LIPID ABNORMALITIES IN TYPE 2 DIABETES MELLITUS WITH SPECIFIC REFERENCE TO HYPERTRIGLYCERIDEMIA

Thesis Submitted to the University of Calicut in Partial Fulfillment of the Rules and Regulations for the award of

Doctor of Philosophy
in Medicine (Faculty of Medicine)

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CERTIFICATE

This is to certify that this thesis titled "Lipid Abnormalities in Type 2 Diabetes Mellitus with Specific Reference to Hypertriglyceridemia" submitted by Dr.Chandni.R, Part-time Research Scholar, Department of Life Sciences, University of Calicut in partial fulfillment of the rules and regulations of the University of Calicut, Kerala for the award of PhD in Medicine under the Faculty of Medicine is the result of her original and independent work carried out by her under my direct guidance and supervision.This work has not formed the basis for the award of any degree, diploma, associateship or similar titles of this University or any other University.

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DECLARATION

I hereby declare that this thesis entitled "Lipid abnormalities in Type 2 Diabetes mellitus with specific reference to Hypertriglyceridemia" has been prepared by me under the guidance and supervision of Dr.K.P.Ramamoorthy, Emeritus professor of Medicine and Formerly HOD of Medicine, Medical College, Kozhikode and is submitted to the University of Calicut, Kerala, in partial fulfillment of University rules and regulations for the award of Doctor of philosophy in Medicine (Faculty of Medicine).This thesis is entirely the result of my work and this work has not formed the basis for the award of any degree, diploma, associateship or similar titles of this University or any other University.

Dr.R.Chandni
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Dedication
to
MY PARENTS

Sri.K.P.Radhakrishnan and
Smt.K.V.P.Ratnakumari

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KEY TO ABBREVIATIONS

ADA	**American Diabetes Association**
Apo	**Apolipoprotein**
BMI	**Body Mass Index**
BP	**Blood Pressure**
CAD	**Coronary Artery Disease**
CHD	**Coronary Heart Disease**
CVD	**Cardio Vascular Disease**
CRP	**C-reactive protein**
CVD	**Cardio Vascular Disease**
DBP	**Diastolic Blood Pressure**
DM	**Diabetes Mellitus**
FFA	**Free Fatty Acid**
HE	**Hard Exudates**
HDL	**High Density Lipoprotein**
HMG-CoA	**3-hydroxy-3-methyl glutaryl coenzyme A**
HRT	**Hormone Replacement Therapy**
IDL	**Intermediate-density lipoprotein**
IL	**Interleukin**
LCAT	**Lecithin:cholesterol acyl transferase**
LDL	**Low Density Lipoprotein**
LPL	**Lipoprotein Lipase**
Lp(a)	**Lipo protein (a)**
ME	**Macular Edema**
MNT	**Medical Nutrition Therapy**
MI	**Myocardial Infarction**
MRFIT	**Multiple Risk Factor Intervention Trial**
MS	**Metabolic Syndrome**
MTP	**Microsomal (triglyceride) transfer protein**
NCEP–ATP III	**National Cholesterol Education Adult Treatment Panel**
NPDR	**Non Proliferative Diabetic Retinopathy**
NMR	**Nuclear magnetic resonance**
OCP	**Oral Contraceptive Pill**
PAI-1	**Plasminogen-activator inhibitor-1**
PDR	**Proliferative Diabetic Retinopathy**
PPAR-α	**Peroxisome proliferator activated receptor-alpha**
PPAR-γ	**Peroxisome proliferator activated receptor-gamma**
RCT	**Reverse cholesterol transport**
SBP	**Systolic Blood Pressure**
UKPDS	**U.K.Prospective Diabetes Study Group**
VLDL	**Very Low Density Lipoprotein**
WHR	**Waist to Hip Ratio**

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INTRODUCTION

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. It is also associated with long term complications involving various organs, especially eyes, kidneys, nerves and heart & blood vessels.

Magnitude of the Problem:

Prevalence of Diabetes is increasing worldwide. In 2000, the prevalence as per WHO is 171,000,000 and the estimated prevalence in 2030 is 366,000,000. India leads the top with 31,705,000 in 2000 with an estimated 79,441,000 in 2030.

Classification of Diabetes mellitus:

This includes four clinical classes [1]

1) Type 1 Diabetes
2) Type 2 DM
3) Other specific types of Diabetes.
4) Gestational Diabetes.

Presently India is experiencing an epidemic of Diabetes mellitus and about 90–95 % of total diabetic patients belong to Type 2 Diabetes mellitus. This group, previously known as non-insulin-dependent diabetes encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive.

Type 2 Diabetes mellitus results from a progressive insulin secretory defect on the background of insulin resistance. This may remain undiagnosed until complications develop. Moreover there is an increase in the incidence of Type 2 Diabetes mellitus in children and adolescents in the last decade. Because of the increasing disease burden**,** India is going to see more number of patients with the complications.

The morbidity and mortality from Diabetes mellitus is due to its complications, both microvascular and macrovascular. Dyslipidemia in Diabetes contribute considerably to the increase in mortality and morbidity in diabetes. In the Framingham study it was documented that the incidence of cardiovascular disease in diabetic men was twice that among non diabetic men, and in diabetic women it was about three times[2]. The absolute risk of cardiovascular death has been found to be much higher for diabetic than non-diabetic people in the large Multiple Risk Factor Intervention Trial, irrespective of the presence of other risk factors[3]

However, apart from dyslipidemia, other risk factors also contribute towards the increased risk of cardiovascular disease in diabetes e.g. hypertension, obesity and smokingError: Reference source not found[4,5].

In Diabetes mellitus, elevated levels of Triglycerides with a low HDL are classically described. An increased LDL is also implicated in Diabetic dyslipidemia. More than the absolute increase; the presence of small dense LDL which is more atherogenic is considered as the cause for increased incidence of cardiovascular complications.

Lipids and Lipoproteins:

All the major lipids in our body, namely cholesterol, triglycerides, and phospholipids have important physiological functions to perform as described.

Cholesterol: a) Structural constituent of cell membranes.
b) Precursor of steroid hormones.
c) Precursor of bile acids.

Triglycerides: a) Major energy store of the body.

Phospholipids: a) Structural constituent of cell membranes.

The major dietary lipids are constituted by triglycerides with small quantities of cholesterol and phospholipids. The average

normal Indian diet contains about 20-30gm of lipids per day. Western diet will contain two or three times than this quantity.

Lipoprotein structure:

Lipoproteins are micro-emulsions composed of lipids (cholesterol, cholesteryl ester, and phospholipid) and proteins (apo-proteins). 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 apo-proteins. Free cholesterol is present primarily in the surface monolayer.

Total plasma lipid is 400-600mg/dl and of this about one-third is cholesterol, one-third is triglyceride and one-third is phospholipids. Since lipids are insoluble in water they are complexed with a protein to form lipo-proteins. The protein part of lipoprotein is called apo-lipoprotein.

Lipoproteins have been classified on the basis of their densities during ultracentrifugation. Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), resides between VLDL and LDL; in clinical practice IDL is included in the LDL measurement.

LDL cholesterol typically takes up 60-70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely apo B-100 (apo B). LDL is the major atherogenic lipoprotein and are those most strongly related to the occurrence of cardiovascular disease. HDL cholesterol normally makes up 20-30 percent of the total serum cholesterol. High-density lipoproteins (HDLs) are the smallest and densest of the lipoproteins. The major apo-lipoproteins of HDL are apo A-1 and apo A-11. HDL- cholesterol levels are inversely correlated with risk for CHD. The VLDL is triglyceride-rich lipoproteins, but contains 10-15 percent of the total serum cholesterol. Very-low-density lipoproteins (VLDLs) are triglyceride-bearing lipoproteins, and are secreted by the liver and carry endogenously produced triglyceride. The major apo-lipoproteins of VLDL are apo B100, apo-Cs (C-1, C-11, and C-111) and apo E. VLDL are produced by the liver and are precursors of LDL; some forms of VLDL, particularly VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester. A fourth class of lipoproteins - chylomicrons is also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat containing meal. The apolipoproteins of chylomicrons are the same as for VLDL except that Apo B-48 is present instead Apo B-100. Partially degraded chylomicrons, called chylomicron remnants probably carry some atherogenic potential.

Lipoprotein (a) or Lp (a) is found to have a strong association with CHD risk. Lp (a) when present is attached to apo B-100 by a disulfide bond. It has significant homology with plasminogen. So it interferes with plasminogen activation and impairs fibrinolysis. This leads to unopposed intravascular thrombosis, and possible myocardial infarction.

The sum of the VLDL + LDL cholesterol is called non HDL cholesterol. It is calculated routinely as total cholesterol- HDL cholesterol. Non-HDL cholesterol includes all lipoproteins that contain apo B.

Diabetic Dyslipidemia:

Diabetes is considered as a CHD risk equivalent. Type 2 Diabetes mellitus is associated with insulin resistance and the diabetic dyslipidemia confers this risk. Identification of the metabolic syndrome will help to organize targeted approach towards modifiable risk factors. The term diabetic dyslipidemia essentially refers to atherogenic dyslipidemia occurring in persons with type 2 diabetes. It is characterized by elevated triglyceride rich lipoproteins, small dense LDL particles and low HDL- cholesterol concentrations.

