ASSOCIATION BETWEEN SERUM LEVELS OF VITAMIN D AND LIPID PROFILES IN TYPE 2 DIABETIC PATIENTS

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LIST OF ABBREVIATIONS USED

α	-	Alpha
β	-	Beta
μg	-	Microgram
1,25(OH)2D3	-	1α, 25-dihydroxyvitamin D3
ADA	-	American Diabetes Association
BMI	-	Body mass index
CDC	-	Center for Disease Control
CoA	-	Co-activator
CoR	-	Co-repressor
DBP	-	Diastolic blood pressure
DCCT	-	Diabetes Control and Complications Trial
DM	-	Diabetes Mellitus
DNA	-	Deoxyribonucleic acid
FPG	-	Fasting plasma glucose
FBS	-	Fasting Blood Sugar
FFA	-	Free Fatty Acids
GDM	-	Gestational diabetes mellitus
HbA1c	-	Glycated hemoglobin
HDL	-	High density lipoprotein
HSL	-	Hormone Sensitive Lipase
ICMR	-	Indian Council of Medical Research
IDDM	-	Insulin dependent diabetes mellitus
IDF	-	International Diabetes Federation
IFG	-	Impaired fasting glycaemia
IGT	-	Impaired glucose tolerance
IU	-	International units
Kg	-	Kilogram

Kg/m^2	-	Kilograms per meter square
LDL	-	Low density lipoprotein
LPL	-	Lipoprotein Lipase
mg/dl	-	Milligram per deciliter
mmol/l	-	Millimoles per litre
mm Hg	-	Millimeter of mercury
MODY	-	Maturity Onset Diabetes of Young
n	-	Total number
ng/l	-	Nanograms per litre
NPDR	-	Non Proliferative Diabetic Retinopathy
NGSP	-	National Glycohemoglobin Standardization Program
OHA	-	Oral Hypoglycemic Agents
OGTT	-	Oral glucose tolerance test
POL II	-	Polymerase II
PPBS	-	Post prandial blood sugar
RNA	-	Ribonucleic acid
RXR	-	Retinoic X receptor
SD	-	Standard deviation
SGOT	-	Serum glutamate-oxaloacetate transaminase
SGPT	-	Serum glutamate-pyruvate transaminase
TCF7L2	-	Transcription factor 7–like 2
VDR	-	Vitamin D receptor
VDRE	-	Vitamin D response element
VDSP	-	Vitamin D Standardization Program
WHO	-	World Health Organization

ABSTRACT

Background

Cardiovascular Disease is the most common cause of mortality in type 2 diabetes mellitus. Diabetic dyslipidemia is one of the contributing factor. The effect of vitamin D on the lipid profiles is one of the proposed mechanisms for the association between diabetes and cardiovascular disease. This present study is intended to find out the association, if any, exists between vitamin D status and lipid profile in patients with type 2 diabetes mellitus.

Objectives

To study the correlation between vitamin D and lipid profile in type 2 diabetes mellitus.

Methodology

The present cross sectional study was conducted for one and half year in the Department of Medicine, BLDE University's Shri B M Patil Medical College and Research Centre, Vijayapur from January 2015 to June 2016. A total of 160 patients with type 2 diabetes mellitus were studied. Anthropometric data was recorded and patients were examined thoroughly. The estimation of Vitamin D was done using Siemens, ADVIA Centraur Vitamin D assay, standardized as per Vitamin D Standardization Program. Fasting Lipid Profile was measured using enzymatic kits and standard reagents. Fasting and post prandial glucose were measured using glucose oxidase method and HbA_1C was measured using a standard procedure.

Results

The prevalence of vitamin D deficiency in our study was 76.2%. 122 patients had vitamin D deficiency (vitamin D < 20 ng/l), 17 patients had insufficiency (vitamin D levels 20 to 30 ng/l) and 21 patients had sufficiency of vitamin D levels (vitamin D

> 30 ng/l). Our study showed almost equal distribution of subjects by sex, with male subjects around 48.1% and female subject around 51.9%. Nearly 65% of the cases involved in our study belonged to the age group of 50 to 70 years. 78.1% of the cases were only on oral hypoglycemic agents treatment, rest of the patients had insulin therapy with or without oral hypoglycemic agents. 91.3% of the cases were having diabetes of duration less than 10 years in our study. Vitamin D deficiency was significant in the diabetic patients with duration of more than 5 years. About 70.6 % of the cases were having BMI in the range of 25 to 29.9 and were classified in the overweight category. 33.8 % of the cases had fasting blood sugar greater than 180mg/dl. And very few cases had fasting blood sugar under control about 16.2% of the cases. 56.9 % of the cases had post prandial blood sugar above the level of 200mg/dl and had significantly poor glycemic control. 55 % of the cases had HbA_1C more than 8, showing the inadequate glycemic control. 60.4 % of the diabetic cases in our study showed hypertriglyceridemia. In 73.8 % of the diabetic patients HDL cholesterol was less than 40 mg/dl. 69.7 % of the overweight diabetic patients had vitamin D deficiency in our study.

Conclusion

The present study has demonstrated that there is a direct relationship of serum levels of vitamin D and HDL cholesterol (p value of 0.036), and an inverse relationship with LDL cholesterol (p value of 0.051).

Keywords

Diabetes Mellitus, Lipid Profile, Vitamin D, Association, HDL cholesetrol, LDL cholesterol.

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INTRODUCTION

Diabetes mellitus is one of the major disorders of the metabolism affecting human race. The very first reports of diabetes encodes in Egyptian manuscript around 3 millenia BC, when it was recognized as a disorder characterized by polyuria. It is basically caused due to derangement of process of glucose control either due to deficient production of insulin or decreased action of insulin at the receptor level.[1]

Type 1 diabetes mellitus is characterized by decreased or absolute no production of insulin by the pancreas due to antibody production against pancreas causing hyperglycemia. Type 2 diabetes mellitus occurs predominantly due to insulin resistance and reduced insulin secretion and β cell dysfunction. Diabetes causes a number of complications like microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischemic heart disease, stroke and peripheral vascular disease). Several comorbid conditions like depression, obesity, osteoporosis, cognitive impairment cause increased barriers to the management of diabetes.[2]

The World Diabetes Day is held on November 14 every year to spread the awareness about Diabetes globally. International Diabetes Federation (IDF) has opted the "Eyes on Diabetes" theme for the year 2016 and has promoted for screening and early diagnosis of serious complications. Previous year theme of "Healthy Eating" has been supported worldwide and social media was also utilized for the awareness campaign. IDF has considered awareness of World Diabetes Day since 1991 in collaboration with World Health Organization (WHO). The Blue Ring is considered as symbol of diabetes used for the awareness. According to IDF diabetes atlas, the global prevalence of diabetes is estimated to be 415 million with significant burden on global health expenditure. India is in second place next to China with a prevalence of

69.2 million individual and more than half of the deaths due to diabetes occur in individuals less than 60 years of age.[3]

Many studies have demonstrated the role of vitamin D in the development of type 2 diabetes mellitus. Vitamin D is also implicated as playing a role in cardiovascular diseases like hypertension, heart failure, ischemic heart disease. It has also been demonstrated that vitamin D deficiency may lead to increased risk of cardiovascular mortality in individuals with pre-existing cardiovascular disease. Cardiovascular Disease is the most common cause of mortality in type 2 diabetes mellitus. Diabetic dyslipidemia is one of the contributing factor. Several studies have demonstrated that vitamin D plays a significant role in endothelial function, regulation of blood pressure, calcification of coronary vessels and prevention of cardiovascular disease.[4]

Vitamin D deficiency has also been demonstrated to be associated with impaired glucose tolerance and diabetes mellitus. Vitamin D has been suggested to play a role in the mechanism of type 2 diabetes mellitus through its action on β cell function and modulating insulin resistance. The effect of vitamin D on the lipid profiles is one of the proposed mechanisms for the association between vitamin D and cardiovascular disease. This present study is intended to find out the association, if any, exists between vitamin D status and lipid profile in patients with type 2 diabetes mellitus

AIMS AND OBJECTIVES

AIM

- To determine the association between fasting serum levels of vitamin D and lipid profile in patients with type 2 diabetes mellitus.

OBJECTIVES

- To study the correlation between vitamin D and lipid profile in type 2 diabetes mellitus patients.
- To study the effect of serum concentration of vitamin D on lipid profile in type 2 diabetes mellitus patients.

REVIEW OF LITERATURE

Diabetes is the most common disorder of metabolism affecting human race. Its affection to mankind can be traced back to ages as early as 1500BC during the time of Egyptians, when it was first mentioned as a disorder characterized by polyuria. [5]

Indian Physicians observed similar features among the affected individuals and mentioned it in Charaka Samhita. They noticed that the urine of the affected individual was attracted by ants and hence the disorder was named as 'Madumeha' meaning 'Honey urine'. It was also found that the urine was sticky and predominantly affected people with excessive food consumption like cereals, rice and sweet. [6]

The term "Diabetes" was first coined by Arateus of Cappodocia around 81 – 133 AD. The word Diabetes is derived from the word "diabaino" which means "I pass through" referring to as passing through the fluid/urine. Ancient Chinese Physicians, notably Chang Chung-Ching (160-219AD) and Chen Chuan (7^{th} century AD) observed polyuria, polydipsia and weight loss features among the affected individuals. During 8^{th} century, it was further observed that the diabetic patients had tendency to develop skin infections and had trouble with eye sight. Arabic Physician, Avicenna (980-1037AD) also confirmed these findings and mentioned that gangrene and sexual dysfunction occur as complication of diabetes. Subsequently, Thomas Willis, an English anatomist and physician, added the term "Mellitus" after rediscovering that the urine of the affected individual had sweet taste like honey. Thomas Willis dedicated a chapter "Pissing Evil" in his publications. In 1776 another English doctor, Mathew Dobson identified for the first time that sugar was responsible for the sweetness of urine in the patients suffering from Diabetes. Mathew Dobson boiled the urine till dryness and noticed that residual crystalline material had taste of sugar.

Later, Claude Bernard, a French physician, did extensive study on Diabetes in 19th century, found upon postmortem analysis that pancreas was either diseased, or atrophic or had stones sometimes. He also analyzed samples from liver and concluded that liver was storing large quantities of sugar which was missing from other organs. [7]

Another major milestone in the history of Diabetes occurred in 1889 after the research of Minkowski and von Mering, together who performed pancreatectomy in a dog, which survived the procedure and developed polyuria. Urine was later examined and found to be having 12 % sugar. Later this experiment was confirmed similar procedure in three more dogs. Furthermore Minkowski implanted a small portion of pancreas subcutaneously and found that sugar levels were controlled by the implant. Minkowski and von Mering's experiment demonstrated that pancreas was the internal organ responsible for sugar homeostasis.[8]

A turning point in the history of diabetic management took place after the discovery of insulin by Fredrick Banting and John MacLeod. Macleod granted laboratory space and dogs for the experiment in the University of Toronto. Fredrick Banting worked with his assistant Charles Best who was a medical student. In 1921, they removed pancreatic extract and injected into depancreatized dogs and found that blood sugar levels dropped considerably after 2 hours. Consequently James Collip, chemist helped them to purify the pancreatic extract which was called "insletin" and later as "insulin". On January 11, 1922, Insulin was first administered to a 14 year old boy Leonard Thompson in Toronto Hospital. Treatment was a success and the boy lived another 13 years and died at 27 years due to pneumonia. Later in 1923 Nobel Committee decided to award Banting and Macleod for their pioneering work in the discovery of insulin. Banting shared prize with Best and Macleod shared prize with Collip. In 1930, H C Hagedorn, a chemist in Denmark, added protamine to insulin to

prolong its action. In Toronto, Scott and Fisher, potentiated this protamine insulin by adding zinc to it. Protamine zinc insulin established sugar control for 24 to 36 hours. Isophane neutral protamine insulin lasted for 24 hours and was compatible with regular insulin. Lente insulin contained various proportions of zinc and was classified as lente, semi lente and ultralente.[9]

In 1978, the first recombinant DNA insulin was synthesized from Escherichia coli by David Goeddel and his colleagues. It was later marketed in 1982 as Humulin. In 1996, Lispro was the first short acting insulin analog was approved. Insulin Aspart was approved for use in 2000. Glulisine Insulin was approved in 2004. Glargine, basal insulin analog with prolonged action was approved in 2000, and Detemir was approved in 2005. Inhaled insulin, Exubera, was marketed in 2006 but failed to gain popularity due to bulky device without any added advantage over conventional insulins.[10]

History of Vitamin D

Although rickets has been known since ages but due to the outbreaks of rickets in 17th century in England led to the discovery of Vitamin D. Sir Edward Mellanby suspected rickets to be due to dietary deficiency and investigated further for the evidence. The disease was rampant that time and was well known as "the English Disease". He supplemented the diets of rickets individuals with cod liver oil and assumed that vitamin A was possible culprit of the disease. Later he found that oxygenated cod liver oil which is lacking in vitamin A also has the ability to cure rickets and he named the new vitamin as "Vitamin D". In the mean time other notable physicians like Huldshinsky, Chick, Hess and Unger also found that sunlight has the ability to cure rickets. Harry Steenbock found that sunlight exposure caused positive

calcium balance. In 1932 Askew et al isolated vitamin D2. Later in 1935, 7-dehydrocholesterol was isolated by Windaus et al and in 1937 vitamin d3 was isolated by Winduas and Bock. In 1978 Esvelt et al found that naturally occurring vitamin D3 was synthesized in body by irradiation of 7-dehrdro cholesterol. Later Holick et al proved that previtamin D3 is formed before conversion of 7-dehydrocholesterol to active vitamin D3.[11]

Definition of Diabetes[12]

Diabetes refers to group of metabolic disorders which share the common phenotype of hyperglycemia resulting from the defects in insulin secretion, insulin action or both.

Deranged metabolism of type 2 diabetes mellitus is associated with impact on multiple organ systems causing significant morbidity and mortality among the sufferers.

Diabetes Mellitus is the leading cause of morbidity and mortality worldwide by its contribution to the development of End Stage Renal Disease, Blindness and Cardiovascular Diseases.

ICD – 10 classification code[13]

Diabetes is classified under Endocrine, Nutritional and Metabolic disorders section under the code E08 – E13. Type 2 diabetes is classified under E11.

E11.1 – diabetes with hyperosmolarity

E11.2 – diabetes with kidney complications

E11.3 – diabetes with ophthalmic complications

E11.4 – diabetes with neurological complications

E11.5 – diabetes with circulatory complications

E11.6 – diabetes with specified complications like skin, periodontal disease, hypoglycemia, hyperglycemia

E11.8 – diabetes with unspecified complications

E11.9 – diabetes without complications

Risk Factors[14]

Many studies have confirmed that the following risk factors contribute to the development of diabetes mellitus and validate for screening and evaluation of diabetes mellitus in asymptomatic individuals.

Risk factors are enumerated as follows –

- Obesity (BMI ≥25 kg/m^2 or ethnically relevant definition for overweight)
- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Physical inactivity
- Previously identified with IFG, IGT, or an hemoglobin A1c of 5.7–6.4%
- Maternal history of GDM or delivery of baby >4 kg (9 pounds weight)
- Hypertension (blood pressure ≥140/90 mmHg)
- HDL cholesterol level <35 mg/dl (0.90 mmol/L) and/or a triglyceride level >250 mg/dl (2.82 mmol/L)
- Polycystic ovarian syndrome or acanthosis nigricans or other signs of insulin resistance
- History of cardiovascular disease

The frequency of screening in the risk prone individuals is at least once in 3 years. Though the individuals can develop complications within 3 years, however this interval is deemed cost-effective globally.

Classification[15]

1. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
    a. Immune-mediated
    b. Idiopathic
2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3. Other specific types of diabetes
    a. Genetic defects of beta cell development or function characterized by mutations in:
        i. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
        ii. Glucokinase (MODY 2)
        iii. HNF-1α (MODY 3)
        iv. Insulin promoter factor-1 (IPF-1; MODY 4)
        v. HNF-1β (MODY 5)
        vi. NeuroD1 (MODY 6)
        vii. Mitochondrial DNA
        viii. Subunits of ATP-sensitive potassium channel
        ix. Proinsulin or insulin
        x. Other pancreatic islet regulators/proteins such as KLF11, PAX4, BLK,GATA4, GATA6, SLC2A2 (GLUT2), RFX6, GLIS3

b. Genetic defects in insulin action
    i. Type A insulin resistance
    ii. Leprechaunism
    iii. Rabson-Mendenhall syndrome
    iv. Lipodystrophy syndromes
c. Diseases of the exocrine pancreas – Pancreatitis, Pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis, Fibrocalculous pancreatopathy, mutations in carboxyl ester lipase
d. Endocrinopathies – Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma
e. Drug- or chemical-induced – glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine
f. Infections – congenital rubella, cytomegalovirus, coxsackievirus
g. Uncommon forms of immune-mediated diabetes – "stiff-person" syndrome, anti-insulin receptor antibodies
h. Other genetic syndromes sometimes associated with diabetes – Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader-Willi syndrome

4. Gestational diabetes mellitus (GDM)

Genetics

The lifetime risk of developing diabetes is 40% for individuals who have one parent with diabetes and 70% if both parents are affected. First degree relatives of individuals with diabetes are about 3 times more likely to develop the disease than individuals without a positive family history of the disease. The concordance rate in monozygotic twins is about 70% whereas in dizygotic twins has been observed to be only 20%-30%. Several genes have been implicated in the pathogenesis of diabetes mellitus and few of them have been discussed below. Linkage studies and genome wide association studies are the methods of identifying these genes. [16]

These studies only revealed two genes, calpain 10 (CAPN10) and transcription factor 7-like 2 (TCF7L2) that were identified as being associated with diabetes. CAPN10 encodes a cysteine protease that is part of the calpain family, a large family of ubiquitously expressed genes that play multiple roles in intracellular remodeling, intracellular signaling and other intracellular functions. It is the first diabetes gene to be discovered by linkage analysis on a locus in chromosome 2. TCF7L2 was discovered as a diabetes susceptibility gene after a strong linkage signal was mapped to chromosome 10q. The relatively few genes that were found to be associated with diabetes include peroxisome proliferator-activated receptor gamma (PPARG), insulin receptor substrate 1 (IRS1) and IRS-2, potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11), Wolfram syndrome 1 (wolframin) (WFS1), HNF1 homeobox A (HNF1A), HNF1 homeobox B (HNF1B), HNF4A, RAPGEF1 and TP53 [17]

Comorbidities

Other comorbid conditions associated with diabetes: depression, obstructive sleep apnea, fatty liver disease, osteoporosis, cognitive impairment or dementia, Parkinson's disease, schizophrenia, heart failure and low testosterone in men[18]

Pathogenesis

Insulin resistance and abnormal insulin secretion are central to the development of Type 2 diabetes. However the basic defect is controversial, most studies support the view that insulin resistance precedes an insulin secretory defect but the fact that diabetes develops only when insulin secretion is inadequate.[19]

Advanced Glycation End Products

Advanced glycation end products (AGEs) are the diverse group of protein and lipids and are created by a non-enzymatic reaction between aldehydes of reducing sugars and the amino groups of proteins, lipids and nucleic acids. The first association between glycated proteins and diabetes happened in 1968 with the discovery of a different form of hemoglobin (presently known as $HbA1_c$) in red blood corpuscles of patients with diabetes. The glycation process involving the reaction between the amino group of proteins and the aldehyde group of sugars is described as Millard Reaction.[20]

In diabetic patients, AGE formation is increased due to higher concentration of circulating glucose, AGE precursors and oxidative stress. In addition, accumulation of AGEs in diabetic patients was shown to have correlation with diabetic complications. AGE-mediated damage takes place through binding of AGEs to the "receptor of advanced glycation end products" (RAGE). RAGE belongs to the immunoglobulin superfamily and additionally interacts with a wide range of ligands.[21]

