJAM	47	F	YES	YES	10 YR	YES	T METFORMIN SR 500 1-0-0	NO	160/100	26.14	6.9	116	170	5.81	264	42	200	96	22
7	LAXMAN G KAMBLE	59	M	YES	NO	1 YR	NO	T METFORMIN 500 1-0-0	YES	120/70	22.84	12.1	164	411	5.93	217	41	150	130	26
8	MALLAPPA S KONNURI	82	M	YES	YES	20 YR	NO	T GLYCOMET 500 1-0-1/2	YES	110/80	19.13	7	110	196	5.11	110	20	6	525	84
9	MUBARAK J HAWALDAR	51	M	YES	YES	1 YR	YES	NO	NO	160/90	24.8	7.8	138	210	5.17	115	35	61	97	19
10	PALRAJ L KAUJALAGI	66	M	YES	YES	2 YR	YES	T GLICLAPACK 30 1-0-0	NO	120/70	27.68	6.6	92	170	5.52	159	35	92	86	32
11	PRABHAKAR S PHUDNIS	52	M	YES	YES	6 YR	YES	irregular	NO	140/90	21.56	12.2	236	541	5.34	162	40	104	94	18
12	RAJASHREE Y VATHARE	46	F	YES	YES	6 MONTHS	YES	NO	NO	140/80	23.83	7.2	178	229	5.91	136	23	85	139	28
13	REVAPPA S TALWAR	46	M	YES	NO	10 YR	YES	irregular	NO	130/78	20.48		137	371	5.39	226	35	171	141	20
14	RUDRAVVA S YALLANNAWAR	70	F	YES	YES	10 YR	NO	T METFORMIN 500 1-0-1, T GLIMY 1MG 1-0-0	NO	160/90	18.42	15.6		458	5.51	259	36	195	142	28
15	RUDRAPPA M MARANNUR	61	M	YES	YES	10 YR	YES	T GLYCOMET 500 1-0-1	NO	130/80	20.8	5.5	118	206	5.91	142	65	62	76	15
16	SADASHIV A PUJARI	47	M	YES		1 MONTH	YES	NO	NO	130/80	21.95	13.6	164	492	5.43	187	31	112	218	44
17	SANJEEVANI V KURAKURI	72	F	YES	YES	15 YR	YES	INSULIN, T GLYCOMET GP-1 1-0-1	NO	170/100	22.77	8	124	249	5.42	213	64	131	90	18
18	SATAPPA N SAPTUSAGAR	80	M	YES	YES	20 YR	YES	T GLYCOMET 500 1-0-1/2	YES	200/100	19.13	7	128	168	5.11	124	54	52	91	18
19	AVINASH B KOCHREKAR	63	M	YES	NO	20 YR	YES	INSULIN	NO	130/80	24.8	7.5	112	210	5.21	216	42	147	134	27
20	SHANTA A SAGARE	65	F	YES	YES	4 YR	NO	T GLYCOMET SR 500 1-0-1	NO	150/90	26.3	7	136	210	5.83	195	30	124	302	41
21	SHIVAPPA S BILLUR	51	M	YES	YES	2 YR	YES	T GLYCOMET 500 1-0-1	YES	130/80	22.77	6.8	130	182	5.71	217	45	152	124	20
22	SUBHASH B ADIKE	62	M	YES	YES	15 YR	YES	T AMARYL M1 1-0-1 INSULIN	YES	140/80	23.66	6.8	118	186	5.31	148	32	86	150	30
23	BHIMAPPA A MALABAR	59	M	YES	YES	1 YR	YES	T GLUCONORM SR 500 1-0-1	NO	150/80	26.42	8.9	85	180	5.65	128	30	80	92	18