Adipose tissue as an Endocrine organ:

Besides being the body's principal site for energy storage, white adipose tissue influences whole-body insulin action both

through the release of FFAs and by secretion of adipose-derived proteins. The important adipose derived proteins are Leptin, Adiponectin, and Resistin. Tumor necrosis factor-α and other pro-inflammatory cytokines (IL-1 and IL-6) are also derived from adipose tissue.

Insulin is a regulator of virtually all aspects of adipocyte biology, and adipocytes are one of the most highly insulin-responsive cell types. Insulin promotes triglyceride stores in adipocytes by several mechanisms, including the fostering of the differentiation of pre-adipocytes to adipocytes and, in mature adipocytes, through the stimulation of glucose transport and triglyceride synthesis (lipogenesis), and the inhibition of lipolysis. Insulin also increases the uptake of fatty acids derived from circulating lipoproteins by stimulating the activity of lipoprotein lipase in adipose tissue.

Large epidemiologic studies reveal that the risk for diabetes, and presumably insulin resistance increases as body fat content [measured by body mass index (BMI)] increases from the very lean to the very obese. Although this relationship is seen with measures of general adiposity such as BMI, it is also seen that all sites of adiposity do not contribute equally to diabetes risk. Central (ie, intra-abdominal) fat depots are much more strongly linked than peripheral (gluteal/subcutaneous) fat depots to insulin resistance, type 2 diabetes and cardiovascular disease.

Leptin is a 16-kDa protein secreted from adipose tissue; this is considered as a marker of obesity and the insulin resistance syndrome. Adiponectin is a 30-kDa adipose-specific secretory protein that appears to enhance insulin sensitivity. Resistin is a 10-kDa adipose tissue-specific hormone; more studies are needed to determine the clinical relevance of Resistin in obesity and in the development of insulin resistance.

Treatment of Diabetic dyslipidemia:

As the patients with Diabetes have an increased prevalence of dyslipidemia and as it considered as a CHD risk equivalent, lipid management is considered as an integral part of diabetes management. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering Triglycerides has been shown to reduce macro vascular disease and mortality in patients with Type 2 diabetes mellitus, particularly those who have had prior cardiovascular events. So in adult patients, test for lipid disorders is recommended at least annually and more often if needed to achieve goals. Target lipid levels recommended are shown in table below.[6]

LDL	<100mg/dl (<2.6mmol/l)
Triglycerides	<150mg/dl (<1.7mmol/l)
HDL	>40mg/dl (>1.1mmol/l)

In 2008, a consensus panel convened by ADA and the American College of Cardiology recommended a greater focus on non-

HDL cholesterol and apolipoprotein B (apo B) in patients who are likely to have small LDL particles such as people with Diabetes.

Current NCEP/ATP III guidelines[7] suggest that in patients with triglycerides ≥200 mg/dl, the "non-HDL cholesterol" (total cholesterol minus HDL) be used. The goal is ≤130mg/dl. For women it has been suggested that the HDL goal be increased by 10mg/dl. People with diabetes and overt cardiovascular disease (CVD) are at very high risk for further events and should be treated for further events and should be treated with a statin. A lower LDL cholesterol goal of <70mg/dl. (1.8mmol/l), using a high dose of a statin, is an option in these high risk patients with diabetes and overt CVD.

Life style intervention including MNT (Medical Nutrition Therapy), increased physical activity, weight loss, and smoking cessation should allow some patients to reach these lipid levels. Nutritional intervention should be tailored according to each patient's age, type of diabetes, pharmacological treatment, lipid levels, and other medical conditions and should focus on the reduction of saturated fat, cholesterol, and Trans unsaturated fat intake. Glycemic control can also beneficially modify plasma lipid levels. Particularly in patients with very high triglycerides and poor glycemic control, glucose lowering may be necessary to control hyper-triglyceridemia.

Pharmacological treatment is indicated if there is an inadequate response to lifestyle modifications and improved glucose control. However, in patients with clinical CVD and LDL > 100 mg/dl,

pharmacological therapy should be initiated at the same time that lifestyle intervention is started. In patients with diabetes aged < 40 years similar consideration for LDL lowering therapy should be given if they have increased cardiovascular risk (e.g, additional cardiovascular risk factors or long duration of diabetes).

The first pharmacological therapy is to lower LDL cholesterol to a target goal < 100mg/dl (2.60 mmol/l) or therapy to achieve a reduction in LDL of 30 – 40% from baseline. For LDL lowering, statins are the drugs of choice. Other drugs that lower LDL include nicotinic acid, ezetimibe, bile acid sequestrants, and fenofibrate.

If the HDL is <40 mg/dl and the LDL is between 100 and 129 mg/dl, a fibric acid derivative or niacin might be used. Niacin is the most effective drug for raising HDL, but can significantly increase blood glucose at high doses.

Combination therapy, with a statin and fibrate or statin and niacin, may be efficacious for patients needing treatment for all three lipid fractions, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis, the risk of rhabdomyolysis seems to be lower when statins are combined with fenofibrate than gemfibrozil.

Triglycerides less than 150mg/dl (1.7 mmol/l) and HDL cholesterol > 40 mg/dl (1.0 mmol/l) in men and > 50 mg/dl (1.3 mmol/l)

in women are desirable. Lowering triglycerides and increasing HDL cholesterol with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL and near-normal levels of LDL. Statin therapy is contraindicated in pregnancy.

In 2008, a consensus panel convened by ADA and the American College of Cardiology (ACC) recommended a greater focus on non-HDL cholesterol and apo lipoprotein B (apo B) in patients who are likely to have small LDL particles, such as people with diabetes. The consensus panel suggested that for statin-treated patients in whom the LDL cholesterol goal would be < 70 mg/dl (non-HDL cholesterol < 100 mg/dl), apo B should be measured and treated to < 80 mg/dl. For patients on statins with an LDL cholesterol goal of < 100 mg/dl (non-HDL cholesterol < 130 mg/dl), apo B should be measured and treated to < 90 mg/dl.

There is a rising epidemic of diabetes mellitus in our country, India; affecting younger age group and there is an increasing mortality and morbidity due to coexisting dyslipidemia, atherosclerosis and CHD. The knowledge in this subject related to our patient population is needed as there is enough scope for interventions with early diagnosis and management.

AIM OF THE STUDY

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The present study is being planned with the following aims:

1) **To study the pattern of dyslipidemia in Type 2 Diabetes mellitus patients in Northern Kerala.**
2) **To assess the relationship of lipid abnormalities with microvascular and macrovascular complications in type 2 diabetes mellitus.**
3) **To assess the effect of obesity and dietary habits in diabetic patients compared to age and sex matched control group belonging to the same socio-ethnic and cultural background.**

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The dyslipidemia in type 2 diabetes mellitus is recognized from the days of the recognition of obese diabetes mellitus itself.

"I believe the chief cause for premature development of arteriosclerosis in diabetes, save for advancing age, is an excess of fat; an excess of fat in the body (obesity); an excess of fat in the diet, and an excess of fat in the blood. With an excess of fat diabetes begins and from an excess of fat diabetics die, formerly of coma, recently of arteriosclerosis."[8] (Dr.Elliot Joslin in 1927).

Clustering of clinical and metabolic risk factors, known as "metabolic syndrome", is defined by the National Cholesterol Education

Program Adult Treatment Panel III (NCEP ATP III) Error: Reference source not found. The metabolic syndrome is identified by the presence of three or more of the components listed in the table below.

Table I: Clinical Identification of the Metabolic Syndrome*

Risk factor		Defining level
Abdominal obesity	Men	> 102 cm.(>40 in)
	Women	> 88 cm (>35 in)
Triglycerides		≥ 150 mg/dl
HDL Cholesterol	Men	< 40 mg/dl
	Women	< 50 mg/dl
Blood Pressure		≥ 130/85 mm Hg.
Fasting Glucose		≥ 110 mg/dl

*The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (eg. plasma insulin), proinflammatory state (eg: high sensitivity C-reactive protein), or prothrombotic state (e.g., fibrinogen or PAI-1) in the diagnosis of the metabolic syndrome.