Recent studies have shown that AGEs may be involved in causing insulin resistance and administration of antioxidants is known to reduce these effects and detrimental complication. AGEs have been demonstrated to have cytotoxic effects on pancreatic β cells, by causing apoptosis and thereby reducing insulin secretion. AGEs are also hypothesized to have role in decreasing the insulin gene transcription and reduce the insulin secretion. AGE-albumin-induced pericyte death has been presumed to be caused by AGE-RAGE interaction. Pericytes are cells which surround the capillaries in the retina and their damage is an early event in diabetic retinopathy results in the formation of acellular capillaries (capillaries without cells), microaneurysms and vascular basement membrane thickening. The interaction of pericyte with endothelial cells is necessary for the maintenance of the blood-retina barrier so that pericyte loss is also associated with the breakdown of the barrier. Similar to pericytes in the retina, AGEs induce apoptosis in mesangial cells of kidneys, specialized pericytes which are located in blood vessels of the kidney. . Mesangial cells in the glomerulus regulate glomerular filtration and provide structural support. Their loss or further VEGF up regulation contributes to increased vascular permeability associated with hyper filtration and proteinuria in kidney diseases, suggesting that AGEs play a role. MCP-1 is a chemokine which regulates macrophage/monocyte migration and infiltration, therefore, MCP-1 up regulation by AGEs may trigger inflammation in renal tissue.[22]

AGEs often build up high concentrations intracellularly. These intracellular AGEs play important part for activation of intracellular signaling pathways and transform the role of intracellular proteins. Glycation of proteins hinders the normal mechanism of those intracellular proteins by interrupting molecular conformation, modifying enzymatic activity, decreasing degradation capacity, and interfering with

receptor recognition. The intermolecular collagen cross-linking caused by AGEs leads to diminished arterial and myocardial compliance, increased vascular stiffness, increase in diastolic dysfunction and systolic hypertension. AGEs are able to form AGE related immune complexes in diabetic patients and may play a role in atherogenesis.[23]

Glycated Hemoglobin (HbA_1C)

Measurement of glycated hemoglobin in diabetic patients is an established procedure for evaluating long-term control of diabetes. The Diabetes Control and Complications Trial (DCCT), as well as the United Kingdom Prospective Diabetes Study (UKPDS), confirmed the direct relationship between the degree of glycemic control as estimated by glycohemoglobin determinations and the development and progression of long-term complications. [24]

Hemoglobin A1c, the component in human erythrocytes, that is formed by the condensation of glucose with the N-terminal amino groups of the beta-chains of Hemoglobin A. The biosynthesis of this glycated hemoglobin was studied by incubating suspensions of reticulocytes and bone marrow cells with leucine or Fe-bound transferrin. These studies show that HbA_1C is slowly formed during the 120-day life-span of the erythrocyte, possibly by a non-enzymatic process. Patients with shortened erythrocyte life-span due to hemolysis had markedly decreased levels of HbA1c. The Diabetes Control and Complications Trial (DCCT) used HbA1c as the primary index of glycemia. The DCCT and, subsequently, the United Kingdom Prospective Diabetes Study (UKPDS) also, established the relationship between glycemic control and the risk of diabetic complications. [25]

The most reliable test for HbA1c is performed in a high quality clinical laboratory, which is standardized to the National Glycohemoglobin Standardization Program (NGSP). One of the limitations of estimating the glycated hemoglobin is the concurrent occurrence of anemia and hemoglobinopathies.[26]

Complications

It is divided into microvascular complications and macrovascular complications.

Microvascular Complications [27, 28]

1. Diabetic Nephropathy
2. Diabetic Retinopathy
    a. Non-Proliferative Diabetic Retinopathy
    b. Proliferative Diabetic Retinopathy
3. Diabetic Neuropathy

Macrovascular Complications [29]

1. Stroke
2. Coronary Artery Disease
3. Peripheral Vascular Disease

Diagnostic Criteria by American Diabetic Association (ADA) [15]

For many years Fasting Plasma Glucose and Oral GTT have proved valuable parameters for the diagnosis of diabetes mellitus and related complications like retinopathy. Glycated Hemoglobin (HbA_1C) is a recent advantage to assess blood glucose levels and glycemic control over 2 to 3 months period. HbA_1C is used as an

index of chronic glycemia. However, the levels of HbA_1C can be often misleading in cases of anemia and hemoglobinopathies.

Criteria for the diagnosis of Diabetes Mellitus are as follows-

1. $HbA_1C \geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay** OR
2. FPG ≥ 126 mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for atleast 8 hour.** OR
3. 2 hour PPG ≥ 200mg/dl(11.1mmol/l) during an OGTT. This test should be performed as described by World Health Organisation, using a glucose load containing the equivalent of 75gm anhydrous glucose dissolved in water.** OR
4. In a patient with classical symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200mg/dl(11.1mmol/l).
** In the absence of unequivocal hyperglycemia, criteria 1 to 3 should be confirmed by repeated testing.

Diagnostic Criteria by International Diabetes Federation (IDF)

Guidelines for screening and diagnosis of Diabetes [30]

Detection programs are usually based on a two-step approach:

Step1 - Identify high-risk individuals using a risk assessment questionnaire.

Step 2 – Glycemic measure in high-risk individuals.

1. Diabetes can be diagnosed on any of the following World Health Organization (WHO) criteria:
    a. Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl)

    Or,

    b. 75 g oral glucose tolerance test (OGTT) with FPG ≥ 7.0 mmol/l (126 mg/dl) and/or 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

    Or,

    c. Glycated hemoglobin (HbA1c) ≥ 6.5%,

    Or,

    d. Random plasma glucose ≥ 11.1 mmol/l (200 mg/dl) in the presence of classical diabetes symptoms
    e. Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally elevated.
2. Where a random plasma glucose level ≥ 5.6 mmol/l (≥ 100 mg/dl) and < 11.1 mmol/l (< 200 mg/dl) is detected, a FPG should be measured, or an OGTT performed, or an HbA1c measured.

3. Use of HbA1c as a diagnostic test for diabetes requires that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.
4. People with screen-detected diabetes should be offered treatment and care.
5. Target HbA_1C maintaining below 7.0%, fasting capillary plasma glucose below 6.5mmol/l (115mg/dl) and post prandial capillary plasma glucose less than 9.0mmol/l (160mg/dl).

Spectrum of Glucose Homeostasis or temporal progression of DM [31]

The degree of hyperglycemia may change over time, depending on the extent of the underlying disease process. A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive b-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

GLUCOSE HOMEOSTASIS IN DIFFERENT CONDITIONS

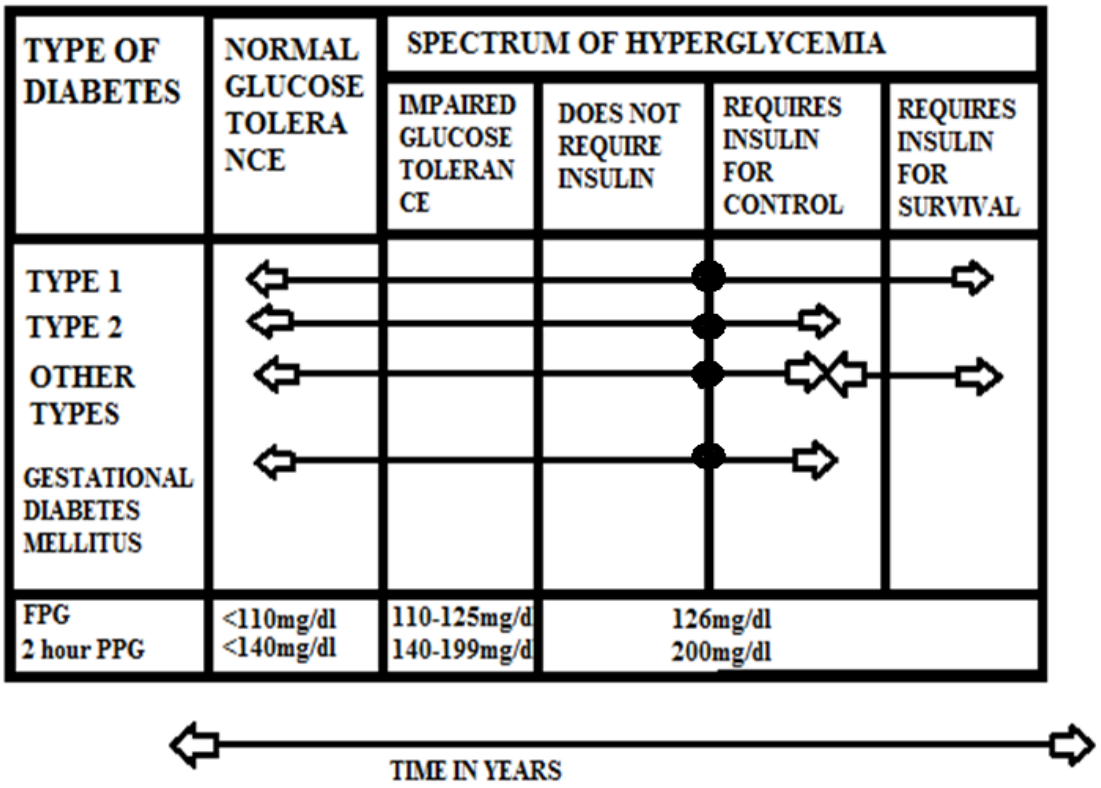


Fig No 1

Epidemiology

Global, National, Regional[6]

Diabetes is considered as a global emergency. The worldwide prevalence of diabetes is estimated to be 415 million and is expected to rise to 642 million by the year 2040. Diabetes is significant cause of mortality and is estimated to be nearly 5 million deaths in 2015. The prevalence has slight male preponderance 215 million males are affected compared with 199 million females. Most of the diabetics belong to Urban dwelling (270 million) compared with rural areas (145 million).

The greatest challenge is to find out the asymptomatic individuals. It is estimated that nearly one out of two adults with diabetes have been undiagnosed.

Diabetes poses a great economic burden as the global health expenditure for diabetes is estimated to be around 650 -750 billion US dollars. [3]

India is in the second place next to China (109.6 million people) with estimated prevalence of 69.2 million affected individuals. [32]

There are patterns of diabetes incidence that are related to the geographical distribution. Studies show that the prevalence of diabetes in rural populations of India is one-quarter than that of urban population and similar distribution in other Indian sub-continent countries such as Bangladesh, Nepal, Bhutan, and Sri Lanka.[33]

Results of several community studies conducted by the Indian Council of Medical research (ICMR) revealed that a lower prevalence of diabetes in Northern Indian states like Chandigarh (0.12 million), Jharkhand (0.96 million) as compared to Southern Indian states like Maharashtra (9.2 million) and Tamil Nadu (4.8 million). The National Urban Survey conducted across the metropolitan cities of India reported similar trend; 11.7 % in Kolkata (Eastern India), 6.1 % per cent in Kashmir Valley (Northern India), 11.6 % in New Delhi (Northern India), and 9.3 % per cent in West India (Mumbai) compared with (13.5 % per cent in Chennai (South India), 16.6 % per cent in Hyderabad (south India), and 12.4 % per cent Bangalore (South India). Therefore, relatively lean Indian adults with a lower BMI may be at equal risk as those who are obese. Furthermore, Indians are genetically predisposed to the development of coronary artery disease due to dyslipidemia and low levels of high density lipoproteins. These determinants make Indians more prone to development of the complications of diabetes at an early age (20-40 years) compared with Caucasians (>50 years) and indicate that diabetes must be carefully screened and monitored regardless of patient age within India. [34]

The Chennai Urban Population Study (CUPS) 53 and CURES 55 provided valuable data from India on the complications related to diabetes. The prevalence of coronary artery disease was 21.4 % among diabetic subjects compared to 9.1 per cent in subjects with normal glucose tolerance. The prevalence of CAD in IGT subjects were 14.9% in the same study. It was also seen that the diabetic subjects had increased subclinical atherosclerosis as measured by intimal medial thickness (IMT) at every age point compared to subjects with normal glucose tolerance.[35, 36]

The prevalence of peripheral vascular disease (PVD) was 6.3 % among diabetic subjects compared to 2.7 % in non-diabetic subjects 56, and these figures are lower than the prevalence reported in western populations. This is probably due to lower age at onset for diagnosis of type 2 diabetes in India. It is well known that PVD is more common in older individuals.[37]

The CURES Eye study is the largest population based data on the prevalence of diabetic retinopathy done in India. This study showed that the overall prevalence was 17.6 per cent, which was lower when compared to the reports from the West. A recent population based study reported that the prevalence of overt nephropathy was 2.2 per cent in Indians while microalbuminuria was present in 26.9 %. Glycated hemoglobin, duration of diabetes and systolic blood pressure were independently associated with diabetic nephropathy. Overall, Asian Indians appear to have a greater predilection for cardiovascular complications whereas the prevalence of microvascular complications appears to be lower than in Europeans.[38]

Standards Of Medical Care In Diabetes Mellitus

Recommendations For Glycemic Control [39]

Target Goals

1. A1C < 7.0%
2. Pre-prandial capillary plasma glucose 90–130 mg/dl (5.0–7.2 mmol/l)
3. Peak post-prandial capillary plasma glucose < 180 mg/dl (<10.0 mmol/l)
4. Blood pressure <130/80 mmHg

Lipids Targets

1. LDL <100 mg/dl (<2.6 mmol/l)
2. Triglycerides <150 mg/dl (<1.7 mmol/l)
3. HDL <40 mg/dl (<1.1 mmol/l)

Key concepts in setting glycemic goals:

- A1C is the primary target for glycemic control
- Goals should be individualized
- Certain populations (children, pregnant women, and elderly) require special considerations
- Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia
- More stringent glycemic goals (i.e. a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes)
- Postprandial glucose may be targeted if A1C goals are not met despite reaching pre-prandial glucose goals

Recommendations for Dyslipidemia in Diabetics

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL<100 mg/dl, HDL <50 mg/dl, and triglycerides <150 mg/dl), lipid assessments may be repeated every 2 years.

BIOCHEMISTRY OF LIPIDS

The lipids are diverse group of compounds including fats, oils, steroids, waxes and related compounds that are related more by their physical than chemical properties.

The lipids are classified as given below [40]

A) **Simple lipids** (esters of fatty acid with various alcohols)

- Fats: esters of fatty acids with glycerol. Oils are fats in liquid state
- Waxes: esters of fatty acids with higher molecular weight monohydric alcohols.

B) **Complex lipids**: These are esters of fatty acids containing groups in addition to an alcohol and a fatty acid groups)

- Phospholipids: lipids containing in addition to fatty acids and an alcohol, a phosphoric acid residue.
- Glycolipids: lipids containing a fatty acid, sphingosine and carbohydrate.
- Other complex lipids: lipids such as sulfolipids and amino-lipids. Lipoproteins may also be placed in this category.

C) **Derived lipids**: These include fatty acids, glycerol, steroids, other alcohols, fatty aldehydes, hydrocarbons, lipid soluble vitamins and hormones.

Lipo-Proteins of Plasma [41]

In plasma, cholesterol and triglycerides form integral component of macromolecule complex called lipoprotein which are conjugated proteins. Lipid part is the prosthetic group and lipid free protein are designated as apolipoproteins or apo proteins. Lipoproteins are micro emulsions composed of lipids (cholesterol, cholesteryl ester, triglyceride and phospholipid) and proteins (apoproteins). Their function is to transport non water soluble cholesterol and triglycerides in plasma. Lipoproteins are spherical particles containing a central core of non-polar lipids (primarily triglycerides and cholesteryl ester) and a surface monolayer of phospholipids and apoproteins. Lipoproteins have been classified on the basis of their densities during ultracentrifugation into-

1. Chylomicrons
2. Very low density lipoprotein (VLDL)
3. Low density Lipoprotein (LDL)
4. High density lipoprotein
5. Lipoprotein a

Characteristics And Mechanisms Of Dyslipidemia In Diabetes[42,43,44]

Dyslipidemia is a comparatively common problem in patient with diabetes mellitus. Patients with diabetes typically have an atherogenic lipid profile characterized by elevated triglycerides, increased LDL, VLDL and cholesterol and decreased HDL. There are several reasons for this association:

First, insulin plays an important role in the regulation of intermediary lipid metabolism and fluctuations in the degree of diabetic control thus produce a variable effect on plasma lipoprotein metabolism.

Secondly, many non-insulin dependent diabetic patients are obese, and obesity leads to the development of hyperlipidemia.

Increased LDL

There is an increased proportion of small dense LDL particles. Total LDL levels may be modestly increased or may be even within target range around 100 mg/dl, but they may actually have more circulating small, dense LDL particles than an individual with normal insulin sensitivity and the same LDL level.

Hypertriglyceridemia

Exogenous triglycerides are derived from diet and circulate as chylomicrons, while endogenous triglycerides combine with hepatic cholesterol to form VLDL particles, which are secreted into the circulation by hepatocytes. Abnormalities of Lipoprotein lipase (LPL) activity and fatty acid metabolism all contribute to baseline and often extreme postprandial hypertriglyceridemia associated with type 2 diabetes and insulin resistance. Although fasting LPL levels are typically increased in the setting of obesity because of the large number of adipocytes, insulin resistance at the level of the fat cell causes decreased LPL activity and therefore, an abnormal response of LPL to a glucose load. Diminished LPL activity leads to an accumulation of atherogenic LDL precursors, such as VLDL in the circulation. Hormone Sensitive Lipase (HSL) activity is increased in type 2 diabetes, which causes increased circulating Free Fatty Acids (FFA). In the setting of insulin resistance, adipocytes take up less circulating FFA. This situation, called reduced fatty acid trapping, allows excess FFA delivery to the liver, which, in turn, causes increased hepatic secretion of VLDL particles. This is most pronounced and prolonged after a meal. [42, 43, 44]

Decreased HDL[45,46,47]

The decreased HDL in type 2 diabetes mellitus is mostly reflected in diabetic dyslipidemia. Although it is not completely understood how hepatic lipase acts in the regulation of HDL, it is possible that the lower HDL concentrations in type 2 diabetes mellitus may in part be attributable to higher hepatic lipase activity. Hepatic lipase is elevated in obese female type 2 diabetes mellitus subjects and increased in thin male type 2 diabetes mellitus individuals, the activity in the latter group decreasing after normalization of glycemia with insulin therapy. Reduced HDL leads to diminished clearance of cholesterol from peripheral tissues. The actions of cholesteryl ester transfer protein illustrate why hypertriglyceridemia and reduced HDL typically go hand in hand in patients with type 2 diabetes. In the setting of elevated circulating triglycerides, cholesteryl ester transfer protein allows an increased influx of VLDL triglycerides into HDL particles. This occurs as an exchange reaction, with a simultaneous efflux of cholesteryl ester out of HDL particles. This process leads to reduced HDL levels owing to increased clearance of HDL particles. There is also reduced production of HDL particles in type 2 diabetes owing to abnormal LPL activity, causing decreased conversion of dense, triglyceride- rich HDL to more buoyant particles.

Qualitative Changes in LDL: LDL Particle Size

In type 2 diabetes mellitus, the LDL level may be normal or only modestly elevated in patients with type 2 diabetes and obesity there are frequently qualitative changes in LDL particles that confer increased risk of Coronary Artery Disease. As individuals proceed from normal insulin sensitivity to insulin resistance, VLDL particles become larger and LDL particles become smaller. Individuals with type 2 diabetes have been shown to have smaller, denser LDL particles.