								INSULIN											
24	TANAJI N KOLI	56	M	YES	YES	5 YR	NO	T GLYCOMET 500 1-0-1 T GLIMY 1 1-0-1	NO	130/70	20.47	11.4	150	320	5.22	206	48	142	84	16
25	VASUDEV I KOLI	77	M	YES	YES	10 YR	NO	T GLYCOMET 500 1-0-1 T VOGLIBOSE 0.3 0-1-0	YES	120/80	19.6	7.5	122	174	5.18	92	45	33	70	14
26	VIJAY N PAWAR	50	M	YES	YES	3 YR	YES	T METFORMIN 500 1-0-1,	NO	180/100	21.95	6.8	130	205	5.72	108	47	44	85	17
27	YALLAWWA S BAJANTARI	72	F	YES	YES	10 YR	YES	irregular	NO	186/100	21.05	7.4	141	329	5.24	167	60	97	51	30
28	CHANDRASHEKKAR G HIREMATH	84	M	YES	NO	10 YR	YES	INSULIN	NO	120/70	21.3	7.2	154	243	5.23	66	29	16	103	11
29	ANNASAHEB B CHOUGALE	49	M	YES	YES	4 YR	YES	irregular	NO	150/90	24	10.6	131	257	5.59	109	27	67	76	15
30	ASHOK M MAOGI	60	M	YES	YES	3 YR	NO	INSULIN T GERMER 1 1-0-1 T ISTAMET (50/500) 1-0-1	YES	110/60	26.21	9.6	226	468	5.46	188	29	82	383	77
31	BABASAHEB P CHOUGALE	79	M	YES	NO	6 MONTHS	YES	T GLYCOMET SR 500 1-0-1	NO	130/90	21.47	7	124	188	5.33	155	22	107	128	26
32	SARASWATI NAHIGADOLLI	65	F	YES	NO	NEWLY DIAGNOSED	YES	NO	NO	130/80	23	14.8	175	447	5.19	213	64	131	90	18
33	BASALINGAPPA ILLURI	59	M	YES	YES	15 YR	YES	T GLUCONORM G2 0-0-1 T GLYPTEN 0-1-0	YES	160/90	25.1	8.9	132	185	5.28	193	23	112	289	58
34	BASAPPA T NEHER	65	M	YES	YES	10 YR	YES	T GLYCOMET 500 1-0-1	YES	110/70	21.77	15.6		240	5.34	86	37	31	90	18
35	BHARMU P NIDAWANI	65	M	YES	NO	2 MONTHS	NO	NO	YES	130/70	26.93	6.8	101	212	5.81	128	41	60	137	27
36	CHANDRAKANT A WADDER	54	M	YES	YES	6 MONTHS	YES	irregular	YES	130/80	22.03	8.2	144	313	5.62	237	27	181	147	29
37	CHIDANAND B BHUSHI	75	M	YES	YES	15 YR	NO	T GERMER 0.5 1-0-1	YES	160/90	21.25	8.4	177	252	5.18	190	40	125	126	25
38	GIRIJADEVI M N	50	F	YES	NO	NEWLY DIAGNOSED	NO	NO	NO	140/90	27.4	13.5	117	268	5.11	123	36	69	88	18
39	GOVIND R GAUDE	54	M	YES	YES	15 YR	YES	T TRIBET 1 1-0-0	YES	130/80	28.02	8.1	146	275	5.35	125	39	61	129	25
40	NIRANJANA P ASHTEKAR	52	F	YES	YES	16 YR	NO	T GLYCOMET 500 1-0-1 T GLIMY 1 0-1-0	YES	170/100	23.74	7.2	139	211	5.66	109	68	28	65	13
41	RAJESHWAR N RAIKAR	68	M	YES	YES	15 YR	YES	INSULIN T GLYCIPHAGE 500 2-0-2 T GP-2 1-0-1		140/90	25.1	9.2	103	204	5.67	117	48	61	56	13
42	SADASHIV S DESAI	50	M	YES	NO	NEWLY DIAGNOSED	YES	NO	NO	130/90	22.23	12.1	133	255	5.01	202	28	141	163	33
43	SAROJINI D MATHAPATI	56	F	YES	YES	8 YR	YES	T GLYCOMET GPI 1-0-1/2	NO	130/80	19	6.8	154	271	5.36	219	37	151	137	31
44	SHILPASHREE T R R T V	30	F	YES	NO	6 MONTHS	YES	NO	NO	130/80	31.62	7.3	115	181	5.39	80	46	21	67	13
45	SHANTA U CHOUGALE	55	F	YES	YES	4 YR	YES	T GLYCOMET GP 1 1-0-0	YES	140/90	27.7	8.5	146	298	5.78	249	39	112	40	98
46	MANISHA R THAKUR	54	F	YES	YES	3 YR	YES	NO	YES	170/100	23.01	6.4	60	204	6.32	93	15	15	468	63
47	MARUTI B KUKANUR	68	M	YES	YES	5 YR	YES	T GLYCOMET 500 1-0-0	YES	130/80	22.12	9.2	118	179	6.12	197	24	112	527	61
48	MARUTI N KERNUKAR	65	M	YES	YES	6 MONTHS	NO	NO	YES	110/70	23.18	11.2	112	200	5.31	107	46	51	48	10
49	PRAKASH M BILLUR	65	M	YES	YES	22 YR	YES	INSULIN	YES	160/80	25.51	7.2	122	220	6.1	174	35	122	158	17
50	RAMANGAUDA S PATIL	65	M	YES	YES	2 YR	YES	T GLYCOMET 500 1-0-0	YES	140/80	21.95	7.5	129	188	5.54	120	30	76	71	14
51	RAVI D PATIL	58	M	YES	YES	15 YR	YES	INSULIN	YES	180/100	20.54		188	416	5.43	233	49	161	115	23
52	SHARADA S BYALI	68	F	YES	YES	15 YR	YES	INSULIN	YES	150/90	26.14	7.4	99	282	5.82	107	36	34	187	33
53	SHIVANAND S KHAVASHI	50	M	YES	YES	4 YR	NO	T GLUCONORM PG-2 1-0-1	YES	140/80	26.67	6.9	133	204	5.15	270	54	176	199	40
54	SIDDRAM S SHANDAGE	60	M	YES	YES	10 YR	NO	T GALVAS 50 1-0-1 T AMARYL MV 1-0-1 INSULIN	YES	150/90	27.08	11	150	221	5.24	131	26	76	147	29