The central pathophysiologic features of the metabolic syndrome include (1) tissue resistance to insulin action, (2)

compensatory hyperinsulinemia (required to maintain blood glucose levels in the normal range), and (3) excessive circulating levels of free fatty acids[9].[10] These features drive development of metabolic syndrome risk factors, which include (1) dyslipidemia, (2) elevated blood pressure, (3) glucose intolerance, (4) increased levels of inflammatory markers, (5) prothrombotic changes in hemostatic factors, and hyperuricemia.Error: Reference source not found, Error: Reference source not found

High predisposition to the development of type 2 diabetes in certain ethnic groups, such as Asian Indians, necessitates early identification of Metabolic Syndrome for the purpose of prevention[11] Anthropometric parameters of Asians are different than those for white Caucasians and blacks. For example, Asian Indians have smaller body size, excess body fat, and truncal and abdominal adiposity but lower average waist circumference than white CaucasiansError: Reference source not found.The cutoffs of waist circumference to define abdominal obesity by the NCEP ATPIII definition underestimate abdominal obesity in adult Asians[12].So the criteria for defining Metabolic Syndrome in adult Asian Indians needs revision. The definition which included modified cutoffs of waist circumference (>90cm. in men and >80cm. in women) and BMI cut off as >23 Kg/m^2, and a measure of truncal subcutaneous fat (sub scapular skin fold thickness (SST) >18mm in addition to the criteria given by the MS ATP definition (Blood pressure, triglycerides, HDL cholesterol, and fasting blood glucose) was found to be the best predictor of Metabolic syndrome[13] .

Body Mass Index (BMI) and Waist Circumference:

The term Insulin resistance generally refers to resistance to the metabolic effects of Insulin, including the suppressive effects of insulin on endogenous glucose production, the stimulatory effects of insulin on peripheral (predominantly skeletal muscle) glucose uptake and glycogen synthesis, and the inhibitory effects of Insulin on adipose tissue lipolysis. Insulin Resistance develops from the complex interplay of genes, obesity, and “environment”, with the latter including nutritional and hormonal factors as well as advancing age. The prevalence of Insulin resistance is likely due to a rapid and dramatic life style progression from hunting and gathering to farming to sedentary overeating. Insulin resistance plays a major role in development of Type 2 Diabetes.

The prevalence of diabetes is 2.9 times higher in over weight (BMI ≥ 27.8 in men and ≥ 27.3 in women) than in normal weight subjects of 20 to 75 years of age[14],[15]. Along with BMI, individuals with upper body obesity or adiposity are at high risk for hyperinsulinemia, insulin resistance and type 2 diabetesError: Reference source not found. Abdominal adiposity, measured by an elevated waist to hip ratio (WHR), is shown to be a strong risk factor for type 2 diabetes mellitus[16]. Prospective studies also support the association of various anthropometric indices of abdominal adiposity and the future development of diabetes[17],[18]. It has been suggested that abdominal

adiposity is an independent predictor of alteration in the plasma lipid, lipoprotein and plasma glucose concentrations 17[,19] ,[20],[21].

Hypertriglyceridaemia and Insulin Resistance

Glucose turnover studies using tracer methods[22] have suggested that the relationship between hypertriglyceridaemia and insulin resistance represents a vicious cycle[23].Most[24],[25],[26]but not all[27] studies have found that reducing triglyceride levels increases insulin sensitivity. It is now widely felt that the insulin resistance syndrome is a precursor of diabetes. The risk of atherosclerosis in diabetes therefore starts long before hyperglycaemia develops and the diagnosis is made[28].

Although there is some disagreement about fibrinogen levels, there is general consensus that plasminogen-activator inhibitor-1 (PAI-1) is increased and that fibrinolysis is decreased in insulin resistance syndrome[29] [30],[31] and in patients with diabetes Error: Reference source not found,[32],[33]

C-reactive protein (CRP), a marker of inflammation that correlates with coronary disease, is also increased[34] in Insulin Resistance syndrome. C-reactive protein, an acute-phase reactant produced by liver, is an extremely sensitive marker of systemic inflammation. It is perceived that chronic low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein (hsCRP) might potentially be a cause underlying the etiology and manifestation

of type 2 diabetes (T2D), although the exact mechanisms are still not well understood. In a Prospective Finnish study high baseline level of serum CRP was associated with an increased risk of diabetes among both men and women, but this association was stronger in women than men.[35] Another study demonstrated the association of low-grade systemic inflammation, as indicated by elevated hsCRP levels, with T2D in North Indian population. This association was independent of obesity. Obesity and glycemic control were the major correlates of hsCRP levels.[36]

Patients with the insulin resistance syndrome have also been found to have increased homocysteine levels and to have increased urinary albumin-to-creatinine ratio (an indicator of microalbuminuria)[37].

Diabetes and Dyslipidemia:

Although the general population has enjoyed a decline in mortality from coronary heart disease (CHD), such a great reduction has not been seen in individuals with diabetes.[38] The most frequent complication of diabetes is atherosclerotic macro vascular disease (i.e., clinical atherosclerosis), which accounts for up to 75% of deaths in patients with diabetes[39].

For reasons that are not fully understood, women without diabetes are partly protected from atherosclerosis in their premenopausal years; however, they lose much of this protection if

they develop diabetes[40],[41].The incidence of heart attacks is greater in patients with type 2 diabetes compared with those with type 1 diabetes because type 2 diabetes is the more common form and age is an additional risk factor. The increase in cardiovascular disease mortality does not, however, occur only in patients with diagnosed diabetes, but also in those with impaired glucose intolerance Error: Reference source not found

Atherogenic factors in Type 2 Diabetes Mellitus:

Atherogenic factors in type 2 diabetes include lipoprotein abnormalities (dyslipoproteinaemias), hypertension, the procoagulant state, hyperglycemia (particularly postprandial hyperglycemia), renal failure, microalbuminuria or proteinuria, hyperinsulinaemia and insulin resistance, and altered vessel wall metabolism and function.

Dyslipoproteinaemia is one of many atherogenic factors in type 2 diabetes. Reducing the risk of CHD in diabetes therefore requires a multifaceted approach[42].

Intensive glycaemic control in type 2 diabetes was shown in the United Kingdom Prospective Diabetes Study (UKPDS) to have a significant effect on microvascular disease, but only a minor effect on macrovascular disease[43] [UK Prospective Diabetes Study (UKPDS) Group, 1998]. Data from clinical trials indicate that correcting

lipoprotein abnormalities reduces coronary risk in diabetes.[44],[45],[46],[47],[48],[49],[50].

Lipoprotein abnormalities in type 2 diabetes

Diabetes is associated with quantitative and qualitative changes in lipoproteins. The quantitative changes most commonly seen in diabetes, particularly in type 2 diabetes, are: an increase in the triglyceride-rich lipoproteins ie, hypertriglyceridemia); and a decrease in HDL, measured as a low plasma concentration of HDL-cholesterol[51] [U.K.Prospective Diabetes Study Group, 1997]. Both these abnormalities may be minor and can be seen at or even before the diagnosis of diabetes Error: Reference source not found,[52].

Low-density lipoprotein and diabetes:

Average low-density lipoprotein-cholesterol (LDL-C) concentrations in patients with diabetes are similar to those in the general population.LDL levels may, however, be decreased with improved diabetes control[53].

The qualitative changes of LDL seen in diabetes are probably more important than the quantitative changes of this lipoprotein. Qualitative changes include:

- changes in the size and density of LDL towards small dense particles (a common feature of hypertriglyceridemia.[54],[55],[56].
- glycation of the lipoprotein[57]; and

- oxidation of the lipoprotein[58],[59].

These qualitative changes make LDL potentially more atherogenic.

Serum cholesterol levels and CHD mortality in diabetes

The Multiple Risk Factor Intervention Trial (MRFIT) Error: Reference source not found has demonstrated that increasing concentrations of serum cholesterol are associated with increasing coronary mortality in individuals with and without diabetes.

At given cholesterol level, the risk in patients with diabetes is two-to-four times greater than it is in individuals without diabetes Error: Reference source not found.

The higher risk in diabetes probably reflects atherogenic changes in LDL and an increased susceptibility of the arteries to atherogenesis. Thus, it must not be concluded that the normal level of LDL in diabetes implies the absence of any risk effect of LDL.

These epidemiological data raise the possibility that reducing LDL levels will reduce CHD in diabetes.

Hypertriglyceridaemia and coronary risk:

There is strong and increasing support for the coronary risk effect of hypertriglyceridaemia, particularly in individuals with diabetes[60] and in women[61]. In the UKPDS, fasting Triglyceride level was associated with CAD after adjusting for age and sex but was not

an independent risk factor when other variables were included in the model Error: Reference source not found.

Examination of the Caerphilly and Speedwell data indicates that hypertriglyceridaemia, high total cholesterol and low HDL-C increase the risk of CHD in an independent manner[62].

Low HDL-C and coronary risk:

There is considerable evidence that low levels of HDL-C increase the risk of coronary artery disease. In those with diabetes, a prospective study in Finland has shown that both higher levels of plasma triglyceride and lower levels of HDL-C increase coronary risk[63].

Multivariate analysis has been used in attempts to differentiate the risk effects of hypertriglyceridaemia from those of the frequently associated low HDL-C, however, the two are so closely correlated that these efforts are probably not justified. Nevertheless, a meta-analysis clearly showed that the plasma triglyceride level is an independent risk factor for Coronary Heart Disease (CHD) Error: Reference source not found.

In patients with type 2 diabetes, acute and chronic hyperinsulinaemia have opposite effects on triglyceride-rich lipoprotein production:

- Acute supply of insulin decreases triglyceride-rich lipoprotein production[64].

- Chronic hyperinsulinaemia increases this production[65].