Diabetes and Atherosclerosis

Atherosclerosis is the basis of a most of the cardiovascular events, and atherosclerosis is accelerated by diabetes and the metabolic syndrome. Studies have presented valuable insights into possible means by which glucose might injure endothelial cells or play a role in atherogenesis. Atherosclerosis is started by the attachment of monocytes to arterial endothelial cells, followed by their migration into the subendothelial space. Monocytes then undergo differentiation into intimal macrophages, which take up lipids (thereby becoming foam cells) and deposit in the artery wall in diabetes, leading to accelerated fatty streak formation. Gradually, these early fatty streak lesions are considered to evolve into advanced lesions, characterized by smooth muscle cell accumulation, necrotic core formation, and lipid deposition. Some of these advanced lesions eventually become unstable and rupture, resulting in the clinical manifestations of CVD. [48]

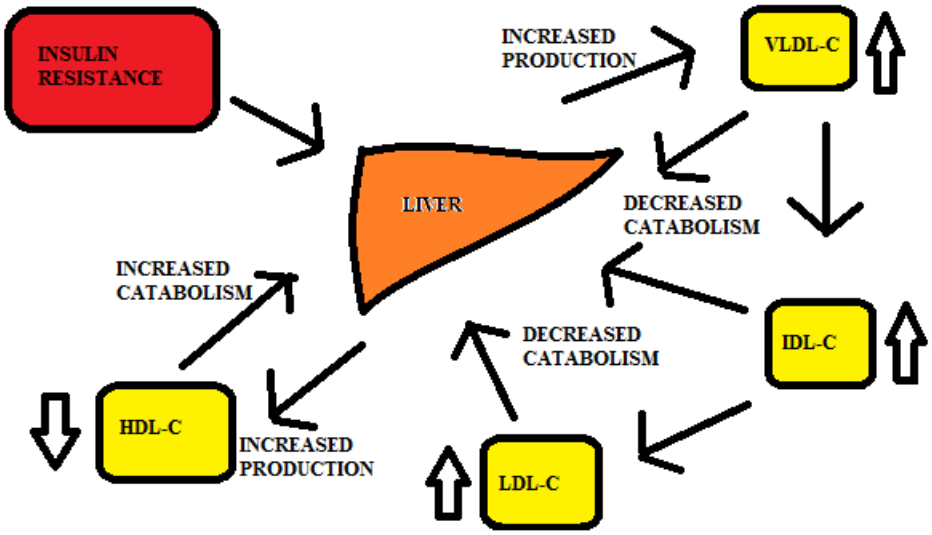
DIABETIC DYSLIPIDEMIA

Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. The availability of multiple lipid-lowering drugs and supplements provides new opportunities for patients to achieve target lipid levels. However, the variety of therapeutic options poses a challenge in the prioritization of drug therapy. The prevalence of hypercholesterolemia is not increased in patients with diabetes mellitus, but mortality from coronary heart disease increases exponentially as a function of serum cholesterol levels, and lowering of cholesterol with statins reduces

diabetic patients' relative cardiovascular risk. Although drug therapy for dyslipidemia must be individualized, most people with diabetes mellitus are candidates for statin therapy, and often need treatment with multiple agents to achieve therapeutic goals. [49]

Dyslipidemia is one of the key risk factors for cardiovascular disease (CVD) in diabetes mellitus. Despite the mounting clinical trial data, the management of dyslipidemia other than lowering the LDL-Cholesterol continues to be controversial. The characteristic features of diabetic dyslipidemia are high plasma triglyceride concentration, reduced HDL-Cholesterol concentration, and increased concentration of small dense LDL particles. These changes are caused by increased free fatty acid flux secondary to insulin resistance and aggravated by increased inflammatory adipokines. The availability of several lipid-lowering drugs and nutritional supplements offers novel and effective options for achieving target lipid levels in people with diabetes. While initiation of drug therapy based on differences in the lipid profile is an option, most practice guidelines recommend statins as first-line therapy. Although the evidence for clinical utility of combination of statins with fibrates or nicotinic acid in reducing cardiovascular events remains inconclusive, the preponderance of evidence suggests that subgroups that have high triglycerides and low HDL-Cholesterol levels may benefit from combination therapy of statins and fibrates. The goal of therapy is to achieve at least 30-40 % reduction in LDL-Cholesterol levels. Preferably the LDL-Cholesterol should be less than 100 mg/dl in low-risk people and less than 70 mg/dl in those at high risk, including people with established CVD.[50]

MECHANISM OF DIABETIC DYSLIPIDEMIA



ATHEROGENIC DIABETIC DYSLIPIDEMIA. Insulin resistance is assoicated with enhanced production of VLDL-Cholesterol along with decreased catabolism of other lipoproteins. Increased production of HDL-Cholesterol is outweighed by increased catabolism. These factors contribute to atherogenic dyslipidemia of diabetes.

Fig No 2

Nevertheless, lifestyle modification and glucose control may improve the lipid profile but statin therapy mediates the biggest benefit with respect to cardiovascular risk reduction. Therefore most diabetic patients should receive statin therapy. The role of other lipid lowering drugs, such as ezetimibe, fibrates, omega-3 fatty acids, niacin and bile acid sequestrants is less well defined as they are characterized by largely negative outcome trials. [51]

NATIONAL CHOLESTEROL EDUCATION PROGRAM GUDELINES [52]

In 1984, National Institute of Health formed a Consensus on lowering blood cholesterol. After reviewing the evidence, the panel concluded that raised blood cholesterol levels is a major cause of CAD and that lowering the cholesterol levels will reduce the risk of atherosclerosis and risk factor for cardiovascular disease. They recommended treating moderate risk adults with a low cholesterol diet and that high-

risk adults are to be considered for drug therapy if not responsive to low cholesterol diet. In 1985, The National Cholesterol Education Program was initiated by the National Heart Lung and Blood institute to reduce the prevalence of elevated blood cholesterol levels.

Presently, the NCEP ATP III guidelines recommended that all adults over the age of 20 years and children of families with premature atherosclerosis should be tested for their serum cholesterol level. Acute illness, myocardial infarction or surgery can lower cholesterol levels, so such patients should have their serum lipids measured again after 8-12 weeks later.

Current recommendations by NCEP ATP III are as follows:

Total Cholesterol levels

1. Desirable: <200 mg/dl
2. Borderline high: 200-239 mg/dl
3. High: >240 mg/dl

If serum cholesterol is less than 200 mg/dl, no further evaluation is required and patient asked to repeat the test in 5 years. Patients with borderline high cholesterol levels should be advised to follow a cholesterol lowering diet and repeat the test in 1 year. Patients with cholesterol levels>200 mg/dl and CHD other cardiovascular risk factors, or with cholesterol>240 mg/dl should have a complete assessment of their lipid status. This requires a fasting sample of blood and measurement of total cholesterol, triglycerides, HDL and LDL (calculated as total cholesterol-HDL-TG/5).

The NCEP ATP III recommends that decisions about treatment of patients with hypercholesterolemia should be based on LDL Cholesterol levels and risk factors.

LDL levels as follows:

1. Desirable: < 100 mg/dl
2. Near or above optimal: 100-129 mg/dl
3. Borderline high: 130-159mg/dl
4. High: 160-189 mg/dl
5. Very High: ≥190 mg/dl

Major Risk Factors (Exclusive of LDL Cholesterol)

1. Cigarette smoking
2. Hypertension (BP > 140/90 mmHg or on antihypertensive medication)
3. Low HDL cholesterol (< 40 mg/dl)
4. Family history of premature CHD (CHD in male first degree relative <55 years; CAD in female first degree relative < 65 years)
5. Age (men >45 years; women >55 years).

INITIATE THERAPEUTIC LIFESTYLE CHANGES (TLC) IF LDL IS ABOVE GOAL

1. TLC Diet:
   - **a.** Saturated fat <7% of calories, cholesterol <200 mg/day
   - **b.** Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering

2. Weight management

3. Increased physical activity.

DRUG THERAPY

Drug therapy should be reserved for patients who after an adequate therapeutic lifestyle change therapy still have:

1. LDL> 129 mg/dl
2. High risk status and HDL<40 mg/dl.

The goal of the therapy is to reduce LDL to below 100 mg/dl and in high risk patients less than 70 mg/dl. The major classes of drugs of consideration are

1) **HMG COA reductase inhibitors**:
    a. Lovastatin (20-80 mg)
    b. Pravastatin (20-40 mg)
    c. Simvastatin (20-80 mg)
    d. Fluvastatin (20-80 mg)
    e. Atorvastatin (10-80 mg)
    f. Cerivastatin (0.4-0.8 mg)

    Side Effects: Myopathy and Increased liver enzymes

2) **Bile acid sequestrants**:
    a. Cholestyramine (4-16 g)
    b. Colestipol (5-20 g)
    c. Colesevelam (2.6-3.8 g).

    Side Effects: Gastrointestinal distress, Constipation and Decreased absorption of other drugs

3) **Nicotinic acid**

    Immediate release (crystalline) nicotinic acid (1.5-3 gm), or extended release nicotinic acid (1-2 g), or sustained release nicotinic acid (1-2 g) formulations.

Side Effects: Flushing, Hyperglycemia, Hyperuricemia (or gout), Upper GI distress and hepatotoxicity

4) **Fibric acid derivatives**

   a. Gemfibrozil (600 mg BID)

   b. Fenofibrate (200 mg)

   c. Clofibrate (1000 mg BID)

Side Effects: Dyspepsia, Gallstones and Myopathy

It often takes 2-3 months of diabetic treatment to see the full effect on lipoprotein profiles and to restore tissue lipoprotein levels to normal. Treatment of hypertriglyceridemia also remains controversial. The National Institute of Health Consensus Conference on Treatment of Hypertriglyceridemia recommended that fasting triglyceride level not be considered elevated unless >200 mg/dl. Hypertriglyceridemia always should be treated with better diabetic control, weight loss, alcohol restriction and fat restricted diet. Drug therapy is advised when TG levels are more than 200mg/dl. Although the Level of HDL is inversely related to risk of CHD there is no evidence that raising isolated HDL levels with drugs in patients with otherwise normal plasma lipid levels reduces cardiovascular risk.

Reduction of high risk of CAD and peripheral arterial disease should be an essential part of diabetic management. Diet and glycemic control can improve serum lipid levels dramatically.

VITAMIN D

Vitamin D was first identified and characterized in 1923 by Goldblatt and Soames. It is an essential vitamin naturally produced by the body on exposure to sunlight.[53]

The term Vitamin D consists of a group of steroid derivatives like secosterols, ergocalciferol (VD2) and cholecalciferol (VD3). Vitamin D2 is produced commercially by irradiation of plant sterols (ergosterol), whereas Vitamin D3 is basically synthesized in the skin from 7-dehydro cholesterol via photochemical synthesis using UV radiation from sunlight and can also be found in food of animal origin. The best food sources of Vitamin D are cod liver oil, fatty fish, and egg yolks. Natural Vitamin D by itself has no hormonal activity. To become biologically active, Vitamin D requires two hydroxylations; one in the liver (at carbon 25) and another in the kidney (at a position of carbon 1). In the liver Vitamin D is hydroxylated at carbon 25 to 25-hydroxy Vitamin D (25(OH)D). Circulating 25(OH)D concentrations is considered an indicator of Vitamin D status. 25-hydroxy vitamin D is converted to 1,25-dihydroxy vitamin D in the kidneys and contributes to the biologically active form of vitamin D. The production of 1,25- dihydroxy vitamin D at proximal tubule of the nephron, is regulated by several factors including the parathormone, which has negative feedback mechanism for the formation of active vitamin D i.e. 1,25-dihydroxy vitamin D(Vitamin D_3). This active form of vitamin D is bound to Vitamin D Binding Protein in the circulation.[54, 55]

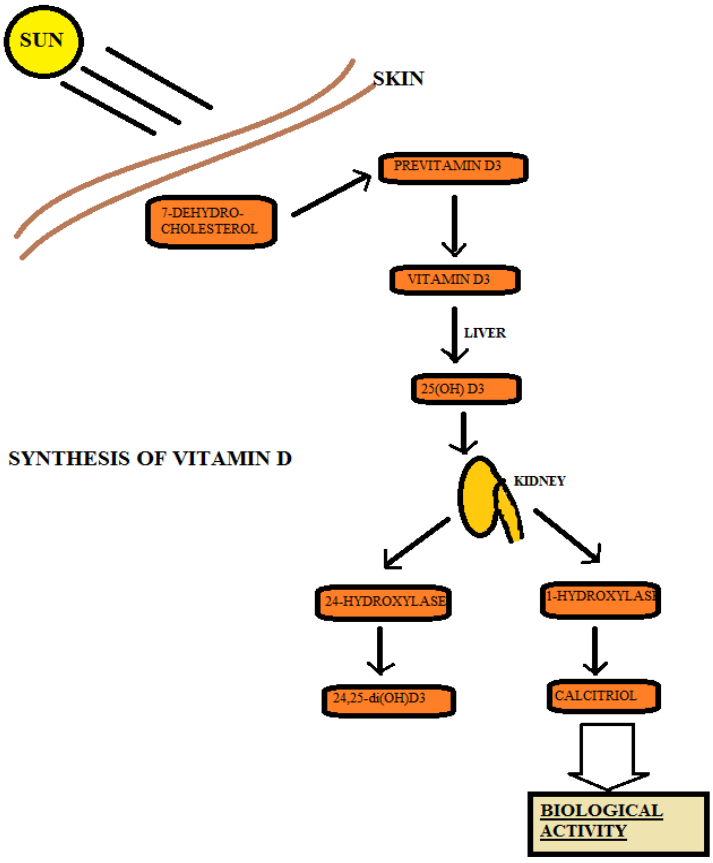


Fig No 3

Vitamin D mediates its action through activation of vitamin D receptor, which is a type of nuclear receptor belonging to the super family of ligand activated transcription factors. The gene locus for this receptor is found at 12q12. Molecules of 1,25(OH)2D3 penetrate the plasma membrane with the help of DBP and exert their genomic effects by activating the VDR. Ligand binding to the VDR induces a conformational change in the receptor and subsequent heterodimerization with RXR. The RXR-VDR complex binds to the VDR Element, which is located within the 5' flanking region of target genes. Thereafter, co-repressor (CoR) proteins are released from the surface of the VDR, allowing interaction with co-activator (CoA) proteins. These molecules modulate chromatin structure and allow the interaction of the receptor with the RNA polymerase II transcriptional complex (POL II), thus

activating transcription of the target gene. The cognate Vitamin D response element (VDRE) to which the VDR binds consists of a hexanucleotide direct repeat spaced by three nucleotides (DR3-type VDRE). The VDR usually binds as a heterodimer with the retinoic X receptor (RXR), and the classical effects of 1,25 (OH)2D3 are the result of interactions with this nuclear receptor. With respect to its relevance in diabetes, the classical VDRE and other response sites are found within genes encoding proteins with important functions in beta-cells and within genes encoding proteins with key roles throughout the immune system, such as cytokines and transcription factors.[56]

Vitamin D deficiency

Serum 25(OH)D is the best indicator of Vitamin D body store levels. The desirable concentration of Vitamin D in normal healthy adult should be greater than 30 ng/ml. Vitamin D deficiency is characterized by circulating levels of 25(OH)D less than 20 ng/ml. Concentrations ranging between 20-30 ng/ml are often considered insufficient. [57]

Low Vitamin D status can be caused by number of factors, including insufficient cutaneous synthesis (due to limited sunlight exposure or aging), inadequate intake and absorption of Vitamin D, obesity or darker skin. Low blood levels of its main metabolite, 25(OH) D, have been linked to poor health outcomes such as fractures, poor physical function, sarcopenia, diabetes, osteoporosis, cancer, cardiovascular, neurodegenerative, autoimmune and infectious diseases.[58]

LITERATURE REVIEW

A study done by Calvo-Romero JM and Ramiro-Lozano JM(2015) found that supplementation of 16000 IU of cholecalifediol every week for a period of 2 months

resulted in improvements of HbA_1C and insulin resistance. This study also showed significant improvement in fasting blood sugar and β cell function.[59]

According to Women Health Initiative CaD trial(1993-1998), Schnatz PF, Jiang X, Vila-Wright S, Aragaki AK, Nudy M, O'Sullivan DM, Jackson R et al proved that supplementation of 400IU vitamin D and 1000mg calcium for a period of 5 years resulted in drop in triglycerides and LDL cholesterol levels compared with the placebo amongst the post menopausal women. This study also showed significant improvement in HDL cholesterol levels among post menopausal women.[60]

According to a study done by Zhou J, Chen H, Wang Z, Li Y, Li M, Xiang H(2014) et al demonstrated that vitamin D supplementation using 0.5 mcg of calcitriol for a period of 12 weeks showed significant improvement in BMI, HbA_1C and insulin resistance.[61]

Another study conducted by Orgaz-Molina J, Magro-Checa C, Rosales-Alexander JL, Arrabal-Polo MA, Buendia Eisman A, Raya Alwarez E(2013) et al showed that vitamin D was inversely associated with fasting blood sugar, total cholesterol, LDL cholesterol and triglycerides amongst the psoriatic patients. This inverse relationship was better demonstrated among the psoriatic patients who did not develop arthritis compared with the patients who did develop arthritis.[62]

Catherin S. Birken, Gerald Lebovic, Laura N, Anderson, Brain W. McCrindle, Muhammad Mamdani, Sharmilaa Kandasamy(2015), studied to find out the relationship between vitamin D concentration and lipids in early childhood. This study showed that vitamin D concentrations were inversely associated with circulating lipids in early childhood and vitamin D exposure in early life may be modifiable risk factor for cardiovascular disease.[63]

A study conducted by Foong-Ming Moy and Awang Bulgiba(2001) in Kuala Lumpur showed that vitamin D insufficiency is associated with greater risk of abdominal obesity and metabolic syndrome in the Malaysian population.[64]

Alba Guasch, Monica Bullo, Antonio Rabassa, Anna Bonada, Daniel Del Castilo, Fatima Sabench(2009-2011) et al studied that serum levels of vitamin D is directly related, and parathormone is inversely related with body mass index, adiposity and dyslipidemia. [65]

An interventional study conducted by Nasser M Al-Dahgri, Khalid M Alkharfy, Abdulaziz AL-Othman, Emad El-Kohlie, Osama Moharram, Majed S Alokail et al showed that oral daily supplementation of 2000 IU vitamin D for a period of 18 months improved the lipid profile and β cell function in diabetes mellitus patients.[66]

A study done by Mazliza Ramly, Foong Ming Moy, Rokiah Pendek, Suhaili Suboh and Alexander Tan Tong Boon et al found that supplementation of 50000 IU of vitamin D every week for initial 2 months and later every month for 1 year, is associated with improvement in cardiovascular and metabolic risk factors.[67]

Another interventional study done by Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami MA, Hadinedoushan H, Mozayan MR demonstrated that single injection of high dose vitamin D of 3 lakh IU intramuscular route, improved serum vitamin D levels for 3 months and also improved insulin resistance and glycemic status.[68]

A study done by Claudia Gagnon, Robin M Daly, Andre Carpentier, Zhong X Lu, Catherine Shore-Lorenti, Ken Shikaris et all showed that supplementation of

calcium 1200mg per day and vitamin D 2000-6000 IU per day, for a period of 6 months improved insulin sensitivity in people with prediabetes. However there was no significant correlation with insulin secretion and β cell function.[69]

Another study done by Kampmann U, Mosekilde L, Juhl C, Moller N, Christensen B, Rejnmark L, Wamberg L et al showed that oral supplementation of cholecalciferol 280 mcg per day for initial 2 weeks and followed by 140 mcg per day for next 10 weeks showed borderline improvements in insulin secretion . No improvement was noted for insulin resistance, blood pressure, inflammation, HbA_1C levels.[70]

Another study done by Bindal ME, Taskapan H showed that there is an inverse correlation between serum levels of vitamin D and insulin resistance amongst non diabetic patients on peritoneal dialysis. [71]

Another study done by Alemzadeh R, Kichler J, Babar G, Calhoun M showed that vitamin D deficiency was associated with higher body mass index, fat mass, parathormone. Vitamin D deficiency group had lower insulin sensitivity index than vitamin D sufficient group.[72]

Another study done by Sharifi F, Mousavinsab N, Mellati AA showed that vitamin D concentration is inversely related with the insulin resistance as measured by HOMA-IR levels in randomly selected iranian children in the age group of 7 to 11 years. [73]

According to VLDL-3, very large database of lipids study(2009-2011), a study doneon 20360 people showed that, vitamin D defifciency is associated with

significantly lower levels of HDL cholesterol and significantly higher levels of LDL and VLDL cholesterol levels and higher levels of triglycerides. [74]

Another study done by Yifan Huang, Xiaoxia Li, Maoqing Wang, Hua Ning, Lima A, Ying Li et al analysed that lipoprotein lipase was inversely associated with insulin resistance and type 2 diabetes mellitus in Chinese population. This study involved 2708 subjects from Harbin, China.[75]