55	SUBHASH H SONWALKER	58	M	YES	NO	NEWLY DIAGNOSED	NO	NO	NO	110/70	29.41	7	107	202	5.76	243	38	89	333	116
56	VIRABHADRAYYA S M HIREMATH	60	M	YES	NO	10 YR	NO	INSULIN	NO	130/80	23.95		142	230	5.82	134	24	94	81	16
57	ALKA GANGARAM PAWAR	76	F	YES	YES	10 YR	NO	T GLYCOMET GP 0.5 1/2-0-1/2	YES	150/90	20.08	8.2	160	331	5.19	135	39	81	74	15
58	AMRAPPA Y HUNSI	58	M	YES	NO	1 YR	NO	T GLYCOMET 500 1-0-1	NO	110/80	21.13	8.4	108	181	6.1	212	32	139	203	41
59	AYUB A KADAR NADAF	59	M	YES	YES	20 YR	NO	INSULIN	YES	140/90	25.65		120	210	6.67	214	29	146	197	39
60	BEERAPPA B CHURAMANI	78	M	YES	YES	10 YR	YES	T GLYCOMET 500 1-0-1	NO	110/70	20.76	8.4	174	372	5.78	114	44	59	56	11
61	KASTHURI R SAVADI	49	F	YES	YES	3 YR	YES	irregular	NO	200/110	23.44	8.5	142	188	5.25	199	59	123	84	17
62	LATA MOHAN KADAM	65	F	YES	YES	18 YR	NO	T GLYCOMET 500 0-1-0	NO	110/70	20.08	7	128	173	5.19	96	46	48	54	2
63	MAHADEV G MALAWAD	53	M	YES	YES	4 YR	NO	T GLYCOMET 500 1-0-1	NO	100/60	22.4	6.8	91	135	5.76	113	36	52	126	25
64	MARUTI N MONTUR	67	M	YES	YES	3 YR	NO	T TELZY MT 1-0-0	YES	110/80	21.38	7.2	112	246	5.87	131	32	53	32	46
65	RAMANNA B RAGATI	60	M	YES	YES	3 MONTHS	NO	irregular	NO	190/100	23.26	7.2	99	224	5.84	145	57	73	76	130
66	RAMESH LAXMAN PATIL	61	M	YES	YES	15 YR	YES	T GLYCOMET 500 1-0-1	NO	130/80	27.35	7.2	180	252	5.43	113	41	42	148	30
67	RUKMINI K JAYANCHE	60	F	YES	YES	NEWLY DIAGNOSED	NO	NO	NO	120/90	26.97	12.2	130	273	5.98	201	35	134	208	32
68	SHASHIKALA M RAO	76	F	YES	YES	NEWLY DIAGNOSED	NO	T GLYCOMET 500 1-0-1	NO	130/70	27.19	8.6	132	258	5.87	188	36	103	245	49
69	SHRIHARI K GHODKE	73	M	YES	NO	4 YR	NO	INSULIN	NO	110/80	24.16	10.3	106	185	5.65	113	33	62	89	18
70	VASUDEV P WAGAMARE	31	M	YES	NO	NEWLY DIAGNOSED	NO	T GLYCOMET GP-1 1-0-0 T GLYCOMET 500 0-0-1	NO	120/70	27.08	9.4	151	337	6.07	131	27	78	129	26
71	AMBAJI N BHOSALE	65	M	YES	YES	2 YR	NO	T GLYCOMET 500 1-0-0	NO	150/80	28.04		138	210	5.24	122	41	63	88	18
72	BASAVANNI B MAGADUM	65	M	YES	YES	20 YR	NO	T JANUMET 50 1-0-1 INSULIN	NO	140/80	24.5	6.8	110	157	5.47	87	18	35	168	34
73	BASAVARAJ C SHABADI	49	M	YES	YES	5 YR	YES	T GLIMI M-1 SR 1-0-1	YES	150/90	24.09	7.8	169	281	6.01	187	37	124	130	26
74	CHANDRASHEKAR M KARUDI	85	M	YES	YES	20 YR	NO	INSULIN	YES	130/80	20.66	5.2	97	124	5.34	99	57	32	49	10
75	DEVKUMAR D CHANDANAVAR	64	M	YES	YES	12 YR	NO	T GLYCOMET 500 1-0-0	YES	130/70	21.63	6.8	122	177	5.28	101	18	56	127	27
76	JAYAVANT NANA KHORATE	73	M	YES	NO	2 YR	NO	T GLYCOMET 500 1-0-0	NO	90/70	21.45	6.8	143	177	5.52	159	52	74	163	33
77	JUGALKISHORE G BIYANI	75	M	YES	YES	20 YR	NO	T METFORMIN SR 500 1-0-1	YES	160/90	22.09		130	229	5.38	232	49	91	173	72
78	KASHAVVA C HANCHIMANI	60	F	YES	YES	1 YR	NO	NO	NO	230/130	32.34	15	125	406	6.26	236	34	180	109	22
79	SHANTA A KAMBLE	70	F	YES	YES	6 MONTHS	YES	NO	NO	170/90	29.5	8.4	108	142	5.42	246	37	170	150	30
80	MALLAPPA R PADASALI	65	M	YES	YES	10 YR	NO	T JANUMET 50/100 0-1-0	YES	170/100	22.94	8.7	116	235	5.76	131	58	61	60	12
81	MALLAPPA D JAVALI	79	M	YES	YES	38 YR	NO	T GLYCOMET GP 2 1-0-0	YES	140/90	22.68	7	75	152	5.68	135	55	66	68	14
82	MALLIKARJUN B AAVALAKKI	63	M	YES	YES	8 YR	NO	NO	NO	110/60	24.13		226	304	6.45	89	20	44	123	25
83	NAJMA S AHAMADI	54	F	YES	YES	3 YR	YES	T GLIMIPRIDE 1 1-0-1	NO	200/100	30.31	6.9	132	238	6.02	205	46	137	112	22
84	SANGAYYA B HUNNUR	50	M	YES	YES	8 YR	NO	T GLYCOMET 500 1-0-1 T GLIMY 1 1-0-0	YES	110/70	23.25		116	262	5.12	151	43	61	233	47
85	SANTOSH T	35	M	YES	YES	NEWLY DIAGNOSED	YES	NO	NO	200/100	29.76		118	273	5.48	166	33	118	77	15
86	SHANTAYYA R KUKADOLIMATH	67	M	YES	YES	10 YR	YES	T GLYCOMET GP 1 1-0-1	NO	130/90	24.46		62	245	5.37	159	37	94	140	28
87	SHIVABASU H SHEKKI	45	M	YES	NO	2 YR	YES	T GLYCOMET 500 1-0-1	NO	110/80	24.8	7.1	116	151	5.26	108	28	59	106	21