Microsomal (triglyceride) transfer protein (MTP) mediates the transfer of triglyceride from the cytoplasm into the endoplasmic reticulum, where it is combined with newly synthesized apo B in an early step of VLDL production. A deficiency of MTP prevents triglyceride-rich lipoprotein production and results in the rare genetic disorder, abetalipoproteinaemia. Up regulation of MTP increases the assembly of triglyceride-rich lipoprotein[66]. Insulin downregulates the MTP gene in vitro[67].

As insulin downregulates the MTP gene in vitroError: Reference source not found, the MTP gene may be upregulated in the insulin-resistant / hyperinsulinaemic state. There is less intracellular proteolysis of apo B in insulin resistance[68].The increase in VLDL production that occurs in the insulin-resistant/hyperinsulinaemic state is probably the combined result of higher lipid substrate availability, enhanced apo B stability and accelerated assembly of apo B-containing lipoproteins[69] .The removal of triglyceride from triglyceride-rich lipoprotein involves lipolysis by lipoprotein lipase (LPL)[70]. Insulin increases the activity of LPL Error: Reference source not found. The activity of LPL is decreased in insulin resistance and type 2 diabetes. Hence, the concentration of triglyceride-rich lipoproteins will increase in insulin resistance and type 2 diabetes.

In patients with mild-to-moderate hypertriglyceridaemia, the triglycerides are transported primarily in smaller triglyceride-rich lipoprotein particles and intermediate-density lipoprotein (IDL)[71].

These smaller triglyceride-rich lipoproteins have been strongly implicated in the development of coronary atherosclerosis in individuals with and without diabetes [72]. If the decrease in LPL activity is sufficiently profound, or if the level of triglyceride is sufficiently high, chylomicrons may also accumulate in the circulation.

Although it is generally thought that hyperchylo-micronaemia is not associated with atherosclerosis[73] , there is evidence to indicate that small apo B48-containing lipoproteins (i.e., remnants of chylomicrons) are atherogenic[74].

In humans, apo B, which is the main apolipoprotein in intestinal particles, is unique in that its molecular weight is 48% that of the normal particles made by the liver – hence, the former is called apo B48 and the latter, apo B100. Apo B48 particles have been found to enter the arterial intima[75]. There is angiographic evidence that chylomicron remnant levels are positively correlated with the rate of angiographic progression of CHD[76].

In diabetes, the clearance of postprandial chylomicrons is delayed [77] and the poorer the patient's glycaemic control, the higher the concentration of postprandial chylomicrons and apo B100-containing triglyceride-rich lipoproteins[78].

High-density lipoprotein:

HDL is produced partly by direct hepatic and intestinal synthesis and can also be produced from the intravascular lipolysis of triglyceride-rich lipoproteins

HDL formation

HDL initially appears in the circulation as a small bilayer of particles comprising apolipoproteins, phospholipids and unesterified cholesterol. The small HDL particles interact with cell surfaces and acquire more unesterified cholesterol. Through the action of lecithin: cholesterol acyltransferase (LCAT) the unesterified cholesterol esterifies and enters the core of the particle and the HDL particle expands to its mature spherical form: LCAT activity is inversely related to insulin sensitivity[79]. These processes are the first steps of reverse cholesterol transport (RCT).

The two major apolipoproteins in HDL are apo A-I and apo A-II. The apo A-I and A-II genes can be upregulated by peroxisome proliferator activated receptor-alpha (PPARα). Drugs such as the fibrates that act by increasing PPARα can enhance the direct production of HDL: these drugs also upregulate the gene for LPL; therefore, they can increase HDL production by increasing the lipolysis of circulating triglyceride-rich lipoproteins [80].Circulating HDL exists as a heterogenous population. There are smaller HDL_3 and larger HDL_2 particles. Some studies have indicated that the coronary protective

effect of HDL is primarily due to HDL_2 and L_p A-1[81], and to their ability to reduce coronary risk.

Low density lipoprotein:

The average LDL-C concentrations in patients with diabetes are similar to those similar to those in the general population; however, the LDL particles are smaller and denser and are potentially more atherogenic.There is increasing epidemiological evidence that small dense LDL particles are more atherogenic than large buoyant LDL particles[82]. LDL particles in patients with diabetes may be glycated.The extent of non- enzymatic glycation is a function of the plasma glucose level and occurs even at levels seen clinically in diabetes[83]. Glycation impedes the ability of apo B to act as a ligand for the LDL receptor Error: Reference source not found, this in turn slows LDL catabolism[84] and increases the amount removed by scavenger receptors on cells such as macrophages. The macrophages can develop into foam cells, which are a fundamental part of the atheromatous plaque[85].

LDL oxidation is increased in patients with diabetes. Oxidation impedes the ability of LDL to interact with the LDL receptor and makes it more cytotoxic Error: Reference source not found.

Non HDL Cholesterol and Apo B:

Non HDL cholesterol is considered as a surrogate marker of Apo B which can be easily derived in clinical practice and this is a

cheaper test compared to Apo B. An important question that often arises is the benefit of ordering more advanced lipoprotein profiles. The main reason for the quandary, as pointed out in the article by Lau and Smith, is that calculated low-density lipoprotein (LDL) cholesterol, measured by standard technologies, or non–high-density lipoprotein (non-HDL) cholesterol, are less predictive of ischemic cardiovascular risk than are Apo-lipoprotein B (Apo B) and nuclear magnetic resonance (NMR)–measured LDL particles in numerous studies. This is especially true in the presence of high triglycerides, or low-HDL cholesterol. Although Apo B levels and the number of NMR-measured LDL particles may be more predictive, no clinical trials comparing the use of these goals versus LDL cholesterol or non-HDL cholesterol goals have been performed. For those who can interpret the results, their use may be justified occasionally to confirm lipid goal attainment in those with mixed dyslipidemias and particularly in patients already at standard lipid goals in the presence of progressive coronary heart disease.[86],[87]

Lipoprotein (a) or Lp(a):

Lp (a) lipoprotein is a lipoprotein of unknown physiologic function that is composed of apolipoprotein B-100 (apo B-100) to which apolipoprotein (a) is covalently bound. Increased plasma levels of Lp(a) lipoprotein are independent predictors of the presence of angiographically documented and clinical coronary artery disease, particularly in patients with hypercholesterolemia[88].

Mean values of lipoproteins and triglycerides level, in healthy controls as observed from different quadrants of India is given in table below[89].

Table: Lipids and lipoprotein nomograms in Indian populations (mean value in mg/dl)

Table II

	Triglycerides	**Total Cholesterol**	**HDL Cholesterol**	**LDL Cholesterol**
East	115	185	42	115
North	132	150	43	101
West	107	188	38	129
South	132	150	43	101
South[96]	119	172	40	108

Dietary Patterns and Risk of Diabetes and Coronary Artery Disease:

Diet has important effects on the risk of diabetes and CAD, independent of other lifestyle factors such as obesity and physical inactivity. Analysis of dietary factors associated with reduced risk for diabetes and CAD suggests a “low-risk” dietary pattern that would include higher intakes of whole grains, legumes, fruits and vegetables, nuts and oils, fish, lean meats, and low fat dairy products (Table 1). Intakes of refined grains, white rice, potatoes, high-fat meats

and dairy products, stick margarine, sodas, sweets, and desserts would be minimized [90].

Table III: Characteristics of a Low- Risk Dietary Pattern

Foods to be Emphasized	Foods to be Eaten Sparingly
Whole grains	Refined grains
Legumes	White rice and potatoes
Nuts and oils	Stick margarine/shortenings
Fruits and vegetables	Sodas, sweets, and desserts
Fish and lean meats	High-fat meats
Low-fat dairy products	High-fat dairy products

First-line therapy for the management of the Metabolic Syndrome is lifestyle modification, including loss of excess body fat, physical activity, and smoking cessation. Data from epidemiologic studies and clinical trials support the view that a diet with low glycemic load, high in whole grains and cereal fibers, a high ratio of unsaturated to saturated fats, and low in trans-fats is associated with markedly reduced risk for diabetes and CAD, even among those with other risk factors such as obesity. A low- risk dietary profile includes higher intakes of whole grains, legumes, fruits and vegetables, nuts and oils, fish and lean meats, and low-fat dairy products. Foods to be eaten

sparingly include refined grains, white rice and potatoes, stick margarine and shortenings, sodas, sweets and desserts, and high-fat meats and dairy productsError: Reference source not found.Trans fatty acids, which are largely consumed from partially hydrogenated vegetable oils, adversely affect circulating lipid and lipoprotein levels and endothelial function, trigger systemic inflammation, and might increase visceral adiposity, body weight, and insulin resistance.

Diabetes mellitus, dyslipidemia and complications:

Lipid lowering recommendations are currently given to all patients with diabetes and elevated cholesterol irrespective of retinopathy status. Appropriate management to normalize lipid is important in patients presenting with significant risk for development of diabetic retinopathy or affecting its course. Proper diet and drug treatment may result in less retinal vessel leakage and hard exudates [91],[92]. Dyslipidemia is considered as a real risk factor in diabetic patients.