N P Suryavanshi, A K Bhutey, A N Nagdeote, A A Jadhav, G S Manoorkar studied the effect of blood glucose on lipid peroxide and lipid profile in diabetic patients and found that there was a significant increase in lipid peroxide and total cholesterol and triglycerides in patients with poor glycemic control especially in type 2 diabetes mellitus. This study concluded that good glycemic control will prevent alteration in lipid peroxidation and lipid metabolism and thus prevent vascular complications in diabetes mellitus.[76]

A study done by El-Hajj Fuleihan G, Baddoura R, Habib RH, Halaby G, Arabi A, Rahme M et al studied that daily supplementation of high dose of vitamin D above recommended dietary allowance did not result in any significant improvement in HOMA-IR index. However this study showed that there was a significant benefit of vitamin D supplementation in patients with insulin resistance. This study was done for a period of 1 year.[77]

A study done by Jose Manuel Ramiro Lazano, Jose Maria Calvo Romero at Coria, Spain, found that supplementation of vitamin D 16000 IU every week for a period of 8 to 16 weeks resulted in significant reductions in the total cholesterol levels. There was no significant reductions in the levels of LDL cholesterol and triglycerides.[78]

A study done by Joanna Mitri, Bess Dawson Hughes, Frank B Hu, Anastassios G Pittas showed that daily oral supplementation of vitamin D 2000 IU and calcium 400mg twice a day for 16 weeks significantly improved β cell function, improved insulin secretion, insulin sensitivity and glucose homeostasis. There was only a marginal effect on HbA_1C levels.[79]

A study done by Toh Peng Yeow, Shueh Lin Lim, Chee Peng Hor, Amir S Khir, Wan Nazaimoon, Wan Mohamud, Giovanni Pacini showed that daily oral supplementation of vitamin D 4000 IU for 6 months significantly improved β cell function and metabolic state in women with gestational diabetes.[80]

A study done by Milica Bozic, Angeles Alvarez, Carmen de Pablo, Maria Dolores Sanchez Nino, Alberto Ortiz et al showed that decreased expression of vitamin D signaling can lead to endothelial inflammation and atherosclerosis. [81]

Another study done by Deborah M Mitchell, Benjamin Z Leder, Enrico Cagliero, Natalia Mendoza, Douglas L Hayden, Joel S Finkelstein et all showed that supplementation of vitamin D 50000 IU every week for a period of 12 weeks improved vitamin D deficiency but did not affect insulin secretion and insulin sensitivity in otherwise normal individuals in the age group of 18 – 45 years.[82]

A study done by Christopher Paul Baker, Bharati Kulkarni, K V Radhakrishna, M S Charyulu, John Gregson, Mika Matsuzaki et all showed that there was association between vitamin D levels and observed BMI in APCAPS study. They suggested that the relationship between vitamin D and cardiovascular may be due to lifestyle factors like physical inactivity.[83]

A study done by Raza Kazlauskaite et among 78 post menopausal age group of 48 to 64 years in Chicago community showed that higher levels of 25-hydroxy vitamin D is associated with larger HDL cholesterol particle. This study confirmed that Vitamin D levels are atheroprotective and protect against cardiovascular risk by promoting formation of large HDL particles.[84]

A study conducted by Christian L. Roth et al in 156 children of pre-pubertal age in Seattle Children's Hospital in Germany, showed that a low level of serum 25-hydroxy vitamin D is associated with higher levels of insulin and insulin resistance in obese children than in normal children. This study also showed that hypovitaminosis D is significantly associated with adiponectin levels.[85]

In 2014, a study conducted by Esmaeil Yousefi Rad, et al in Tehran, Iran, demonstrated in 28 patients who received vitamin D supplementation of 4000 IU, compared with placebo showed that there was considerable improvement in glycemic status of the patients. It was demonstrated by significant improvement in HbA^1C and decrease in HOMA-IR as a measure of insulin resistance. This study confirmed that Vitamin D supplementation has significant beneficial role in improving glucose homeostasis in adults with type 2 diabetes mellitus.[86]

A study conducted by Jaydip Ray Chaudari et al during the period of October 2011 to March 2012, at Hyderabad, showed that among 150 randomly selected subjects vitamin D deficiency was around 39.3% and was independently associated with dyslipidemia. Nearly 30% of the patients had Diabetes. Patients had other risk factors also like smoking and alcoholism.[87]

A large study done by Edward Giovannucci et al, at Southampton University, United States, for a period of 10 years (1994-2004) follow-up amongst 18225 patients

diagnosed with cardiovascular disease at the time of registering, 454 patients developed myocardial infarction and fatal coronary heart disease. After analysis of data, the patients who were deficient in vitamin D (<15ng/ml) were found to have more risk of myocardial infarction compared with the patients who had vitamin D sufficiency (>30ng/ml). This study demonstrated that optimal levels of vitamin D at least 30ng/ml is required to lower the risk of myocardial infarction.[88]

A recent study conducted in 2015 by Xiaomin Sun et al, amongst 107 adults of age group 40 to 79 years, at Japan, showed that higher levels of 25-hydroxy vitamin D had strong correlation with lowered insulin resistance and improved cardio-respiratory fitness regardless of abdominal fat. This study concluded that higher 25-hydroxy vitamin D may strengthen cardio-respiratory fitness and reduce insulin resistance in middle aged and elderly Japanese men with optimum cardio-respiratory fitness.[89]

A study done by Hui Ma et al, amongst 671 euglycemic normotensive postmenopausal women in Shangai, China in 2014 showed that 25-hydroxy vitamin D is independently and inversely associated with carotid atherosclerosis by measuring the carotid intima-media thickness (CIMT) bilaterally. The mean age of the subjects was 58.8 years. [90]

A study done by Surya Prakash Bhatt et al amongst 137 Non-diabetic Asian Indians residing in North India during the period of 2006 to 2011 at AIIMS, New Delhi, showed that most of the individual had insufficient levels of 25-hydroxy vitamin D(87.6%) and it was associated with higher values of total abdominal fat at the level of L2 – L3 intervertebral level. The study concluded that other

anthropometric parameters like BMI, waist and hip circumferences and skin fold thickness did not correlate significantly with 25-hydroxy vitamin D concentrations.[91]

A study conducted by Amy Moore et al amongst the young adults who were residents of Jerusalem born in the year 1974 to 1976 who were registered in Jerusalem Perinatal Study, underwent follow-up during the period of 2007 to 2009 and analyzed for 25-hydroxy vitamin D status and insulin resistance. The follow-up study found that there was inverse association between 25-hydroxy vitamin D and markers of insulin resistance. This correlation was established among males, but not in females. This study showed that insulin resistance was higher in middle aged males than in females and contributed to pathogenesis of type 2 diabetes mellitus.[92]

A study done by Truong-Minh Pham et al amongst the 6682 Canadians enrolled in the preventive health program and followed up in between 2007 to 2014, found that improvement in serum vitamin D status lowered the risk of metabolic syndrome significantly. The preventive health program promoted vitamin D supplementation in the region of Northern part of Canada with low sunlight exposure.[93]

A double-blind trial study done by Mohammed E. Al-Sofiani et al amongst 22 diabetic patients in Saudi Arabia, showed that supplementation of cholecalciferol (5000IU/day) for 12 weeks significantly improved homeostasis model assessment of β cell activity (HOMA-β) compared to placebo. Vitamin D supplementation also significantly improved β cell activity, but not HbA^1C levels and insulin sensitivity.[94]

A study done by Jared P. Reis et al amongst the 3577 US adolescent non diabetic individuals who participated in National Health And Nutritional Examination Survey (NHANES) during the period 2001 – 2004 were examined for vitamin D

status and cardiovascular risk factors. The study found that hypovitaminosis D was more prevalent amongst the black ethnicity, and was strongly associated with overweight and abdominal obesity. This study also found that 25-hydroxy vitamin D concentrations were inversely associated with systolic blood pressure and plasma glucose concentrations and showed significant correlation with metabolic syndrome. Even after adjustment for age and BMI this correlation remained significant.[95]

A study done in Cairo, Egypt, by Nehal Hamdy Al-Said et al amongst 78 patients with type 2 diabetes mellitus found that low levels of vitamin D can lead to increase in carotid intima-media thickness without significant correlation with derangement in lipid profile. This study suggested a possibility that the underlying causes of atherosclerosis in diabetes could be other than dyslipidemia.[96]

According to a study done at Rome, Italy by Ilaria Barchetta et al of 65 patients who underwent the study, were supplemented with high dose oral vitamin D for 24 weeks did not improve non alcoholic fatty liver disease in type 2 diabetic patients.[97]

A cross-sectional study conducted by Giacomo Zoppini et al found that the serum levels of 25-hydroxy vitamin D is inversely associated with HbA^1C levels in 715 diabetic patients attending Diabetic Clinic in Verona, Italy during the period of 2011 – 2012. [98]

A study done by Jaividhya Dasarathy et al, at Cleveland, Ohio amongst the 148 patients who were having non alcoholic fatty liver disease, confirmed by biopsy demonstrated that the serum levels of vitamin D were low in such patients compared to healthy subjects. This study proved that low levels of vitamin D is associated with greater degree of hepatic steatosis, hepatocyte ballooning and fibrosis.[99]

A study done by Amal M.H. Mackawy and Mohammed E.H. Badawi at Egypt during 2012-2013 amongst 190 subjects, found that there is an interaction between vitamin D receptor polymorphisms and components of metabolic syndrome in type 2 diabetic patients. These vitamin D receptor polymorphisms are also linked to inflammatory markers and insulin resistance and pomote the development of metabolic syndrome.[100]

A study done by Mohammad Hassan Eftekhari et al amongst 70 type 2 diabetes patients aged 30 to 75 years received 0.25mcg of calcitriol for 12 weeks showed that there was significant reduction in total cholesterol, LDL cholesterol and triglyceride levels. There was a significant reduction in lipid profile and oxidative stress in the subjects supplemented with vitamin D compared to the placebo group.[101]

A study done by Sung Su Jung et al at Korea amongst the 115 diabetic children showed marked seasonal variation which was not associated with changes in diabetic status of the children. The seasonal variation of vitamin D deficiency in winter was similar in the control group, but was not associated with change in clinical parameters.[102]

A study conducted by Gianluca Bardini et al in Florence, Italy used a parameter called lipid accumulation product defined by product of sex-specific waist circumference and triglycerides. This parameter showed that diabetes patients with higher lipid accumulation product had high risk of vitamin D deficiency and suggested that overweight has worsening effect on vitamin D status. This study found that overweight subjects with or without diabetes had low levels of 25-hydroxy vitamin D.[103]

A study done by May A. Al-Shahwan et al in Riyadh, Saudi Arabia amongst 45 type 2 diabetic patient enrolled for the study between January 2013 to January 2014 were supplemented with 2000 IU of vitamin D daily for period of 1 year, found that there was significant improvement in systolic blood pressure, insulin levels and insulin resistance.[104]

Another study done by Guri Grimnes et al amongst the 52 participants enrolled in Tromso study were selected and randomized to receive 20000 IU vitamin D supplementation and placebo treatment. There was significant change in insulin sensitivity index and drop in HbA^1C levels among the subjects who had high serum 25-hydroxy vitamin D than amongst the subjects with low levels of 25-hydroxy vitamin D. But this study failed to demonstrate considerable statistical significance. [105]

A study done by Joaquin Portilla et al at Spain amongst 89 non - diabetic HIV infected males found that vitamin D insufficiency was associated with increased risk of subclinical atherosclerosis as measured by carotid intima media thickness in non diabetic HIV infected males. This association remained significant after having adjusted for confounding factors.[106]

A study done by Ohk-Hyun Ryu et al in Korea amongst the 62 type 2 diabetic patients enrolled for this study. Patients were supplemented with 2000 IU of cholecalciferol with 200mg of calcium daily for 24 weeks and were analyzed for insulin resistance and arterial stiffness using ankle brachial pulse wave velocity. After the analysis of results this study found that the serum levels of vitamin D improved in supplemented group compared with placebo group, however there was no significant

improvement in insulin resistance or measures of arterial stiffness for 24 week supplementation.[107]

A study done by Amena Sadiya et al among 309 patients with type 2 diabetes mellitus and obesity in United Arab Emirates found that there was high prevalence of vitamin D deficiency (83.2%) and was strongly associated with BMI, waist circumference, triglyceride and LDL cholesterol levels and suggested the role of vitamin D in the development of cardio-metabolic disease in the affected population.[108]

A current ongoing trial in Australia conducted by Barbora de Courten et al amongst 50 overweight individuals aged 18 to 60 years old who will be randomly assigned for vitamin D supplementation and placebo group. Intervention group will receive 1 lakh IU of vitamin D as first dose followed by 4000 IU daily for a period of 16 weeks. Placebo group will receive an identical capsule. After 16 weeks results will be analyzed for change in insulin sensitivity and secretion and anthropometric data. The results of the trail will be out by 2017.[109]

A study done by Mattia Bellan et al amongst 524 obese patients in Italy, analyzed for the vitamin D status and markers of calcium and glucose metabolism and lipid profile. This study found that serum levels of vitamin D significantly correlated with levels of triglycerides, HDL cholesterol and LDL cholesterol levels. There were also notable associations between vitamin D levels and markers of glucose metabolism like HbA^1C levels. And hence the study conclude that vitamin D has independent role in glucose metabolism in obese patients with or without diabetes.[110]

MATERIALS AND METHODS

This study is conducted in the Department of Medicine, BLDE University's Shri B. M. Patil Medical College and research Centre, Vijayapur from January 2015 till June 2016 amongst the patients with type 2 diabetes mellitus who attended outpatient department and inpatient department.

Study Design

This study is cross sectional study

Study duration

The current study is one and half year duration

Place of study

This study is conducted in the Department of Medicine, Shri B. M. Patil Medical College, Vijayapur.

Source of Data

All the patients with type 2 diabetes mellitus attending OPD and IPD of BLDEU's Shri B. M. Patil Medical College, Vijayapur during the study period who are eligible are enrolled in the present study.

Ethical clearance

The ethical clearance for this study was obtained from Institutional Ethics Committee, BLDE University's Shri B. M. Patil Medical College, Vijayapur.

Informed Consent

The patients fulfilling the inclusion criteria were explained about the nature of the study. Those who consented for participation were enrolled in the study after obtaining written informed consent.

Sample Size

A total of 167 patients with type 2 diabetes mellitus were selected for the current study.

Sample Size Calculation

With 95% confidence level, the expected prevalence of type 2 diabetes mellitus in the urban area is 12.4 % and margin of error as ±5%. The minimum sample size is 167.

The formula used in the calculation is

$$N = \frac{z^2 \times p \times (1 - p)}{D^2}$$

N= Sample Size

z = Statistic for level of confidence(1.96@95%level of confidence)

p = Prevalence of the disease

D= Margin of error

Statistical analysis

Data will be analysed by using the following

- Mean ±SD
- Graphical Representation
- Chi Square test
- Regression Analysis

Inclusion Criteria

- All type 2 diabetic patients with age in between 20 to 80 years attending Diabetic Clinic, OPD and admitted in IPD of Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur

Exclusion Criteria

- Pregnancy
- Lactation
- Use of drugs affecting lipid profile
- Use of drugs affecting calcium and bone metabolism
- Chronic disorders of liver and kidney
- Disorders of thyroid or parathyroid gland
- Use of anticonvulsive drugs
- Vitamin D/ Calcium supplementation

Method of collection of data

Preliminary data of the patient is noted like name, age, sex, inpatient registration number, occupation, address, date of admission. Patient is enquired for present illness. And history of type 2 diabetes mellitus is noted for duration of disease, diet, medication, exercise. History regarding other existing comorbid conditions is enquired. General Physical examination is done. Vitals are noted. BMI is calculated using height and weight of the patient. Height is measured to nearest 0.5 cm, and weight is measured to nearest 0.1kg using standard equipments. A thorough systemic examination is done. These findings were recorded in preexisting proforma designed for the present study. The patients were subjected to following blood investigations

- Complete blood count
- FBS, PPBS, HbA^1C
- 25-hydroxyvitamin D
- Fasting Lipid profile
- Renal Function tests

Method of collection of samples

- After overnight fasting, 5 – 10 ml of peripheral venous blood is taken from the patients. Serum is separated and analyzed for the following tests
- Serum levels of 25-hydroxyvitamin D is measured by chemiluminescence assay or CLIA method. Fasting levels of serum 25-hydroxyvitamin D is estimated by Siemens, ADVIA Centaur Vitamin D Assay, which uses a antibody immunoassay method for estimation of 25-hydroxyvitamin D. This method uses a fluorescent monoclonal antibody derived from mouse and another antibody labeled with acridinium ester, directed against 25-

hydroxyvitamin D and a vitamin D analog tagged with fluorescein. This test is standardized as per Vitamin D Standardization Program (VDSP).[111]

- Fasting levels of blood glucose is measured using glucose oxidase method and HbA_1C is measured using an analyzer according to the procedure provided. Post prandial glucose was measured by glucose oxidase method.
- Fasting levels of triglycerides, total cholesterol and HDL cholesterol are measured using enzymatic kits and standard reagents.

Interpretation of the results

Diagnostic criteria for Diabetes (ADA Guidelines) [15]

Parameter	**Range**
FBS	≥126 mg/dl
PPBS	≥200mg/dl
HbA^1C	≥6.5%
RBS(in cases of hyperglycemic crisis)	≥200mg/dl

Body Mass Index (BMI)

After recording the height and weight of the patients body mass index was calculated using the following formula

$$\text{Body Mass Index} = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in meter)}}$$

BMI is measured and classified as follows[112]

Nutritional Status	BMI Values (WHO Criteria)	BMI Values (Asian Criteria)
Underweight	<18.5	<18.5
Normal	18.5-22.9	18.5-22.9
Overweight	23-29.9	23-24.9
Pre – obese	-	25-29.9
Obese Grade 1 (Obese)	30-40	30-40
Obese Grade 2 (Morbid)	40.1-50	40.1-50
Obese Grade 3 (Super)	>50	>50

Lipid profile

The fasting serum levels of triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol were noted and interpreted as follows

Lipid Parameters	Normal Range
Triglycerides	25-200mg/dl
Total Cholesterol	125-200mg/dl
HDL Cholesterol	35-80mg/dl
LDL Cholesterol	85-130mg/dl
VLDL Cholesterol	5-40mg/dl

Fasting Serum 25-hydroxy Vitamin D[113]

Vitamin D Status	Observed Levels
Deficiency	<20ng/ml
Insufficiency	20-30ng/ml
Sufficiency	30-100ng/ml
Toxicity	>100ng/ml

The data hence collected is entered into Microsoft excel worksheet for statistical analysis and relevant statistical calculations are done and results are obtained for further analysis.

RESULTS

FIGURE 1: SEX DISTRIBUTION AMONG CASES

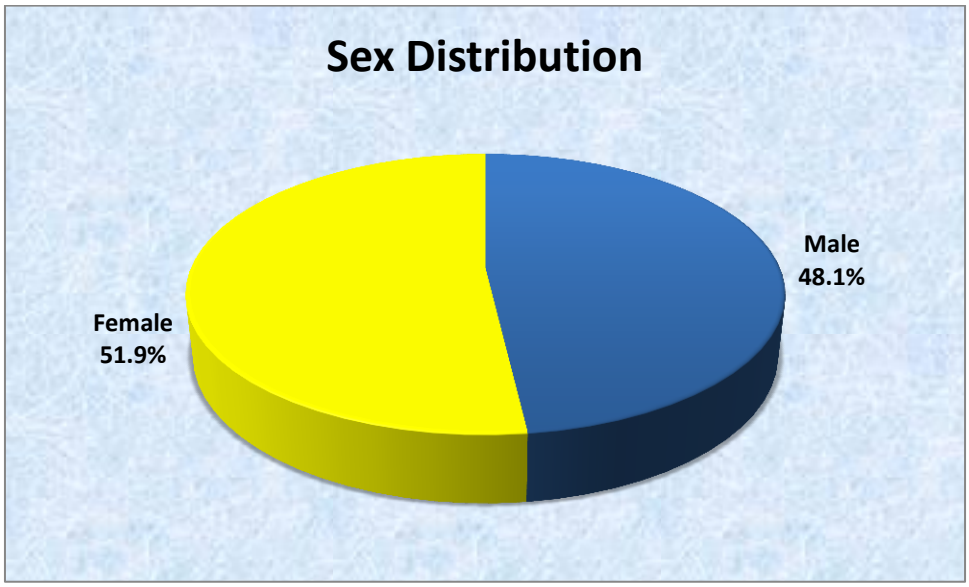


TABLE 1: SEX DISTRIBUTION AMONG CASES

Sex	N	%
Male	**77**	**48.1**
Female	**83**	**51.9**
Total	**160**	**100**

Our study showed almost equal distribution of subjects by sex with male subjects around 48.1% and female subject around 51.9%.