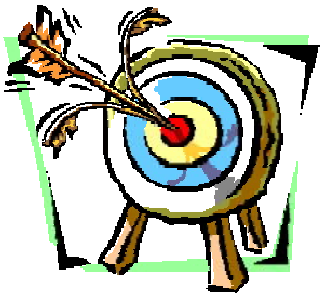
88	SHIVAPPA C BYALI	74	M	YES	YES	10 YR	NO	T SWITGLIM MV 2/0.3 1-0-0	NO	150/90	24.68	6.8	140	186	5.71	110	29	62	95	19
89	SUBHASH N PUKALE	70	M	YES	NO	7 YR	NO	irregular	YES	110/70	25.3		165	226	5.97	141	37	82	109	22
90	VIJAYABASAPPA M PATTED	85	M	YES	YES	20 YR	NO	irregular	NO	170/90	21.55	9.2	120	285	6.12	144	37	53	277	54
91	YALLAPPA B BHAJANTRI	52	M	YES	YES	7 YR	YES	irregular	YES	180/110	26.53		160	374	5.64	212	47	152	261	13
92	EDWINA M SALDANA	58	F	YES	NO	15 YR	YES	T JANUMET 50/500 1-0-0	NO	140/90	26.23	9.3	97	281	5.44	237	78	139	98	20
93	KALLAPPA P KADEMANI	55	M	YES	YES	NEWLY DIAGNOSED	NO	NO	NO	180/90	26.57	6.4	94	226	6.45	113	34	53	130	26
94	MASHNU N DANGARLE	54	M	YES	YES	5 YR	YES	irregular	YES	80/40	26.53		112	241	6.21	129	79	28	111	22
95	SHANKAR R MOKASHI	55	M	YES	YES	NEWLY DIAGNOSED	YES	NO	NO	160/100	25.82	6.7	112	199	6.12	211	34	150	134	27
96	SHIVANAPPA G RADDERATTI	60	M	YES	YES	20 YR	YES	T GLYCOMET 500 1-0-1	NO	120/80	26.33	6.8	97	242	5.36	126	33	77	79	16
97	SOMANGOUDA B PATIL	55	M	YES	YES	28 YR	YES	T AMARYL 1 1-0-0 T TENGLYN 20 1-0-0 T PIOZ 15 1-0-0	NO	150/90	25.46	10.2	177	274	5.82	178	39	88	255	51
98	SUNANDA I UNDRE	72	F	YES	YES	40 YR	NO	irregular	NO	140/90	24.39	8.1	138	199	5.65	160	39	98	116	23
99	YALLAWWA S NAVALGI	78	F	YES	YES	20 YR	NO	T GLYCOMET GP-1 1-0-1	NO	140/90	25.72		112	222	5.78	173	39	108	128	26
100	ASHOK Y BHAJANTRI	55	M	YES	NO	5 YR	NO	INSULIN	YES	130/80	27.74		119	206	5.28	242	36	187	97	19