A number of lipid abnormalities have been observed in patients with diabetic nephropathy, with hypertriglyceridemia and low levels of HDL cholesterol being the most common. However combined hyperlipidemia and isolated elevations in LDL cholesterol levels are also seen in patients with diabetic renal disease[93].

Table IV: Degree of Risk of Coronary Heart Disease by Lipoprotein Level (mg/dl) in Type 2 Diabetes

Risk	LDL	HDL	S.Triglyceride

		Men	Women	
High	≥130	<35	<45	≥400
Borderline	100-129	35-45	45-55	200-399
Low	<10	>45	>55	<200

Data from American Diabetes Association.Management of Dyslipidemia in adults with diabetes.Diabetes Care 2000;23[suppl 1]:S57-S60.

Treatment of lipoprotein abnormalities in Diabetes mellitus:

As the atherogenic lipoprotein profile is an important risk factor for CHD in patients with Diabetes mellitus, lipid modifying therapy is indicated in these patients and lipoprotein goals have been defined [94],[95].

In studies using HMG (hydroxymethale glutaryl) CoA reductase inhibitors (statins), patients with diabetes achieved significant reductions in coronary and cerebro vascular events Error: Reference source not found,[96],[97],[98].In two studies using the fibric acid derivative gemfibrozil, reductions in cardiovascular end points were also achieved.Error: Reference source not found,[99].

The first priority of pharmacological therapy is to lower LDL cholesterol to a target goal of <100mg/dl (2.60 mmol/l) or therapy to achieve a reduction in LDL of 30- 40%. For LDL lowering, statins are the drugs of choice. Other drugs that lower LDL include nicotinic acid,

ezetimibe, bile acid sequestrants, and fenofibrate Error: Reference source not found,[100].

The heart protection study Error: Reference source not found demonstrated that in people with diabetes over the age of 40 years with a total cholesterol > 135 mg/dl, LDL reduction of ~ 30% from baseline with the statin simvastatin was associated with an ~ 25% reduction in the first event rate for major coronary artery events independent of baseline LDL, preexisting vascular disease, type or duration of diabetes, or adequacy of glycemic control. Similarly in the Collaborative Atorvastatin Diabetes Study (CARDS)[101], patients with type 2 diabetes randomized to Atorvastatin 10mg daily had a significant reduction in cardiovascular events including stroke. These trials concluded that statins confer a benefit regardless of initial LDL level in those with diabetes.

Recent clinical trials in high- risk patients, such as those with acute coronary syndromes or previous cardiovascular events[102],[103],[104] have demonstrated that more aggressive therapy with high doses of stains to achieve an LDL of <70 mg/dl led to significant reduction in further events. The risk of side effects with high doses of statins is significantly outweighed by the benefits of such therapy in these high risk patients. Therefore a reduction in LDL to a goal of <70 mg/dl is an option in very high risk patients with overt CVD.

Several studies suggest that statins may reduce the risk of CAD not only through their effects on lipid levels but also through

mediation of inflammatory processes[105],[106]. An analysis by Bark et al Error: Reference source not found of statin studies published between 1980 and 2003 suggests that all statins are effective at lowering C-reactive protein levels, and the effect is not dose dependent. Moreover, Bays et al Error: Reference source not found have shown that simvastatin reduces C-reactive protein levels, even in hypertriglyceridemic patients. High-sensitivity C-reactive protein (hs-CRP) has evolved as an important predictor of cardiovascular events and is highly correlated with the metabolic syndrome. The greater the number in any given patient of the 5 metabolic syndrome criteria – visceral obesity, low HDL, hypertriglyceridemia, hypertension, or impaired fasting glucose – the more likely the hs-CRP will be elevated. Lowering hs-CRP to a therapeutic target of <1.0mg/dl may indicate adequate management of the various risk factors. Proving this hypothesis will require more intensive investigation. It is hoped that the ongoing Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which, which is evaluating the effects of rosuvastation 20mg in placebo in 15,000 patients with LDL cholesterol levels <130mg/dl and hs-CRP >2.0, will shed light on this very important issue[107].

If the HDL is <40 mg/dl and the LDL is between 100 and 129 mg/dl, a fibric acid derivative or niacin might be used. Niacin is the most effective drug for raising HDL but can significantly increase blood glucose at high doses. More recent studies demonstrate that a modest doses (750- 2000 mg./day), significant benefit with regards to LDL, HDL, and triglyceride levels are accompanied by only modest changes

in glucose that are generally amenable to adjustment of diabetes therapy[108].

Some oral anti-diabetic medications (metformin, pioglitazone) have been shown to improve the lipoprotein profile in patients with type 2 diabetes, their lipid-modifying properties are limited and treatment with additional lipid lowering therapy is warranted for CHD risk reduction in these patients[109],[110].

Therapeutic approaches that lower FFA levels and restore FFA metabolism can be expected to have substantial beneficial effects in patients with diabetes. Metformin has been shown to lower triglyceride levels in individuals with type 2 diabetes[111]. All thiazolidine diones substantially increase HDL cholesterol level with Troglitazone (no more in clinical use) and Pioglitazone also decreasing the triglyceride levels[112],[113],[114],[115]. LDL and total cholesterol levels increase with thiazolidine -diones use, however the rise in LDL cholesterol is predominantly in the large buoyant particles and the small dense atherogenic particles decrease in concentration[116] that result in an increased resistance of LDL cholesterol to oxidationError: Reference source not found, [117].

MATERIALS AND METHODS

MATERIALS AND METHODS

The study included Type 2 diabetes mellitus patients attending Medical College, Kozhikode and who are under regular medical follow up. This study subjects were compared with age, gender matched normal subjects as control to know the lipid level of our population who do not have diabetes or pre-diabetes based on history and laboratory investigations. This was an observational study.

Cases were selected from patients diagnosed to have Type 2 diabetes mellitus of varying duration and who are under regular medical follow up from the Medical and Diabetic OPD of Medical College, Kozhikkode.

The exclusion criterias included:

a. Patients already on Lipid lowering drugs or Glitazones and OCP or HRT in females
b. Familial hypercholesterolemias with a family history
c. Hypothyroidism including Subclinical hypohyroidism (TSH values above 5.5 µIU/ml)
d. Who are seriously ill and / or requiring hospitalization or having chronic liver disease or chronic kidney disease with Serum Creatinine ≥ 2 mg%
e. Problem drinkers using CAGE questionnaire with score ≥ 2[118],[119].

Control group included age and sex matched people having no significant illnesses or there is no history suggestive of familial hypercholesterolemia. Those who are on any regular medical treatment were excluded.

Those having Hypertension were not excluded. Smoking and Alcohol use were matched among the groups. Women with pregnancy or lactation not included in both the groups.The subjects and controls were enrolled from the same socio-cultural and religious backgrounds including dietary habits.

A detailed history and thorough physical examination was done in both the study subjects and the controls. All patients with Type 2 Diabetes mellitus above 25 years were included in the study. Patients having other major illnesses or infections, liver diseases, renal diseases which is unexplained due to diabetes, pregnancy, hypothyroidism, those on lipid lowering drugs, oral contraceptive pills, hormone replacement treatments and those having genetically determined lipoprotein disorders (eg: familial combined hyperlipedemia and familial hyper triglyceridemia) were excluded from the study. In short, subjects who were taking medications for hyperlipidemia or medications known to affect the lipid profile were excluded. Subjects with familial hyperlipidemia as well as those with signs and/or symptoms of active infection or stressful conditions were also excluded.

History included symptoms on presentation when diabetes mellitus was first detected, duration of diabetes mellitus, symptoms relating to micro and macro vascular complications, history of any hospital stay, mode of treatment and type of follow up. History of hypertension, CAD, smoking, alcohol use, use of drugs belonging to

OCP, HRT, Lipid lowering drugs, Glitazones, family history of diabetes. Patient's general living conditions were also assessed.

A detailed dietetic history was taken by a three days diet recall method and evaluated by a qualified dietician. Dietary details, dietary concepts, cooking oil, meat, fish and egg consumption, intake of sugar, vegetables and fruits were also taken. The total calories intake, carbohydrate, protein and fat were used for calculation in diabetic subjects as well as control group.

Physical examination included height, weight, BMI (Body Mass Index), waist circumference. BMI is calculated by determining weight in kilograms and dividing by the height in meters squared. This measurement has been used to define four classes of body weight and carries a modestly increased risk of morbidity and mortality. A BMI between 18.5 and 24.9 is considered normal. A BMI of 25.0 but less than 29.9 is considered overweight or pre-obese and, statistically carries a slightly increased risk of co morbidities such as diabetes and cardiovascular disease compared with the risk in normal weight individuals. A BMI of more than 30 is considered in obese category, which is further divided into class I (BMI, 30 to 39.9, class II (BMI 40 to 49.9) and class III (BMI>50).