FIGURE 2: AGE DISTRIBUTION AMONG CASES

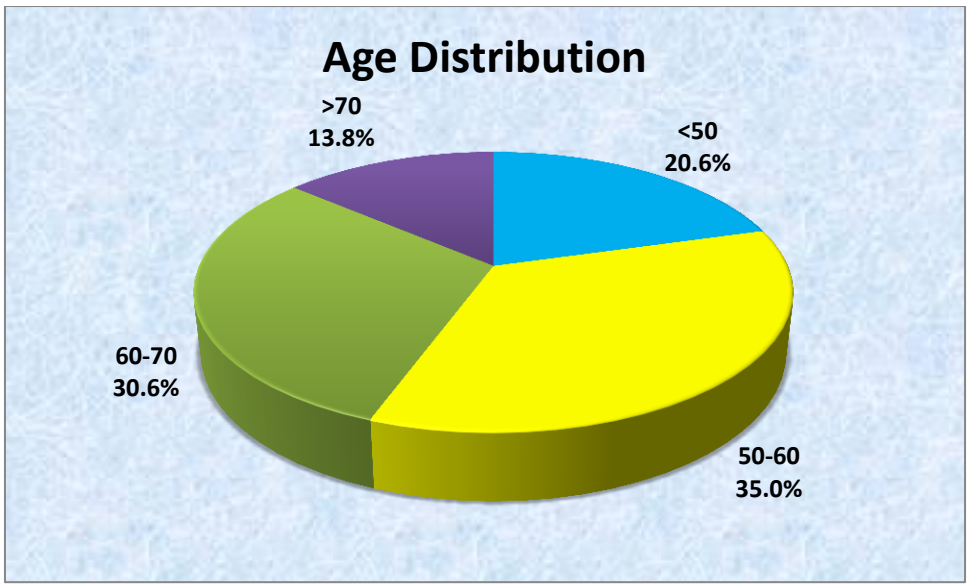


TABLE 2: AGE DISTRIBUTION AMONG CASES

Age (Yrs)	N	%
<50	33	20.6
50-60	56	35
60-70	49	30.6
>70	22	13.8
Total	160	100

Nearly 65% of the cases involved in our study belonged to the age group of 50 to 70 years.

FIGURE 3: AGE DISTRIBUTION BY SEX AMONG CASES

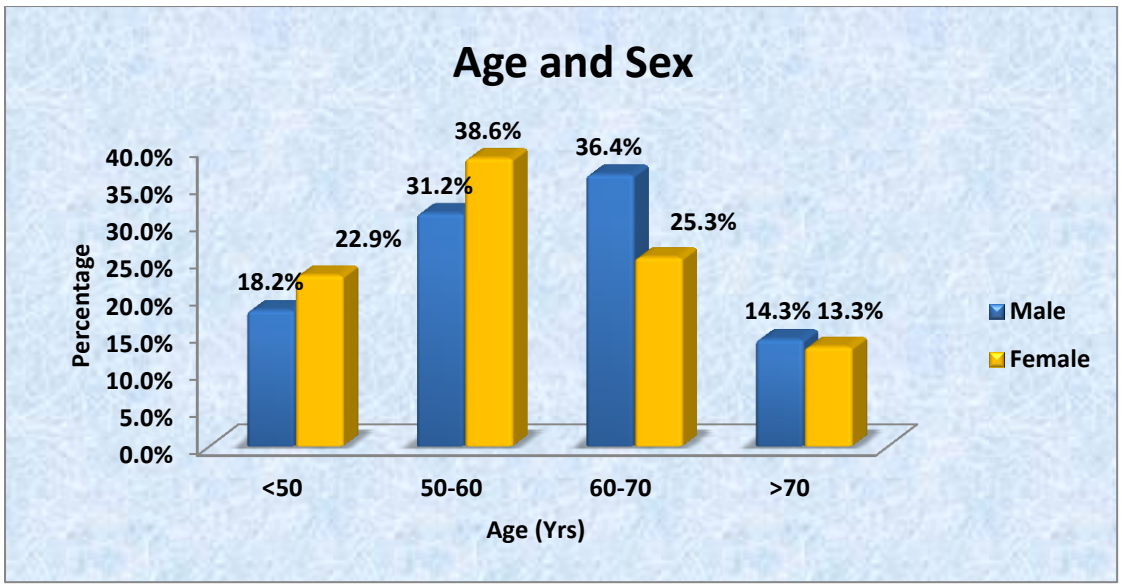


TABLE 3: AGE DISTRIBUTION BY SEX AMONG CASES

AGE (YRS)	MALE		FEMALE		TOTAL	p value
	N	%	N	%	N	
<50	14	18.2%	19	22.9%	33	0.444
50-60	24	31.2%	32	38.6%	56	
60-70	28	36.4%	21	25.3%	49	
>70	11	14.3%	11	13.3%	22	
Total	77	100.0%	83	100.0%	160	

The distribution of cases according to sex is shown as in the above table with female predominance among the 50 – 60 years age group and male predominance among the 60 – 70 years age group

FIGURE 4: MODE OF TREATMENT

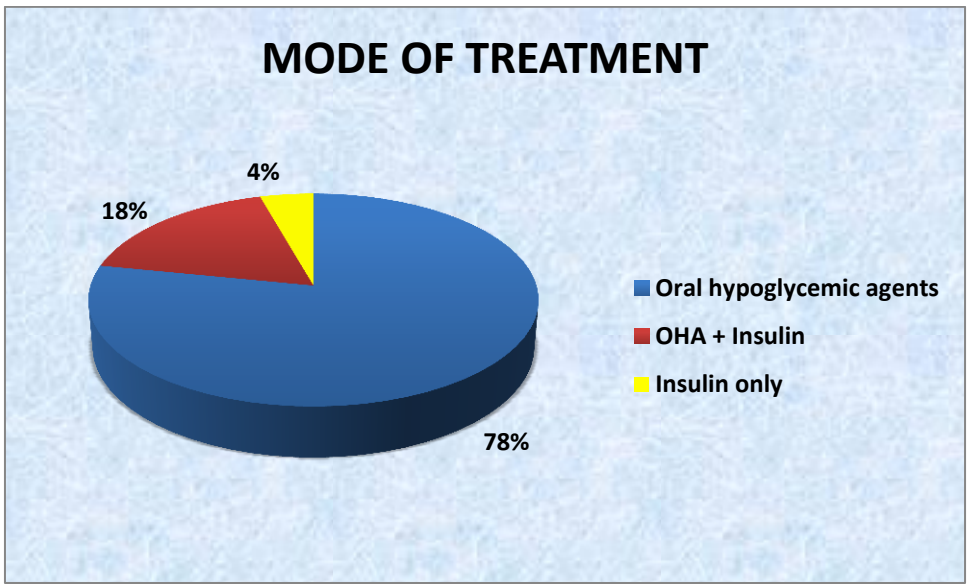


TABLE 4: MODE OF TREATMENT

MODE OF TREATMENT	N	%
Oral hypoglycemic agents	125	78.1
OHA + Insulin	28	17.5
Insulin only	7	4.4
Total	160	100

Most of the cases taken for this study were on oral hypoglycemic agents. 78.1% of the cases were solely on oral hypoglycemic agents.

FIGURE 5: DURATION OF DM (YRS)

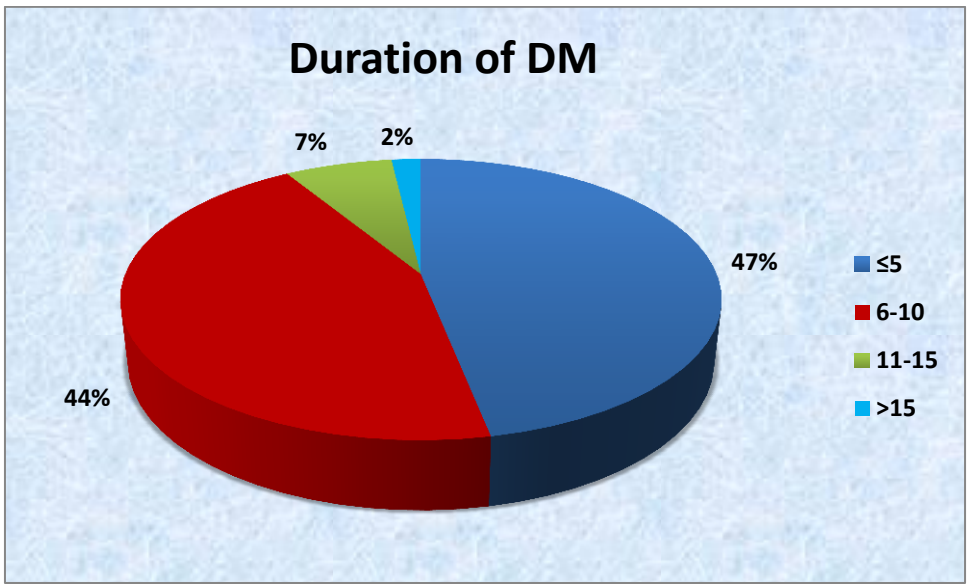


TABLE 5: DURATION OF DM (YRS)

DURATION OF DM (YRS)	N	%
≤5	75	46.9
6-10	71	44.4
11-15	11	6.9
>15	3	1.9
Total	160	100.0

91.3% of the cases were having diabetes of duration less than 10 years in our study.

FIGURE 6: DISTRIBUTION OF BMI (Kg/m2)

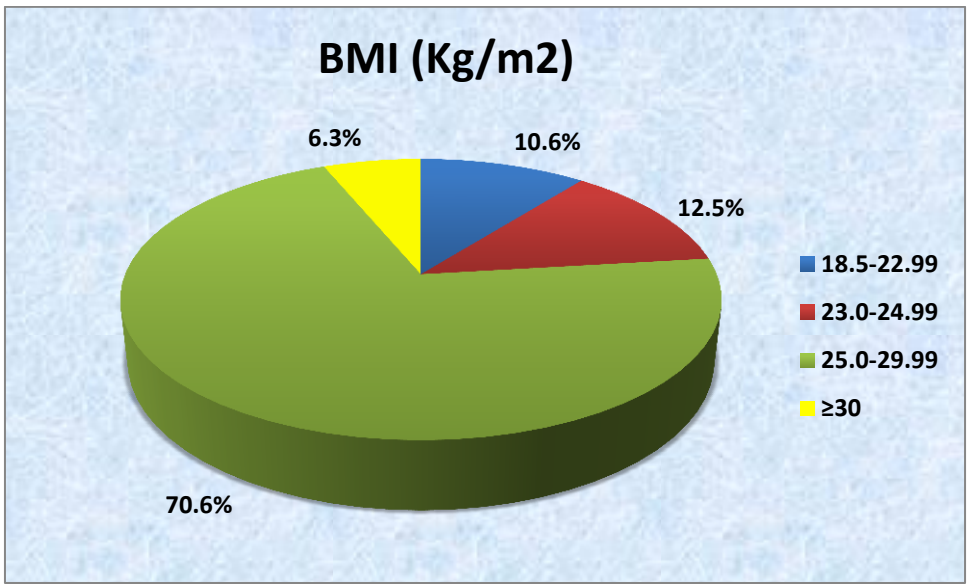


TABLE 6: DISTRIBUTION OF BMI (Kg/m2)

BMI (Kg/m2)	N	%
18.5-22.99	17	10.6
23.0-24.99	20	12.5
25.0-29.99	113	70.6
≥30	10	6.2
Total	160	100

About 70.6 % of the cases were having BMI in the range of 25 to 29.9 and were classified in the overweight category.

FIGURE 7: DISTRIBUTION OF FBS (mg/dL)

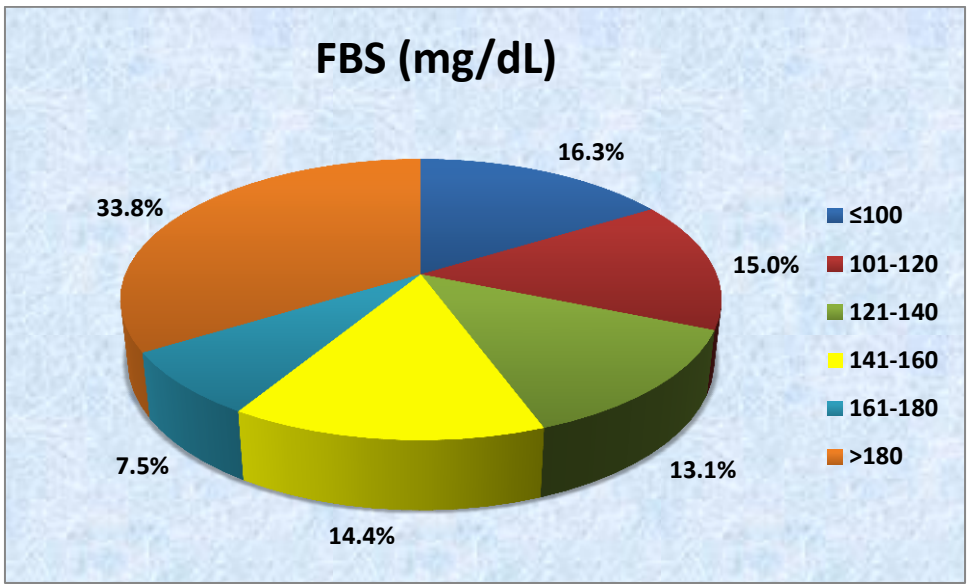


TABLE 7: DISTRIBUTION OF FBS (mg/dL)

FBS (mg/dL)	N	%
≤100	26	16.2
101-120	24	15
121-140	21	13.1
141-160	23	14.4
161-180	12	7.5
>180	54	33.8
Total	160	100

33.8 % of the cases had fasting blood sugar greater than 180mg/dl. And very few cases had fasting blood sugar under control about 16.2% of the cases.

FIGURE 8: DISTRIBUTION OF PPBS (mg/dL)

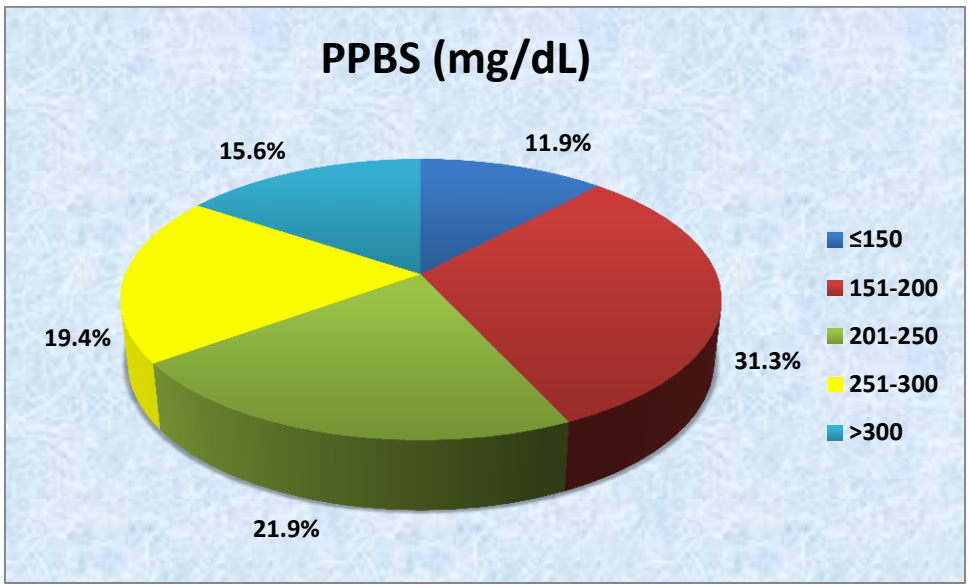


TABLE 8: DISTRIBUTION OF PPBS (mg/dL)

PPBS (mg/dL)	N	%
≤150	19	11.9
151-200	50	31.2
201-250	35	21.9
251-300	31	19.4
>300	25	15.6
Total	160	100

56.9 % of the cases had post prandial blood sugar above the level of 200mg/dl and had significantly poor glycemic control.

FIGURE 9: DISTRIBUTION OF HBA1C (%)

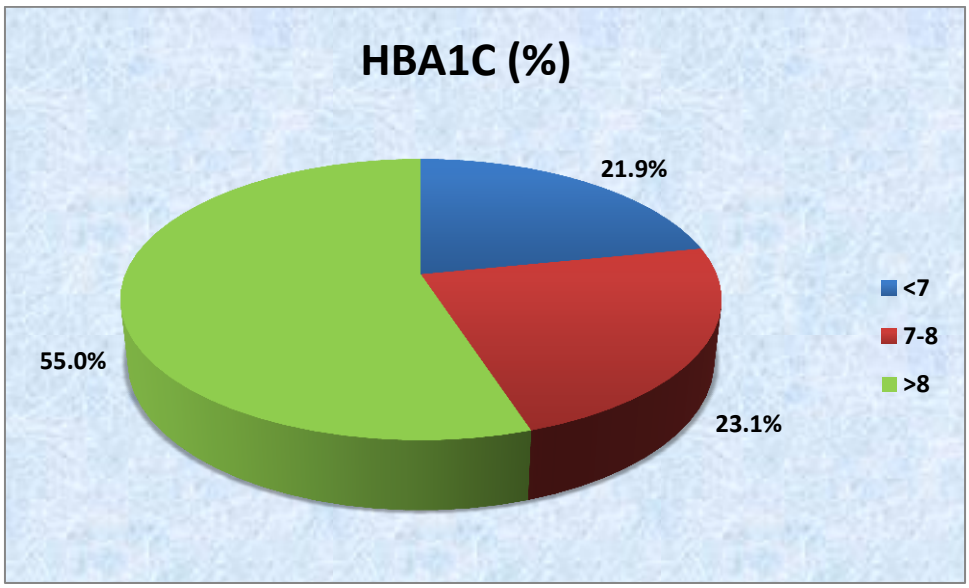


TABLE 9: DISTRIBUTION OF HBA1C (%)

HBA1C (%)	N	%
<7	35	21.9
7-8	37	23.1
>8	88	55
Total	160	100

55 % of the cases had HbA_1C more than 8, significantly showing the inadequate control of blood sugars.