ANNEXURE-V

KEY TO MASTER CHART

BMI	-	Body Mass Index
HbA1C	-	Hemoglobin A1c
HDL	-	High Density Lipoproteins
LDL	-	Low Density Lipoproteins
mg/dl	-	Milligram per decilitre
U/ml	-	Units per millilitre
VLDL	-	Very Low Density Lipoproteins
kg/m^2	-	Kilogram per square metre
mm/hg	-	Millimetres of mercury

Introduction



Objectives

Review of Literature

Methodology

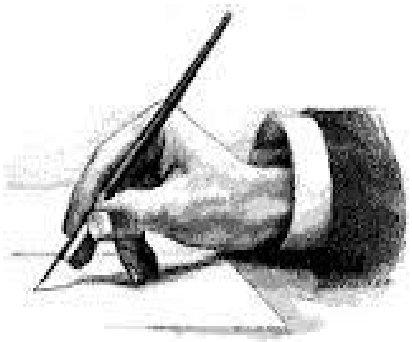
Results

Discussion

Conclusion

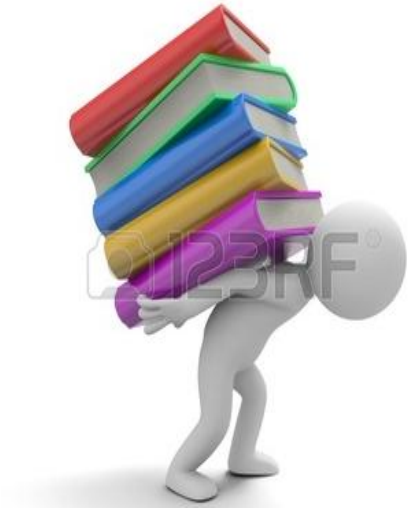
Summary

Bibliography



Annexure-I

Annexure-II



Annexure-III

Annexure-IV

Annexure-V