As the Asian Indians have lower BMI and abnormal fat distribution, cutoffs of waist circumference (>90cm. in men and >80cm. in women) and BMI cut off as >23 Kg/m^2, were opted. Based on Body Mass Index the groups were categorized into <23 kg/m^2=Normal; ≥23 -

24.9 kg/m^2 = Overweight; ≥25-29.9 kg/m^2 = Obese; ≥30 kg/m^2 as morbidly obese. Groups were divided into normal and abnormal according to the waist circumference. In males ≥ 90 cm and in females ≥ 80 cm considered abnormal.

The definition of obesity can be refined on the basis of the realization that the accumulation of adipose tissue in different depot has different consequences. Thus, many of the most important complications of obesity, including insulin resistance, diabetes, hypertension, and hyperlipidemia, are linked to the amount of intra abdominal fat, rather than to lower-body fat (i.e.; buttocks and leg) or subcutaneous abdominal fat.

To define the level at which waist circumference is measured, a bony landmark is first located. The subject stands and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the mid axillary line. The measuring tape is placed on a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at a normal minimal respiration[120,121].

Systolic and diastolic blood pressure (SBP and DBP) were measured using standard mercury sphygmomanometer on the right arm of seated participants who had rested for 5 min.

A search for the presence of micro vascular and macro vascular complications was also done. Examination included blood pressure, neuropathy assessment with vibration perception using tuning fork of 128 Hz, bilateral ankle jerks and testing with monofilament of 5.07 size (thickness), equivalent of 10gm. of linear force.

Testing with monofilament: It tests sense of touch (large nerve fiber function). When applied perpendicular to the foot, it buckles at a given force of 10gm.The patient should be able to sense the monofilament by the time it buckles. The filament should be pressed at several sites eg. Plantar aspects of the first toe, the first, third and fifth metatarsal heads, the heel and dorsum of the foot. The patient's inability to feel the filament indicates a loss of protective sensation.

Assessment of Retinopathy:

Retina examination through dilated pupils is done to determine level of NPDR (non-proliferative diabetic retinopathy), level of PDR (proliferative diabetic retinopathy), and level of ME (macular edema) by a qualified ophthalmologist. The definitions were based on International Classification of Diabetic Retinopathy[122],[123]. International Classification of Diabetic Retinopathy and Diabetic Macular Edema described five clinical levels of diabetic retinopathy: no apparent retinopathy (no abnormalities), mild NPDR (micro aneurysms only), moderate NPDR (more than micro aneurysms only but less than severe NPDR), severe NPDR (any of the following : >20 intra retinal

haemorrhages in each 4 quadrants, definite VB in 2+quadrants, prominent IRMA in 1+ quadrant and no PDR), and PDR (one or more of retinal neovascularization, vitreous haemorrhage, or pre-retinal haemorrhage).

Additionally, the International Classification identified two broad levels of diabetic macular edema (DME): macular edema apparently absent (no apparent retinal thickening or hard exudates [HE] in the posterior pole) and macular edema apparently present (some apparent retinal thickening or hard exudates [HE] in the posterior pole); if present, macular edema was sub classified as mild DME (some retinal thickening or HE in the posterior pole but distant from the center f the macula), moderate DME (retinal thickening or HE approaching the center of the macula but not involving the center), or severe DME (retinal thickening or HE involving the center of the macula).

International Classification of Diabetic Retinopathy and Diabetic Macular Edema simplify the descriptions of categories when compared to the ETDRS levels of diabetic retinopathy[124],[125].

Assessment of Diabetic Nephropathy:

Persistent albuminuria in the range of 30-299 mg/24 h (microalbuminuria) is a marker for development of nephropathy in type

2 diabetes mellitus. Micro albuminuria is also a well established marker of increased CVD risk[126].

Table V: Definitions of Abnormalities in Albumin Excretion

Category	Spot collection (µgm/mg creatinine)
Normal	<30
Microalbuminuria	30-299
Macro(clinical)-albuminuria	300

Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6- month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. exercise within 24 h, infection, fever, CHF, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

Screening for microalbuminuria can be performed by three methods: 1) measurement of the albumin-to-creatinine ratio in a random, spot collection (preferred method); 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and 3) timed (eg; 4-h or overnight collection. The analysis of a spot sample for the albumin-to-creatinine ratio is strongly recommended by most authorities Error: Reference source not found.

The following biochemical investigations were done in all patients. Fasting and 2 hr.postprandial plasma glucose, blood urea and

Serum creatinine. Blood samples were drawn from an ante cubital vein for biochemical analysis. Samples were taken for blood sugars, HbA_{1c} as well as Fasting Serum Lipid Profile after a complete history and detailed physical examination.

Estimation of fasting serum lipid profile:

Serum is collected after a 12hrs. overnight fasting. The measurement is performed with the person in a baseline stable condition, that is, in the absence of acute illnesses including stroke, trauma, surgery, acute infection, weight loss, pregnancy, or recent change in usual diet; as these conditions often result in values that are not representative of the person's usual level. Venous blood will be collected in tubes without anticoagulant.

Plasma glucose and lipids (Total cholesterol, Triglycerides and HDL) were estimated using Olympus AU-400 Auto Analyzer. VLDL is calculated. The LDL Cholesterol was estimated directly in all diabetic subjects. The value of LDL cholesterol is calculated using Friedewald's equation in the control group[127]. If the triglyceride level is below 400mg/dl, this value can be divided by five to estimate the VLDL-cholesterol. Since total cholesterol is the sum of LDL cholesterol, HDL cholesterol and VLDL cholesterol, LDL cholesterol can be calculated as follows:

LDL-C* = TC*- HDL-C*-TG*/5(*-all values are in mg/dl.).

For persons with triglycerides over 400mg/dl, estimation of LDL cholesterol is done by direct method among the control group.

HbA1c was estimated using High Performance Liquid Chromatography (HPLC) method. Normal control with an HbA1c < 7, bad control between 7 to 10 and very poor control between > 10.

Lipoprotein (a) [Lp (a)] was done by Turbidimetric Immunoassay. The reference value for Lp (a) in normal population is < 30mg/dl.

CRP-US (Ultrasensitive CRP) was estimated using Turbidimetric Immunoassay. <5mg/L was considered normal.

Quantitative determination of Apolipoprotein B was done by Turbidimetric Immunoassay. The reference values for the normal population are 55-140 mg/dl.

Electrocardiogram was done in all patients.

Statistical analysis was done using SPSS version 13.0 for Windows. Categorical variables were analysed using chi-square test and Spearman's rank correlation. Continuous variables by t-test and Pearson's correlation when data was normally distributed and by Mann Whitney U test when data was not normally distributed. Binary logistic regression was used to analyse the association of retinopathy with lipid profile. Continuous values were expressed as mean ± 1 standard deviation**.** Analysis of variance (ANOVA) was used to compare means

of variables in more than two groups. A p value < 0.05 was considered to indicate statistical significance.

PROFORMA

Lipid abnormalities in Type 2 Diabetes mellitus with specific reference to Hypertriglyceridemia

1) Name & Address Age: Sex Male/ Female
PIN Code Phone no:

2) Duration of Diabetes Mellitus
3) Smoking Yes/ No / Ex. Alcohol Yes/ No / Ex
4) H/o Hypertension Yes/ No CAD Yes/ No
5) Current treatment Diet / OAD / Insulin / OAD & Insulin.
6) H/o OCP / HRT Yes / No / Not applicable
7) H/o lipid lowering treatment Yes / No
8) If YES drugs? Statin / Fibrates / others (TZD)
9) Family h/o Diabetes Mellitus Yes / No.

10) SE status APL / BPL Electricity / Water source/ Phone
NO / Two / Three / Four wheeler.
TV / Fridge.
Education Primary / High School / College / Graduate / Professional.

11) Height m. Weight Kg. BMI Kg/m^2.
12) Blood pressure: mm.of Hg. Waist circumference: cm.
13) Neuropathy

	Rt.	Lt.
Monofilament	Y / N	Y / N.
Ankle jerk	Y / N	Y / N.
VP (128 Hz.)	Y / N	Y / N.

Rt. Lt.
14) Retinopathy: Non proliferative
Proliferative
Maculopathy.

15) Hb TLC DLC ESR
16) Urine albumin creatinine ratio: µgm. /mg. creatinine.
17) FBS 2 hrs. PPBS:
18) Blood Urea S. Creatinine:
19) ECG
20) Fasting S. Lipid profile
S. Cholesterol LDL
S. Triglycerides HDL
VLDL: Non HDL Cholesterol
21) Hb A_{1c}
22) Serum C Reactive protein / hs CRP: In possible cases only.
23) Apo B
24) Lp (a)
25) Detailed diet history with three days diet recall method.