FIGURE 10: DISTRIBUTION OF TRIGLYCERIDES (mg/dL)

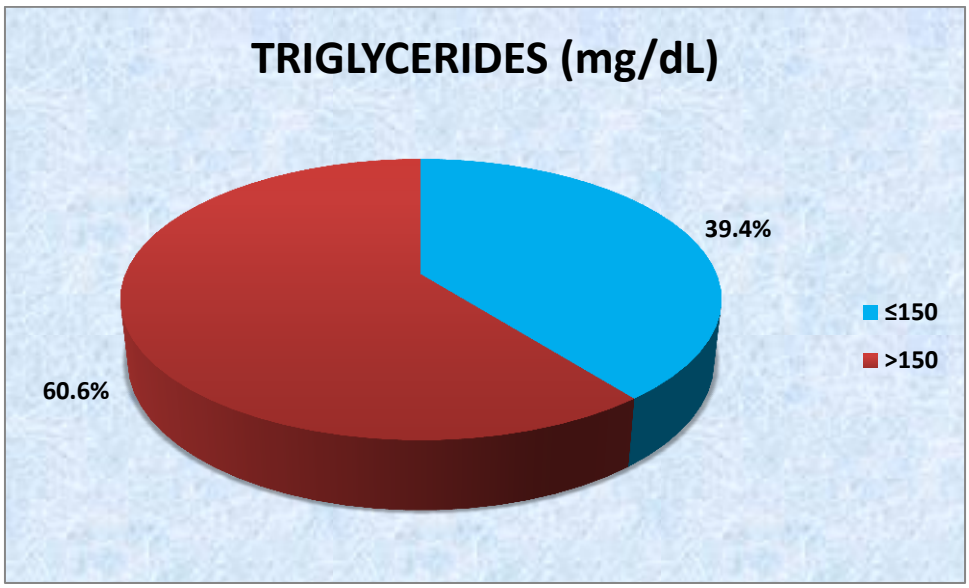


TABLE 10: DISTRIBUTION OF TRIGLYCERIDES (mg/dL)

TRIGLYCERIDES (mg/dL)	N	%
≤150	63	39.4
>150	97	60.6
Total	160	100

60.6 % of the diabetic cases in our study showed hypertriglyceridemia.

FIGURE 11: DISTRIBUTION OF TOTAL CHOLESTROL (mg/dL)

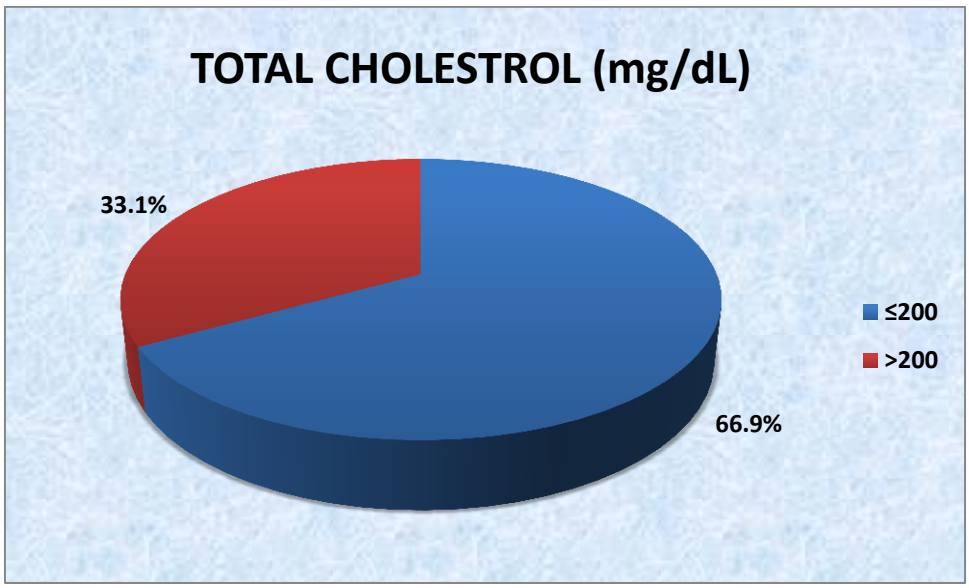


TABLE 11: DISTRIBUTION OF TOTAL CHOLESTROL (mg/dL)

TOTAL CHOLESTROL (mg/dL)	N	%
≤200	107	66.9
>200	53	33.1
Total	160	100

Hypercholesterolemia was found only in 33.1% of the cases.

FIGURE 12: DISTRIBUTION OF HDL CHOLESTROL (mg/dL)

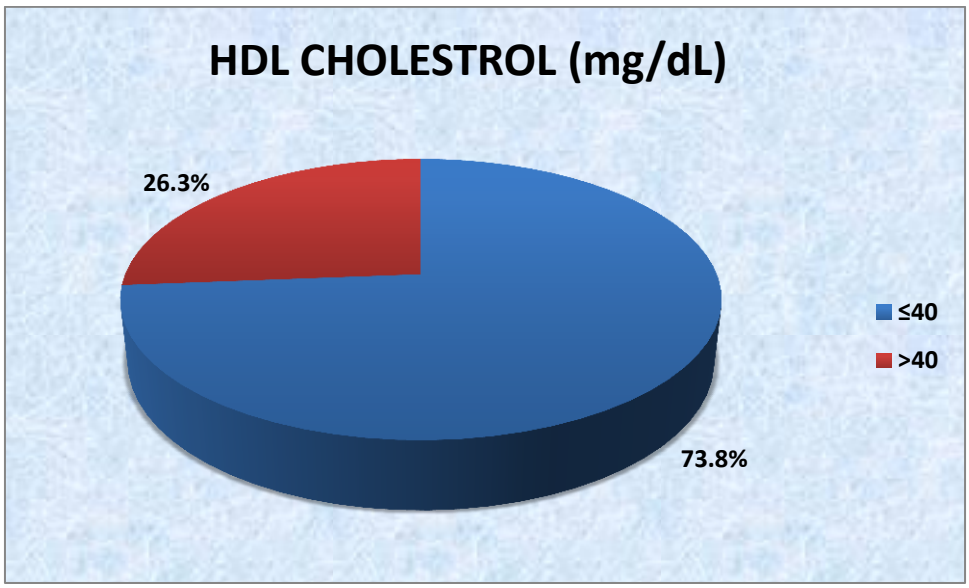


TABLE 12: DISTRIBUTION OF HDL CHOLESTROL (mg/dL)

HDL CHOLESTROL (mg/dL)	N	%
≤40	118	73.8
>40	42	26.2
Total	160	100

In 73.8 % of the diabetic patients HDL cholesterol was less than 40 mg/dl.

FIGURE 13: DISTRIBUTION OF LDL CHOLESTROL (mg/dL)

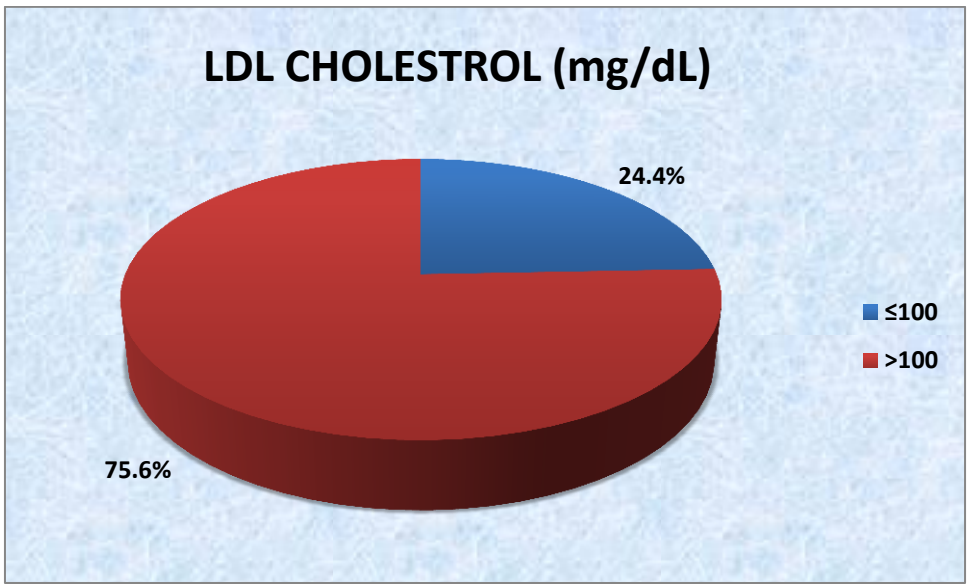


TABLE 13: DISTRIBUTION OF LDL CHOLESTROL (mg/dL)

LDL CHOLESTROL (mg/dL)	N	%
≤100	39	24.4
>100	121	75.6
Total	160	100

In 75.6% of the diabetic cases in our study showed LDL cholesterol more than 100mg/dl.

FIGURE 14: VIT D DEFICIENCY AMONG CASES

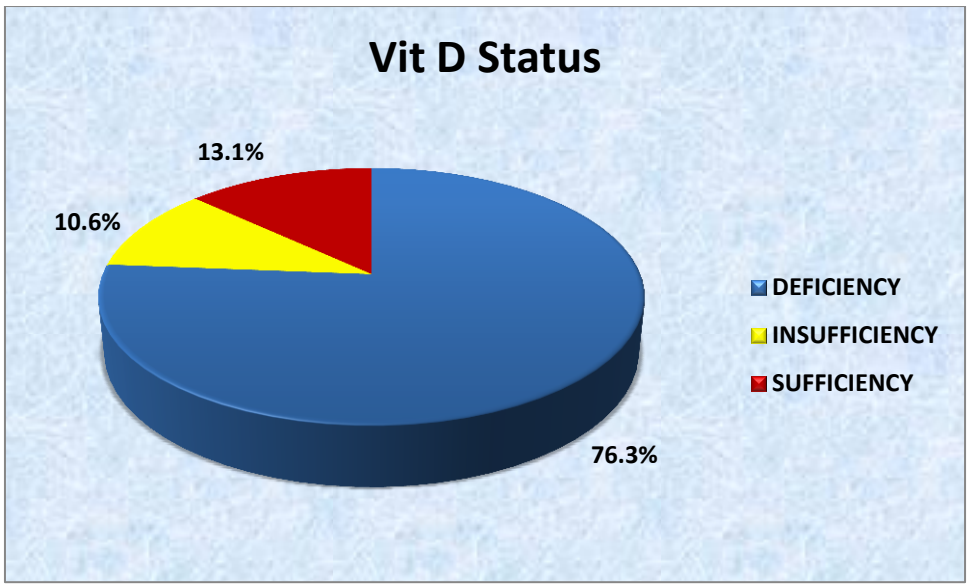


TABLE 14: VIT D DEFICIENCY AMONG CASES

Vit D status	N	%
DEFICIENCY (<20)	122	76.2
INSUFFICIENCY (20 to 30)	17	10.6
SUFFICIENCY (>30)	21	13.1
Total	160	100

Our study showed prevalence of Vitamin D deficiency of 76.2%.

FIGURE 15: DISTRIBUTION OF AGE (YRS) BY VIT D DEFICIENCY

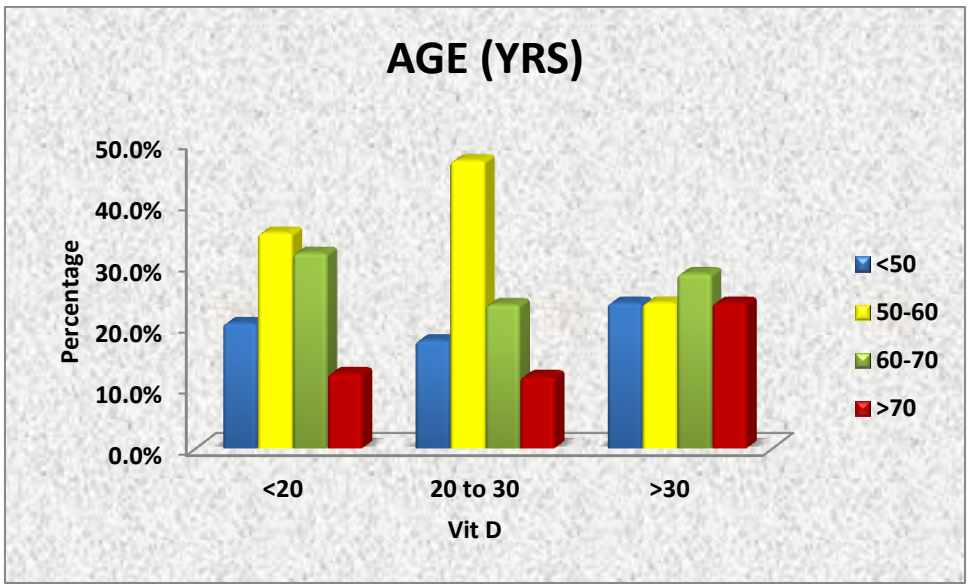


TABLE 15: DISTRIBUTION OF AGE (YRS) BY VIT D DEFICIENCY

AGE (YRS)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
<50	25	20.5%	3	17.6%	5	23.8%	33	0.704
50-60	43	35.2%	8	47.1%	5	23.8%	56	
60-70	39	32.0%	4	23.5%	6	28.6%	49	
>70	15	12.3%	2	11.8%	5	23.8%	22	
Total	122	100.0%	17	100.0%	21	100.0%	160	

Vitamin d deficiency and insufficiency is found predominantly amongst cases above the age of 50 years.

TABLE 16: MEAN VITAMIN D VALUES

Mean	Vit D	Mean	SD	ANOVA p value
AGE	DEFICIENCY (<20)	59.7	10.3	0.727
	INSUFFICIENCY (20 to 30)	59.3	10.3	
	SUFFICIENCY (>30)	61.6	14.3	
	Total	59.9	10.8	

FIGURE 16: DISTRIBUTION OF SEX BY VIT D DEFICIENCY

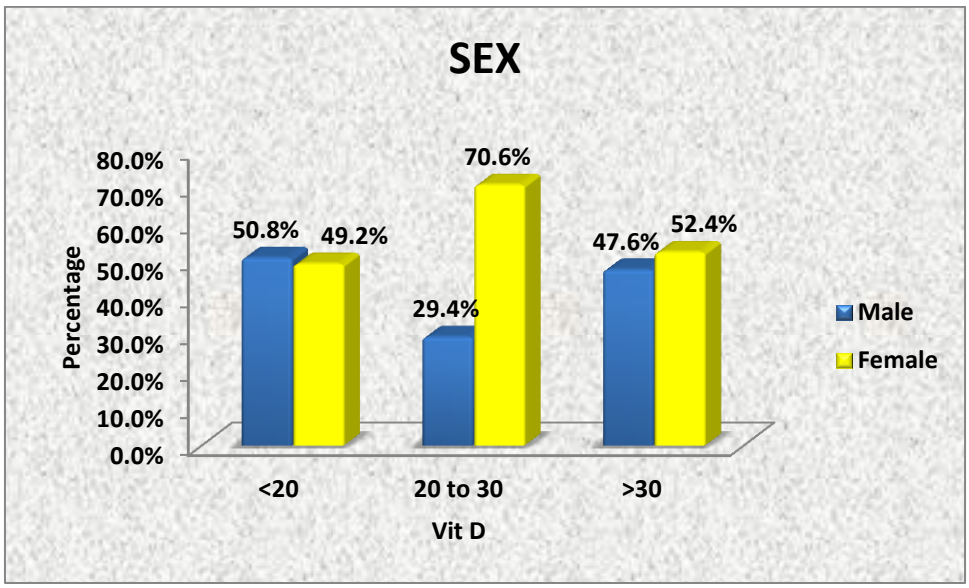


TABLE 17: DISTRIBUTION OF SEX BY VIT D DEFICIENCY

SEX	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
Male	62	50.8%	5	29.4%	10	47.6%	77	0.254
Female	60	49.2%	12	70.6%	11	52.4%	83	
Total	122	100.0%	17	100.0%	21	100.0%	160	

Vitamin D deficiency was found almost equally distributed with slight female preponderance.

TABLE 18: MEAN DURATION OF DIABETES MELLITUS

Mean	Vit D	Mean	SD	ANOVA p value
DURATION OF DM	DEFICIENCY (<20)	6.0	2.7	0.116
	INSUFFICIENCY (20 to 30)	7.4	2.6	
	SUFFICIENCY (>30)	5.6	3.2	
	Total	6.1	2.8	

FIGURE 17: DISTRIBUTION OF DURATION OF DM (YRS) BY VIT D DEFICIENCY

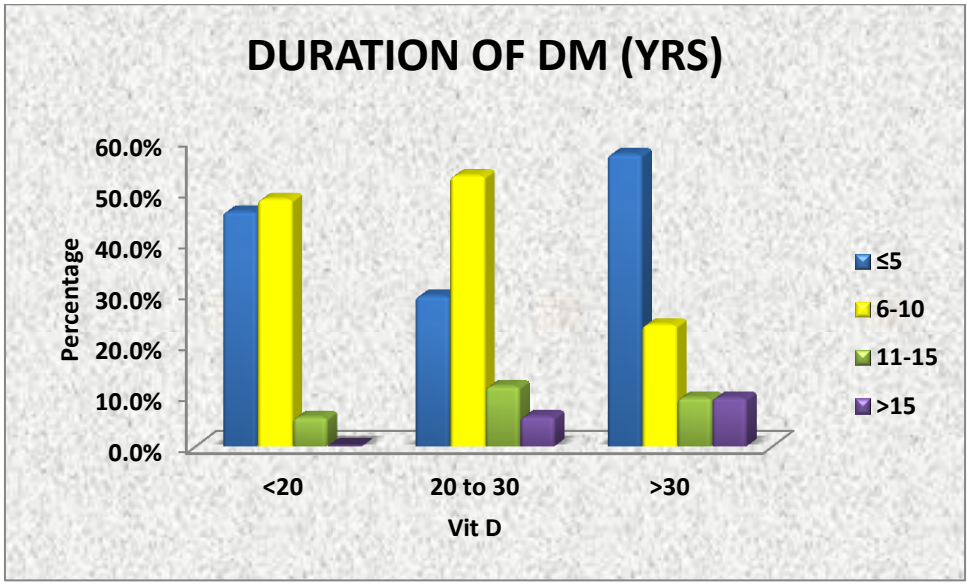


TABLE 19: DISTRIBUTION OF DURATION OF DM (YRS) BY VIT D DEFICIENCY

DURATION OF DM (YRS)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤5	56	45.9%	5	29.4%	12	57.1%	73	0.141
6-10	59	48.4%	9	52.9%	5	23.8%	73	
11-15	7	5.7%	2	11.8%	2	9.5%	11	
>15	0	0.0%	1	5.9%	2	9.5%	3	
Total	122	100.0%	17	100.0%	21	100.0%	160	

Vitamin D deficiency was significant in the diabetic patients with duration of more than 5 years

FIGURE 18: DISTRIBUTION OF BMI (Kg/m2) BY VIT D DEFICIENCY

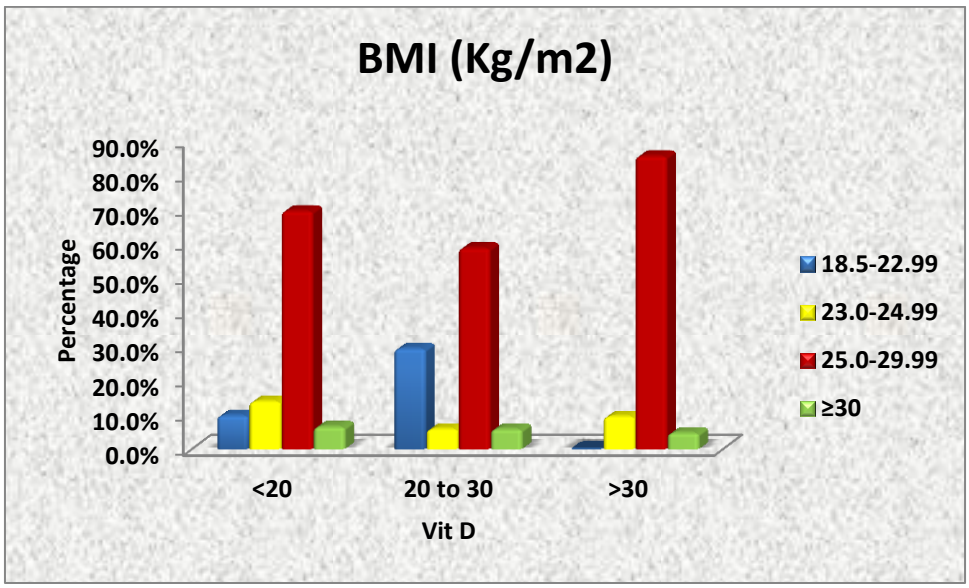


TABLE 20: DISTRIBUTION OF BMI (kg/m2) BY VIT D DEFICIENCY

BMI (Kg/m2)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
18.5-22.99	12	9.8%	5	29.4%	0	0.0%	17	
23.0-24.99	17	13.9%	1	5.9%	2	9.5%	20	
25.0-29.99	85	69.7%	10	58.8%	18	85.7%	113	0.124
≥30	8	6.6%	1	5.9%	1	4.8%	10	
Total	122	100.0%	17	100.0%	21	100.0%	160	