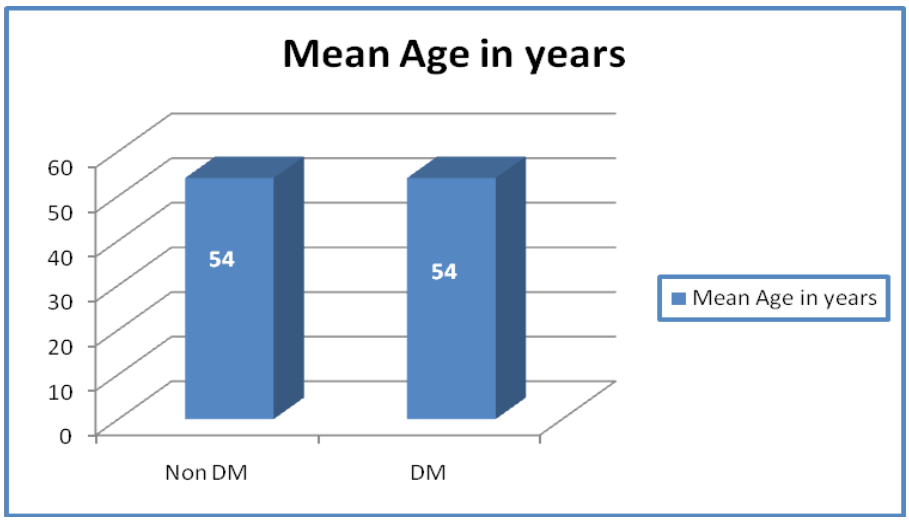
OBSERVATIONS

OBSERVATIONS

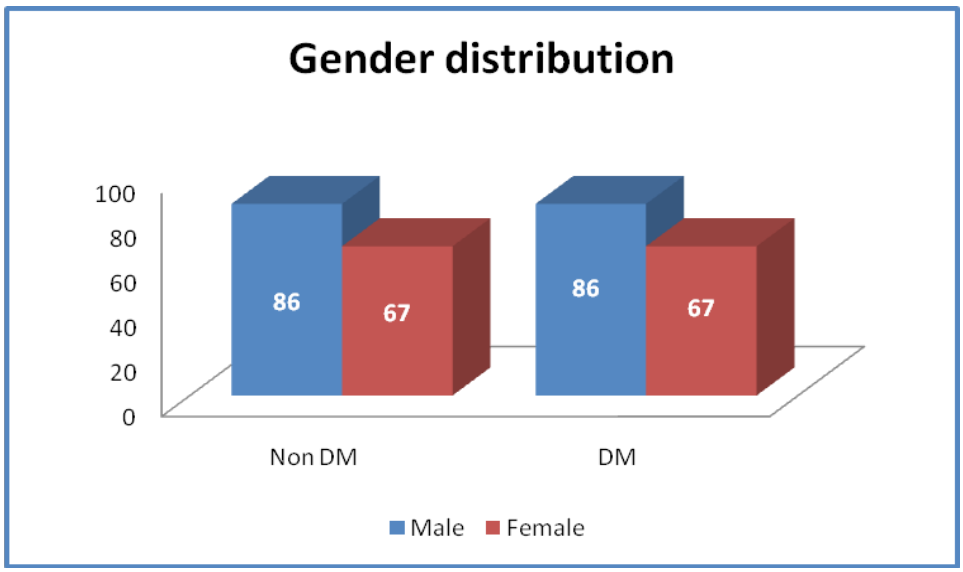
The study included a total of 153 cases having diabetes and was compared to an age and sex matched control group.

Age and Sex distribution

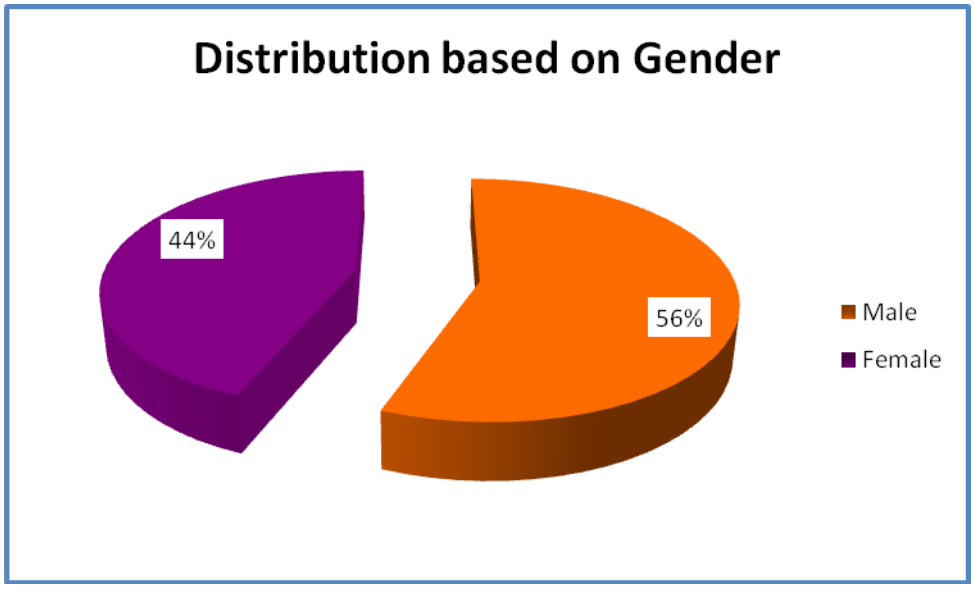
The age group ranged between 26 years and 85 years with mean age of 53.93 ±10.66 (Figure 1). There were 86 (56.2%) males and 67 (43.8%) females among both the groups (Figure 2 & 3).



(Figure 1)



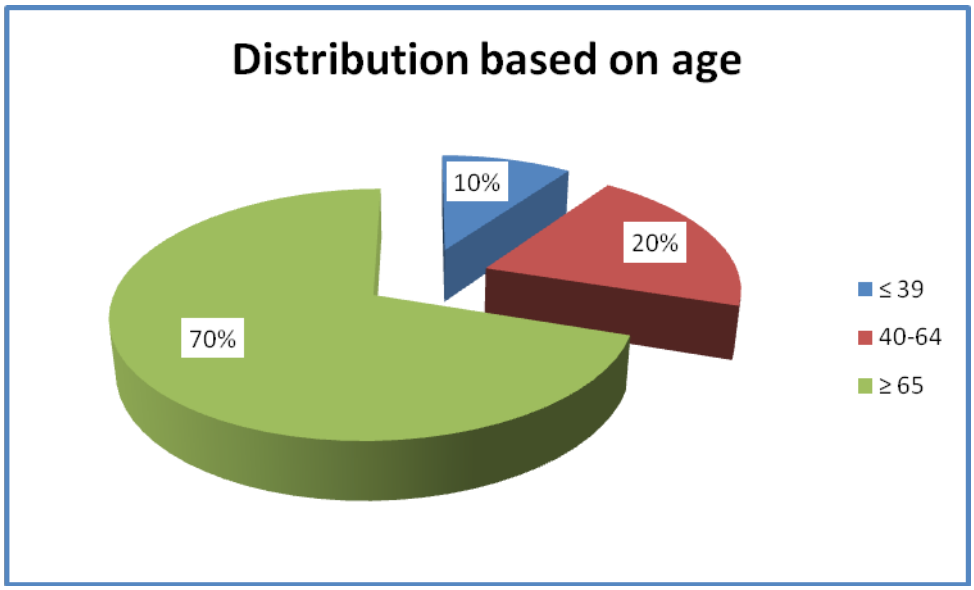
(Figure 2)



(Figure 3)

Distribution based on age:

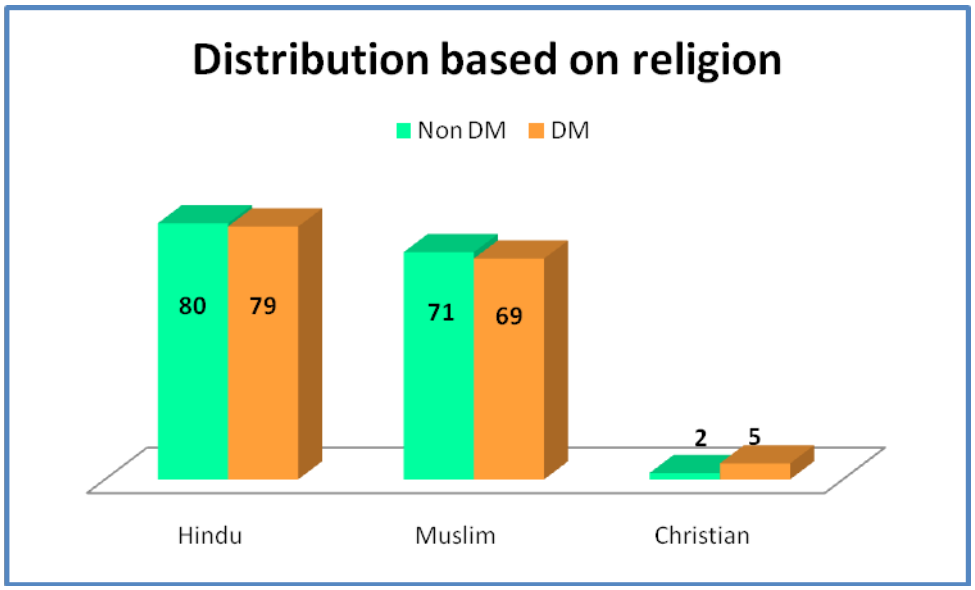
Among the subjects and controls 15 (10%) belonged to ≤39 years of age, 107(70%) were in the age group 40-64 years and 31 (20%) in the age group ≥ 65 years (Figure 4).