69.7 % of the overweight diabetic patients had vitamin D deficiency in our study

TABLE 21: MEAN FBS VALUES

Mean	Vit D	Mean	SD	ANOVA p value
FBS	DEFICIENCY (<20)	164.6	69.0	0.235
	INSUFFICIENCY (20 to 30)	143.4	53.3	
	SUFFICIENCY (>30)	182.0	80.6	
	Total	164.7	69.4	

FIGURE 19: DISTRIBUTION OF FBS (mg/dl) BY VIT D DEFICIENCY

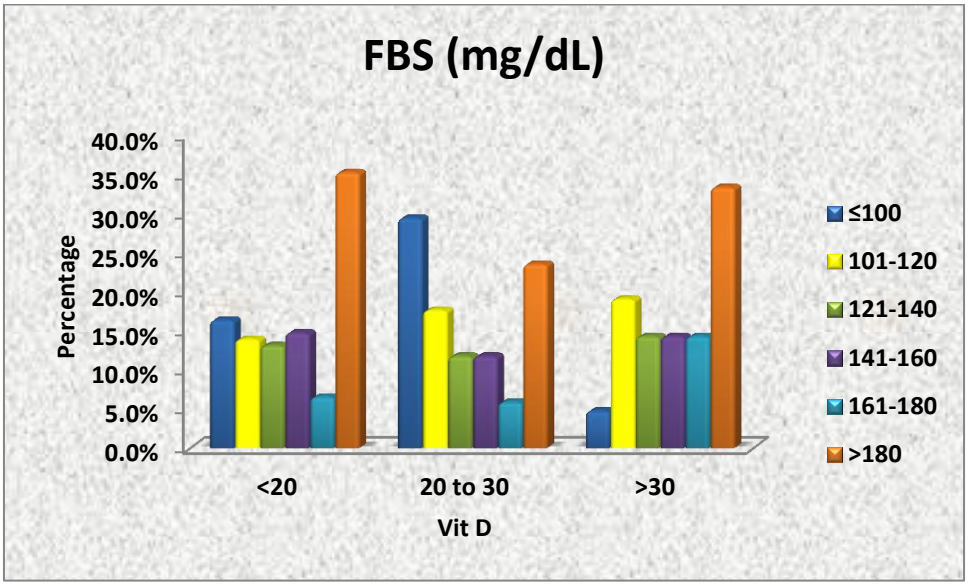


TABLE 22: DISTRIBUTION OF FBS (mg/dl) BY VIT D DEFICIENCY

FBS (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤100	20	16.4%	5	29.4%	1	4.8%	26	0.802
101-120	17	13.9%	3	17.6%	4	19.0%	24	
121-140	16	13.1%	2	11.8%	3	14.3%	21	
141-160	18	14.8%	2	11.8%	3	14.3%	23	
161-180	8	6.6%	1	5.9%	3	14.3%	12	
>180	43	35.2%	4	23.5%	7	33.3%	54	
Total	122	100.0%	17	100.0%	21	100.0%	160	

43 out of 54 patients with high levels of fasting blood sugar above 180 mg/dl, had vitamin D deficiency. However there was no significant correlation between FBS and vitamin D levels.

TABLE 23: MEAN PPBS VALUES

Mean	**Vit D**	**Mean**	**SD**	**ANOVA p value**
PPBS	DEFICIENCY (<20)	225.1	68.3	0.757
	INSUFFICIENCY (20 to 30)	221.9	76.3	
	SUFFICIENCY (>30)	236.7	75.4	
	Total	226.3	69.7	

FIGURE 20: DISTRIBUTION OF PPBS (mg/dL) BY VIT D DEFICIENCY

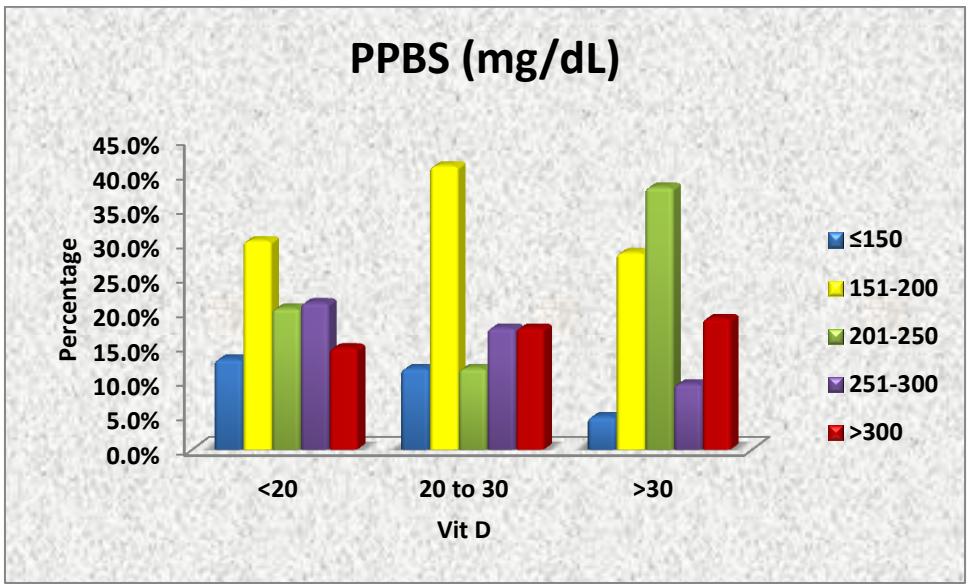


TABLE 24: DISTRIBUTION OF PPBS (mg/dL) BY VIT D DEFICIENCY

PPBS (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤150	16	13.1%	2	11.8%	1	4.8%	19	0.572
151-200	37	30.3%	7	41.2%	6	28.6%	50	
201-250	25	20.5%	2	11.8%	8	38.1%	35	
251-300	26	21.3%	3	17.6%	2	9.5%	31	
>300	18	14.8%	3	17.6%	4	19.0%	25	
Total	122	100.0%	17	100.0%	21	100.0%	160	

69 out 122 patients with vitamin D deficiency had post prandial sugar above 200 mg/dl. But the distribution of postprandial blood sugar is not significant amongst the study groups.

TABLE 25: MEAN HBA1C VALUES

Mean	Vit D	Mean	SD	ANOVA p value
HBA1C	DEFICIENCY (<20)	8.5	2.0	0.552
	INSUFFICIENCY (20 to 30)	8.1	2.0	
	SUFFICIENCY (>30)	8.8	2.4	
	Total	8.5	2.1	

FIGURE 21: DISTRIBUTION OF HBA1C (%) BY VIT D DEFICIENCY

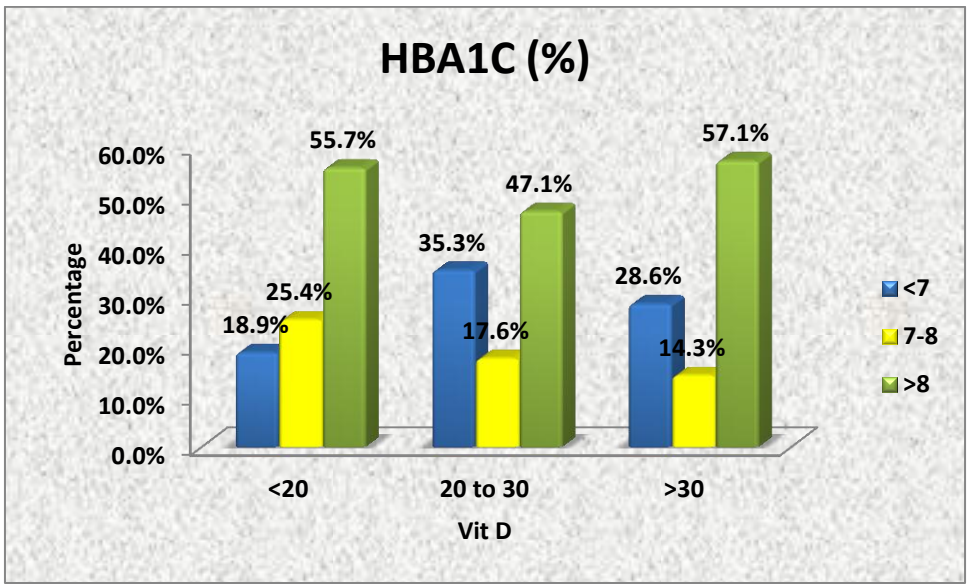


TABLE 26: DISTRIBUTION OF HBA1C (%) BY VIT D DEFICIENCY

HBA1C (%)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
<7	23	18.9%	6	35.3%	6	28.6%	35	0.438
7-8	31	25.4%	3	17.6%	3	14.3%	37	
>8	68	55.7%	8	47.1%	12	57.1%	88	
Total	122	100.0%	17	100.0%	21	100.0%	160	

About 55.7% of vitamin D deficient patients had HbA_1C levels more than 8. However, there is no significant correlation between HbA_1C levels amongst the study groups.

TABLE 27: MEAN TRIGLYCERIDE VALUES

Mean	Vit D	Mean	SD	ANOVA p value
TRIGLYCERIDES	DEFICIENCY (<20)	171.0	77.5	0.952
	INSUFFICIENCY (20 to 30)	168.2	110.6	
	SUFFICIENCY (>30)	175.8	32.6	
	Total	171.3	77.0	

FIGURE 22: DISTRIBUTION OF TRIGLYCERIDES (mg/dL) BY VIT D DEFICIENCY

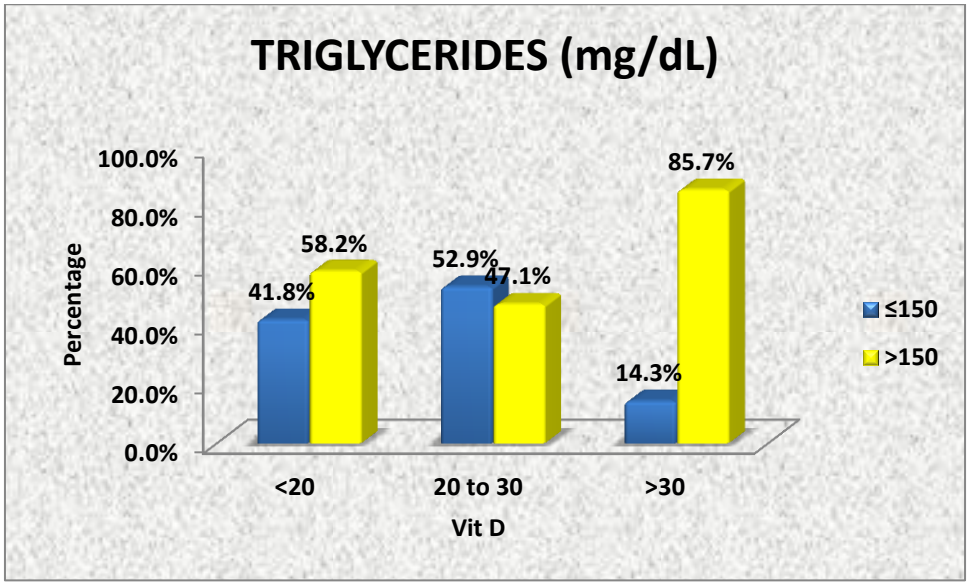


TABLE 28: DISTRIBUTION OF TRIGLYCERIDES (mg/dl) BY VIT D DEFICIENCY

TRIGLYCERIDES (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤150	51	41.8%	9	52.9%	13	61.9%	73	0.189
>150	71	58.2%	8	47.1%	8	38.1%	87	
Total	122	100.0%	17	100.0%	21	100.0%	160	

There was a significant variation in the levels of triglycerides among the vitamin D deficient group and insufficient group. The triglyceride levels in deficient group was 171±77.5 and sufficient group was 175.8±32.6.

TABLE 29: MEAN TOTAL CHOLESTEROL VALUES

Mean	**Vit D**	**Mean**	**SD**	**ANOVA p value**
TOTAL CHOLESTROL	DEFICIENCY (<20)	186.9	32.1	0.063
	INSUFFICIENCY (20 to 30)	184.0	57.1	
	SUFFICIENCY (>30)	180.1	25.7	
	Total	189.1	35.2	

FIGURE 23: DISTRIBUTION OF TOTAL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

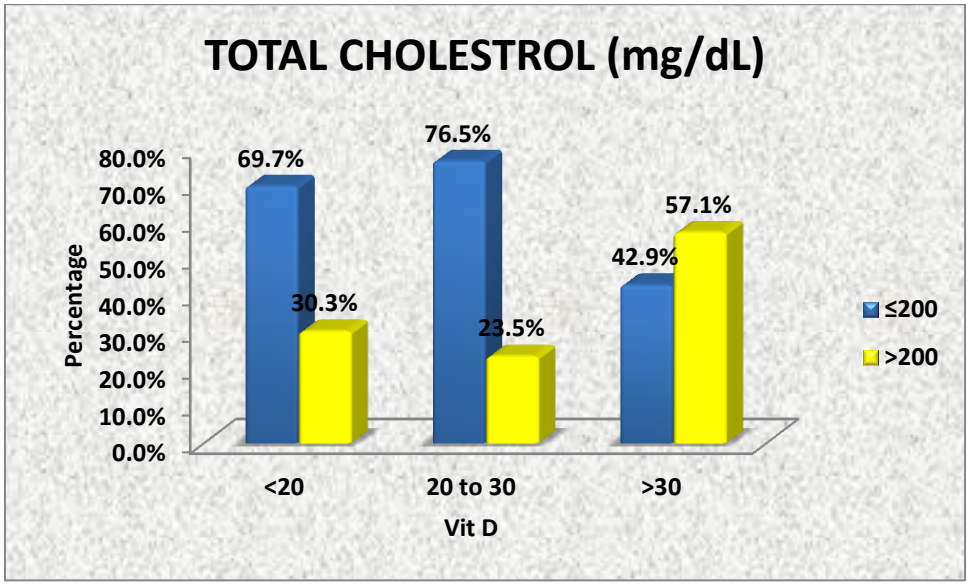


TABLE 30: DISTRIBUTION OF TOTAL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

TOTAL CHOLESTROL (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤200	85	69.7%	13	76.5%	14	66.7%	112	0.037 (Sig)
>200	37	30.3%	4	23.5%	7	33.3%	48	
Total	122	100.0%	17	100.0%	21	100.0%	160	

There was significant difference of total cholesterol in the deficient group (186.9±32.1) compared with sufficient group(180.1±25.7). This difference is statistically significant with p value < 0.037.

TABLE 31: MEAN HDL CHOLESTEROL VALUES

Mean	Vit D	Mean	SD	ANOVA p value
HDL CHOLESTROL	DEFICIENCY (<20)	36.6	7.8	0.301
	INSUFFICIENCY (20 to 30)	34.9	4.6	
	SUFFICIENCY (>30)	38.6	5.4	
	Total	36.7	7.2	

FIGURE 24: DISTRIBUTION OF HDL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

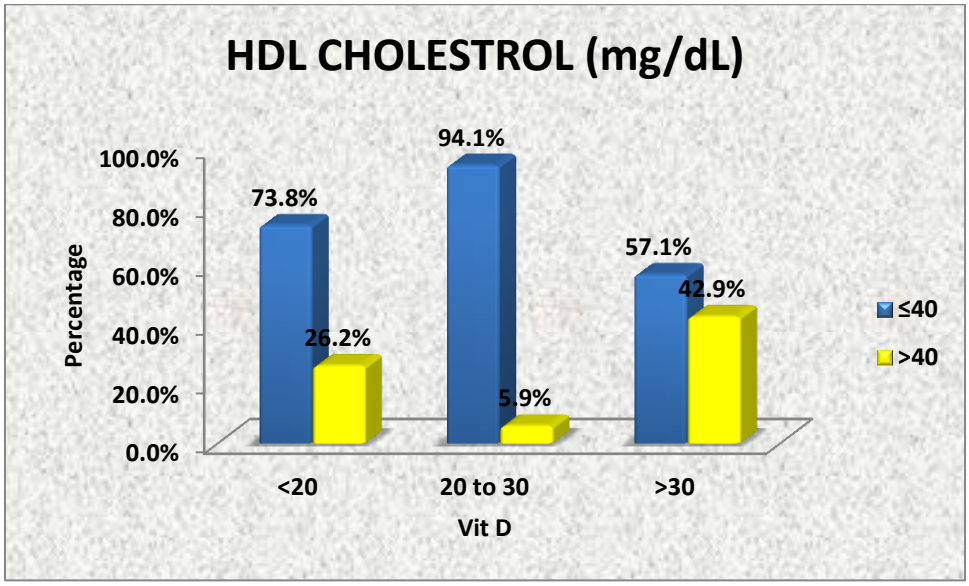


TABLE 32: DISTRIBUTION OF HDL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

HDL CHOLESTROL (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤40	90	73.8%	16	94.1%	12	57.1%	118	0.036 (Sig)
>40	32	26.2%	1	5.9%	9	42.9%	42	
Total	122	100.0%	17	100.0%	21	100.0%	160	

A significant difference was found for the HDL Cholesterol amongst the deficient and sufficient groups with a p value of 0.036. The mean values of HDL Cholesterol in deficient group and sufficient group were 36.6±7.8 and 38.6±5.4 respectively.

TABLE 33: MEAN LDL CHOLESTEROL VALUES

Mean	Vit D	Mean	SD	ANOVA p value
LDL CHOLESTROL	DEFICIENCY (<20)	115.7	24.1	0.027
	INSUFFICIENCY (20 to 30)	114.8	38.6	
	SUFFICIENCY (>30)	112.0	22.8	
	Total	117.8	26.2	

FIGURE 25: DISTRIBUTION OF LDL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

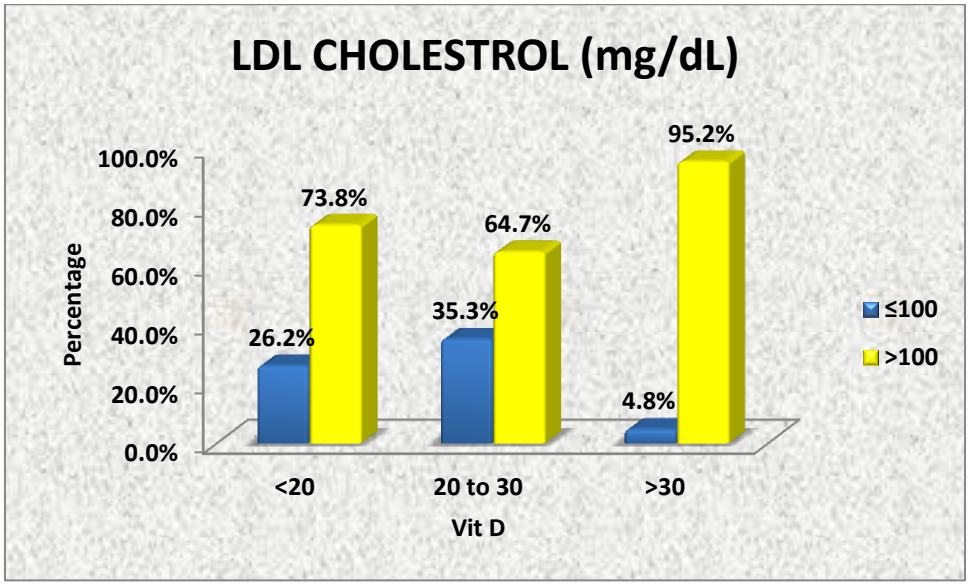


TABLE 34: DISTRIBUTION OF LDL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

LDL CHOLESTROL (mg/dL)	Vit D							p value
	<20		20 to 30		>30		Total	
	N	%	N	%	N	%	N	
≤100	32	26.2%	6	35.3%	11	52.4%	49	0.051
>100	90	73.8%	11	64.7%	10	47.6%	111	
Total	122	100.0%	17	100.0%	21	100.0%	160	

There was significant higher prevalence of raised LDL Cholesterol levels amongst the deficient group and sufficient group. The mean values of LDL Cholesterol in the deficient group and sufficient groups were 115.7±24.1 and 112±22.8 respectively.

TABLE 35: DISTRIBUTION OF VLDL CHOLESTROL (mg/dL) BY VIT D DEFICIENCY

Mean	Vit D	Mean	SD	ANOVA p value
VLDL CHOLESTROL	DEFICIENCY (<20)	34.5	15.6	0.973
	INSUFFICIENCY (20 to 30)	34.0	22.3	
	SUFFICIENCY (>30)	32.3	6.5	
	Total	34.5	15.6	

TABLE 36: REGRESSION ANALYSIS OF 25(OH) VITAMIN D AS INDEPENDENT VARIABLES AND PARAMETERS OF LIPID PROFILE IN DIABETIC PATIENTS

Parameters	Model 1				Model 2			
	B	p value	95% CI		B	Sig.	95% CI	
LDL-C	0.23	0.004	0.03	0.13	0.23	0.005	0.02	0.13
HDL-C	0.01	0.938	-0.19	0.21	0.02	0.842	-0.18	0.22
TC	0.18	0.022	0.01	0.09	0.19	0.021	0.01	0.09
TG	0.03	0.736	-0.02	0.02	0.03	0.689	-0.02	0.02
VLDL-C	0.03	0.739	-0.08	0.11	0.03	0.707	-0.08	0.11

Note B: Standardized regression Coefficients, CI: Confidence Interval.

Model 1: crude.

Model 2: adjusted for age, gender.

‡: Regression test P-value.

25(OH) D: 25-hydroxy vitamin D (ng/Ml

TG: triglycerides(mg/dL).

TC: total cholesterol (mg/dL);

HDL-C: high density lipoprotein cholesterol;

LDL-C (mg/dL): low density lipoprotein

cholesterol (mg/dL)

VLDL-C: very low density lipoproyein cholesterol

TABLE 37: COMPARISON OF MEAN OF SELECTED PARAMETERS BY VIT D DEFICIENCY

Mean	Vit D	Mean	SD	ANOVA p value
CBC - HEMOGLOBIN	DEFICIENCY (<20)	11.9	2.2	0.864
	INSUFFICIENCY (20 to 30)	12.2	2.8	
	SUFFICIENCY (>30)	12.1	1.9	
	Total	12.0	2.3	
RBC COUNT	DEFICIENCY (<20)	4.4	0.9	0.78
	INSUFFICIENCY (20 to 30)	4.5	1.0	
	SUFFICIENCY (>30)	4.4	0.6	
	Total	4.4	0.9	
PCV	DEFICIENCY (<20)	35.6	6.3	0.808
	INSUFFICIENCY (20 to 30)	36.5	8.0	
	SUFFICIENCY (>30)	36.2	6.3	
	Total	35.7	6.5	
MCV	DEFICIENCY (<20)	82.6	8.6	0.748
	INSUFFICIENCY (20 to 30)	81.0	6.7	
	SUFFICIENCY (>30)	82.2	7.4	
	Total	82.4	8.2	
MCH	DEFICIENCY (<20)	27.7	3.6	0.684
	INSUFFICIENCY (20 to 30)	26.9	2.5	
	SUFFICIENCY (>30)	27.5	2.8	
	Total	27.6	3.4	
MCHC	DEFICIENCY (<20)	33.3	2.5	0.944
	INSUFFICIENCY (20 to 30)	33.1	2.0	
	SUFFICIENCY (>30)	33.4	1.3	
	Total	33.3	2.3	
RDW	DEFICIENCY (<20)	14.8	3.6	0.684
	INSUFFICIENCY (20 to 30)	14.4	1.6	
	SUFFICIENCY (>30)	14.2	2.6	
	Total	14.7	3.3	
CBC - TOTAL COUNT	DEFICIENCY (<20)	12197.5	5182.6	0.295
	INSUFFICIENCY (20 to 30)	13476.5	7512.0	
	SUFFICIENCY (>30)	10749.0	4469.6	
	Total	12143.3	5392.7	

NEUTROPHILS	DEFICIENCY (<20)	74.5	12.4	0.749
	INSUFFICIENCY (20 to 30)	73.4	13.7	
	SUFFICIENCY (>30)	72.2	15.8	
	Total	74.1	13.0	
LYMPHOCYTES	DEFICIENCY (<20)	20.6	11.4	0.715
	INSUFFICIENCY (20 to 30)	21.5	12.4	
	SUFFICIENCY (>30)	22.8	13.8	
	Total	21.0	11.8	
EOSINOPHILS	DEFICIENCY (<20)	1.8	2.4	0.871
	INSUFFICIENCY (20 to 30)	2.1	2.7	
	SUFFICIENCY (>30)	1.9	1.9	
	Total	1.8	2.4	
MONOCYTES	DEFICIENCY (<20)	3.1	1.3	0.98
	INSUFFICIENCY (20 to 30)	3.1	1.3	
	SUFFICIENCY (>30)	3.1	1.3	
	Total	3.1	1.3	
BASOPHILS	DEFICIENCY (<20)	0.0	0.0	0.014
	INSUFFICIENCY (20 to 30)	0.2	1.0	
	SUFFICIENCY (>30)	0.0	0.0	
	Total	0.0	0.3	
ESR	DEFICIENCY (<20)	57.0	29.8	0.8
	INSUFFICIENCY (20 to 30)	51.6	37.8	
	SUFFICIENCY (>30)	56.0	34.3	
	Total	56.3	31.2	
PLATELET COUNT	DEFICIENCY (<20)	2.7	1.0	0.578
	INSUFFICIENCY (20 to 30)	2.7	1.0	
	SUFFICIENCY (>30)	2.9	0.9	
	Total	2.7	1.0	
PDW	DEFICIENCY (<20)	11.9	2.5	0.792
	INSUFFICIENCY (20 to 30)	12.2	2.7	
	SUFFICIENCY (>30)	12.2	1.8	
	Total	12.0	2.4	
MPV	DEFICIENCY (<20)	10.3	1.2	0.666
	INSUFFICIENCY (20 to 30)	10.3	1.3	
	SUFFICIENCY (>30)	10.6	1.0	
	Total	10.4	1.2	

URINE SUGAR	DEFICIENCY (<20)	0.5	0.7	0.426
	INSUFFICIENCY (20 to 30)	0.6	0.8	
	SUFFICIENCY (>30)	0.7	0.8	
	Total	0.5	0.7	
SERUM CREATININE	DEFICIENCY (<20)	1.1	0.6	0.554
	INSUFFICIENCY (20 to 30)	1.0	0.6	
	SUFFICIENCY (>30)	1.0	0.5	
	Total	1.1	0.6	
BLOOD UREA	DEFICIENCY (<20)	31.7	16.0	0.249
	INSUFFICIENCY (20 to 30)	37.8	30.0	
	SUFFICIENCY (>30)	28.0	15.8	
	Total	31.9	17.9	
SERUM SODIUM	DEFICIENCY (<20)	135.1	6.8	0.699
	INSUFFICIENCY (20 to 30)	136.1	6.2	
	SUFFICIENCY (>30)	136.2	7.1	
	Total	135.4	6.7	
SERUM POTASSIUM	DEFICIENCY (<20)	3.9	1.0	0.504
	INSUFFICIENCY (20 to 30)	4.2	1.3	
	SUFFICIENCY (>30)	3.9	1.1	
	Total	4.0	1.1	

DISCUSSION

The present study was done amongst the 160 diabetic patients who attended the inpatient department of the Department of Medicine, Shri B. M. Patil Medical College during the period of January 2015 till June 2016. All the enrolled patients were explained about the study and an informed consent was taken prior to the study. The enrolled patients were examined thoroughly and results were recorded and tabulated in Microsoft Excel worksheet and analyzed using SPSS software version 23.

The number of patients enrolled in the study was 160. In this study, almost equal distribution of male and female with slight female preponderance was seen. About the patients enrolled in the study, 77 patients were male (48.1%) and 83 patients were female (51.9). The mean age of the patients in the study was 59.93years. Nearly 65% of the cases involved in our study belonged to the age group of 50 to 70 years. The distribution of cases according to sex showed female predominance among the 50 – 60 years age group and male predominance among the 60 – 70 years age group.

Most of the cases taken for this study were on oral hypoglycemic agents. 125 patients (78.1% of the cases) were on oral hypoglycemic agents only. 146 patients (91.3% of the cases) were having diabetes of duration less than 10 years in our study. About 113 patients, (70.6 % of the cases) were having BMI in the range of 25 to 29.9 and were classified in the overweight category. 54 patients (33.8 % of the cases) had fasting blood sugar greater than 180mg/dl. And very few cases had fasting blood sugar under control, in about 26 patients (16.2% of the cases). 91 patients (56.9 % of the cases) had post prandial blood sugar above the level of 200mg/dl and had

significantly poor glycemic control. 88 patients (55 % of the cases) had HbA_1C more than 8, significantly showing the inadequate control of blood sugars.

A study done by N. P. Suryavanshi et al [76] showed significant correlation between lipid metabolism and glycemic control and concluded that poor glycemic control is associated with higher levels of total cholesterol and triglycerides.

The prevalence of vitamin D deficiency in our study was 76.2%. 122 patients had vitamin D deficiency (vitamin D < 20 ng/l), 17 patients had insufficiency (vitamin D levels 20 to 30 ng/l) and 21 patients had sufficiency of vitamin D levels(vitamin D > 30 ng/l). Vitamin D deficiency and insufficiency is found predominantly amongst cases above the age of 50 years. Vitamin D deficiency was found almost equally distributed with slight female preponderance.

73 out of 160 patients were having duration of diabetes more than 5 years. Out of this 59 patients had deficiency of vitamin D. This difference was having a statistical significance with p value of 0.116. The mean duration of diabetes in this study was 6.1±2.8 years. Vitamin D deficiency was significant in the diabetic patients with duration of more than 5 years

100 patients (60.6 % of the cases) in our study showed hypertriglyceridemia. The average triglyceride in our study was 171 mg/dl. There was no significant variation in the levels of triglycerides among the vitamin D deficient group and insufficient group. The triglyceride level in deficient group was 171±77.5 and insufficient group was 168.2±110.6 and sufficient group was 175.8±32.6. These values were statistically insignificant with p value of 0.189.

Hypercholesterolemia was found only in 53 patients (33.1% of the cases). The average total cholesterol level in our study was 189mg/dl. The mean total cholesterol levels in deficient group was 186.9±32.1, in insufficient group was 184±57.1 and in sufficient group was 180.1±25.7. These findings were statistically less significant with a p value of 0.063.

In 118 patients (73.8 % of the cases), HDL cholesterol was less than 40 mg/dl. Out of these 118 patients, 90 patients had vitamin D deficiency. The mean HDL Cholesterol in our study was 36.7±7.2. The average value of HDL Cholesterol in deficient group was 36.6±7.8, whereas in insufficient group 34.9±4.6 and sufficient group 38.6±5.4. These differences were statistically significant with a p value of 0.036.

Nearly 121 patients in our study (75.6% of the cases), showed LDL cholesterol more than 100mg/dl. Out of these 121 patients, 90 patients were vitamin D deficient. The mean LDL Cholesterol value in our study was 117.8±26.2. The average value of LDL Cholesterol levels in deficient group, insufficient group and sufficient group were 115.7±24.1, 114.8±38.6, 112±22.8 respectively. These findings were statistically significant with a p value of 0.051.

About 34 patients out of 160 patients had high VLDL Cholesterol values above 40 mg/dl. However the mean VLDL cholesterol value of deficient and sufficient group did not vary significantly. The mean VLDL Cholesterol value of this study was 35 mg/dl. The average VLDL Cholesterol value of the vitamin D deficient group was 34.8 mg/dl and that of sufficient group was 35 mg/dl. There was no statistical significance with these findings.

These findings are consistent with the findings of VLDL-3 (Very Large Database of Lipids-3) study, which demonstrated lower levels of vitamin D is associated with significantly lowers levels of HDL Cholesterol and higher levels of LDL and VLDL Cholesterol[74]

A study done by Raza Kazalauskaite among the people in Chicago community also found similar findings and confirmed that higher levels of vitamin D are protective against atherosclerosis and cardiovascular risk.[84]

Other notable studies done by Orgaz-Molina J et al[62], Catherine S. Birken et al[63], Alba Guasch et al[65], Amena Sadiya et al[108], Mattia Bellan et al[110], found similar findings and concluded that vitamin D is associated with dyslipidemia.

69.7 % of the overweight diabetic patients had vitamin D deficiency in our study. 43 out of 54 patients with high levels of fasting blood sugar above 180 mg/dl, had vitamin D deficiency. However there was no significant correlation between FBS and vitamin D levels. 69 out of 122 patients with vitamin D deficiency had post prandial sugar above 200 mg/dl. But the distribution of postprandial blood sugar is not significant amongst the study groups. About 55.7% of vitamin D deficient patients had HbA_1C levels more than 8. However, there is no significant correlation between HbA_1C levels amongst the study groups.

Jared P. Reis et al[95] studied among the participants in the National Health and Nutritional Examination Survey (NHANES), found that lower levels of vitamin D was associated with overweight and abdominal obesity and was inversely associated with plasma glucose concentrations

Foong-Ming Moy et al [64] found that lower level of vitamin D was associated with greater risk of abdominal obesity and metabolic syndrome. Alemzadeh R et al [72] showed that vitamin D deficiency was associated with higher BMI and low insulin sensitivity. Surya Prakash Bhatt et al [91] showed that lower level of vitamin D was associated with higher values of abdominal fat.

Several studies were done to analyze the effect of supplementation of vitamin D on lipid profile. In a large study called Women Health Initiative Calcium- Vitamin D trial[60], found that vitamin D supplementation in post menopausal women resulted in drop in triglyceride and LDL Cholesterol levels, improvement in HDL Cholesterol levels. Other studies done by Naseer M Al-Dhagri et al[66], Mazliza Ramly et al[67], Jose Manuel Ramiro Lazano et al[78], Mohammad Hassan Efthekhari et al[101], have showed similar findings and confirmed the benefit of supplementation of vitamin D on lipid profile.

CONCLUSION

The present study has analyzed the data from 160 diabetic patients admitted in BLDE University's Shri B. M. Patil Medical College and Research Centre, Vijayapur. The results of the study have shown the possible relationship between the serum levels of vitamin D and fasting serum levels of lipid profile. These findings are statistically significant and have confirmed the relationship between the vitamin D and lipid profile.

Important findings of this study are-

- The prevalence of vitamin D deficiency was 76.2% in this study with slight female preponderance.
- 65% of the cases belonged to age group of 50 to 70 years.
- 70.6% of patients had BMI of 25 to 29.9, were considered overweight.
- 56.9% of cases included in the present study, had high PPBS and poor glycemic control. 55% of patients had glycated hemoglobin > 8.
- 60.6% of cases had high levels of triglycerides (> 150mg/dl).
- 73.8% of cases had low levels of HDL Cholesterol (<40mg/dl)
- 75.6% of cases had high LDL Cholesterol (> 100mg/dl).
- Significant correlation showing vitamin D levels are directly proportional to the HDL Cholesterol levels. (p value of 0.036).
- Significant correlation showing vitamin D levels are inversely proportional to the LDL Cholesterol levels. (p value of 0.051).

SUMMARY

Diabetes mellitus is a major public health problem throught the world and is increasing very rapidly has major economic burden worldwide. The incidence of type 2 diabetes mellitus is rising rapidly in India. Cardiovascular Disease is the most common cause of mortality in type 2 diabetes mellitus. Diabetic dyslipidemia is one of the contributing factor. Diabetes causes a number of complications like microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischemic heart disease, stroke and peripheral vascular disease). Several comorbid conditions like depression, obesity, osteoporosis, cognitive impairment cause increased barriers to the management of diabetes. Many studies have demonstrated the role of vitamin D in the development of type 2 diabetes mellitus. The effect of vitamin D on the lipid profiles is one of the proposed mechanisms for the association between vitamin D and cardiovascular disease. The present study has intended to find out this association between vitamin D status and lipid profile in patients with type 2 diabetes mellitus.

The present study has analyzed the data from 160 diabetic patients admitted in BLDE University's Shri B. M. Patil Medical College and Research Centre, Vijayapur. Patients were examined and data was recorded and analyzed using required statistical analysis.

The results from the present study showed that there is a direct relation between the serum levels of HDL cholesterol and inverse relation with the serum levels of LDL cholesterol.

This study signifies that vitamin D has relationship with cardiovascular disease in type 2 diabetes mellitus through its association with the lipid parameters. A

lower level of vitamin D is associated with derangement of lipid parameters in this study. However, further studies with large sample sizes are required to support this correlation. Further research is awaited to find out the nature and effect of low levels of serum vitamin D and the possible ways of its correction and its implications on human health are yet to be discovered.

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ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 5414
Date 24/11/14
B.L.D.E.U's Shri B.M. Patil Medical College,

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Association between serum level of vitamin D and lipid profiles in type-2 diabetic patients"

x x x

Name of P.G. student Dr Deepak. R. Chinagi
Dept of Medicine

Name of Guide/Co-investigator Dr L.S. Patil, Professor
Dept of Medicine

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

CONSENT FORM

B.L.D.E.U.'s SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/ RESEARCH

I, the undersigned----------S/O.D/O.W/O----------aged -------years ordinarily resident of----------do here by state/declare that Dr Deepak Rajendra Chinagi of Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur has examined me thoroughly on ----------at----------(place) and has explained to me in my own language----------that I am suffering from----------disease (condition) and this disease/condition mimic following diseases ----------Further Dr Deepak Rajendra Chinagi has informed me that he is conducting dissertation/research titled "ASSOCIATION BETWEEN SERUM LEVEL OF VITAMIN D AND LIPID PROFILES IN TYPE 2 DIABETIC PATIENTS", under the guidance of Dr L. S. PATIL, requesting for my participation in this study. Further, the doctor has informed me that my participation in this study help in evaluation of results of the study which is useful reference for treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The doctor has also informed me that information given by me, observations made/ photographs/video graphs taken upon me by the investigator will be kept a secret and not accessed by the person other than me or my legal hirer except for

academic purposes.

The doctor did inform me that though my participation is purely voluntary based on information given to me, I can ask any clarification during the course of treatment/study related to diagnosis, procedure of the treatment, result of the treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or investigator can terminate me from the study at any time from the study but not the procedure of treatment & follow up unless I request to discharge.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I, the under signed, Shri/Smt----------under my full conscious state of mind I agree to participate in the said research/dissertation .

Signature of the Patient:

Signature of the Doctor:

Witness 1:

Witness 2:

PROFORMA

BLDE'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR

"ASSOCIATION BETWEEN SERUM LEVEL OF VITAMIN D AND LIPID PROFILES IN TYPE 2 DIABETIC PATIENTS"

PROFORMA

Name: **Age/Sex:**

I.P. No.

Occupation:

Address:

Date of Admission:

Chief Complaints:

History of Present Illnes:

Past history:

- History of type 2 DM
- History of IHD
- History of any chronic liver disease,
- History of any chronic renal disease
- Drug history

Family history:

- Any history of T2DM

Personal History

1. Smoking

2. Alcoholism

3. Diet

4.Marital status

5. Number of Children

GENERAL PHYSICAL EXAMINATION

Vitals

Pulse Rate : Weight:

B.P. : Height:

R.R. : BMI:

Temperature :

Pallor Icterus Cyanosis Clubbing

Systemic examination:

- CVS

- Per abdomen

- Respiratory system

- CNS

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour
PCV	%
MCV	fl
MCH	pg
MCHC	
RDW	
MPV	
PDW	

BIOCHEMISTRY–

Diabetic Profile

FBS	
PPBS	
HBA1c	

Vitamin D

25 (OH) D	

Renal Profile

Blood Urea	
Serum Creatinine	
Serum Sodium	
Serum Potassium	

URINE EXAMINATION -

Albumin	
Sugar	
Pus cells	
RBC’s	
Casts	

KEY TO MASTER CHART