(Figure 4)

Religion:

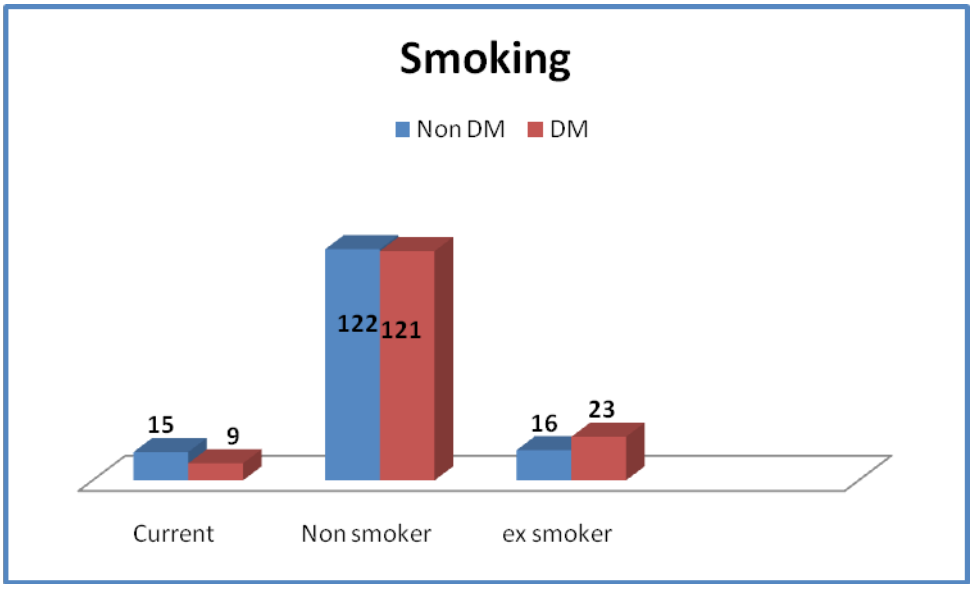
There were 80(51.6%) Hindus, 71(45.1%) Muslims and 2(3.3%) Christians among the control and 79(52.3%) Hindus, 69(46.4%) Muslims and 5(1.3%) Christians among the cases (p = 0.52) (Figure 5).



(Figure 5)

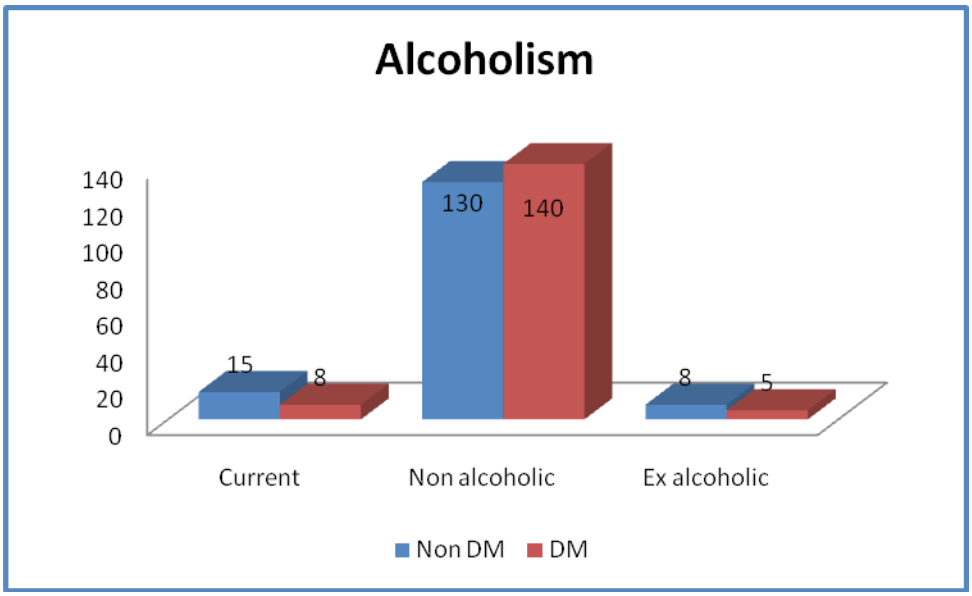
Social habits - Smoking and Alcoholism:

There were 15(9.8%) current smokers, 122(79.74%) non smokers and 16(10.46%) ex- smokers among controls and 9(5.88%) current smokers, 121(79.08%) non smokers and 23(15.03%) ex-smokers among the diabetic cases (p = 0.25) (Figure 6).



(Figure 6)

Going through the history of alcoholism, there were 8(5.23%) current alcoholics, 140(91.50%) non-alcoholics and 5(3.27%) ex alcoholics among cases and 15(9.80%) current alcoholics, 130(84.97%) non alcoholics and 8(5.23%) ex- alcoholics among the non-diabetic controls (p = 0.20) (Figure 7).

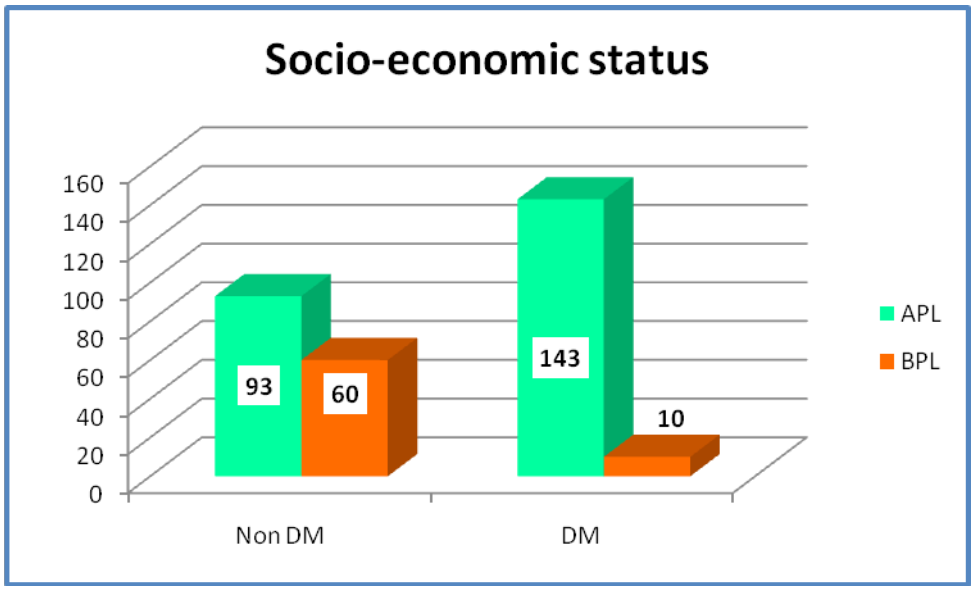


(Figure 7)

Socioeconomic background:

(Based on the assessment done at presentation)

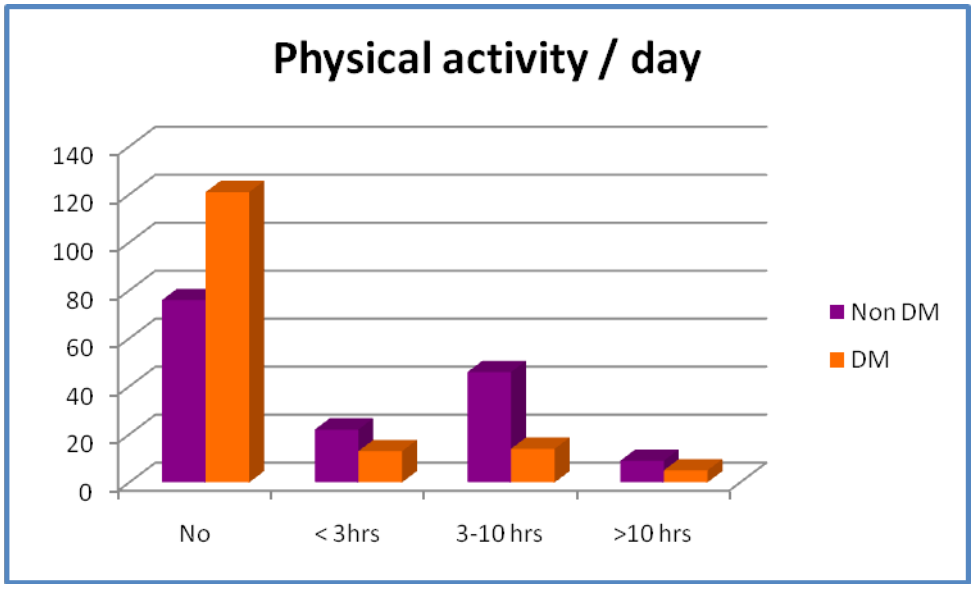
There were 93(61%) from the APL category and 60(39%) from the BPL category in the controls as against 143 (93%) from the APL and 10 (7%) from the BPL categories in the diabetic patients (p = 0.00) (Figure 8).



(Figure 8)

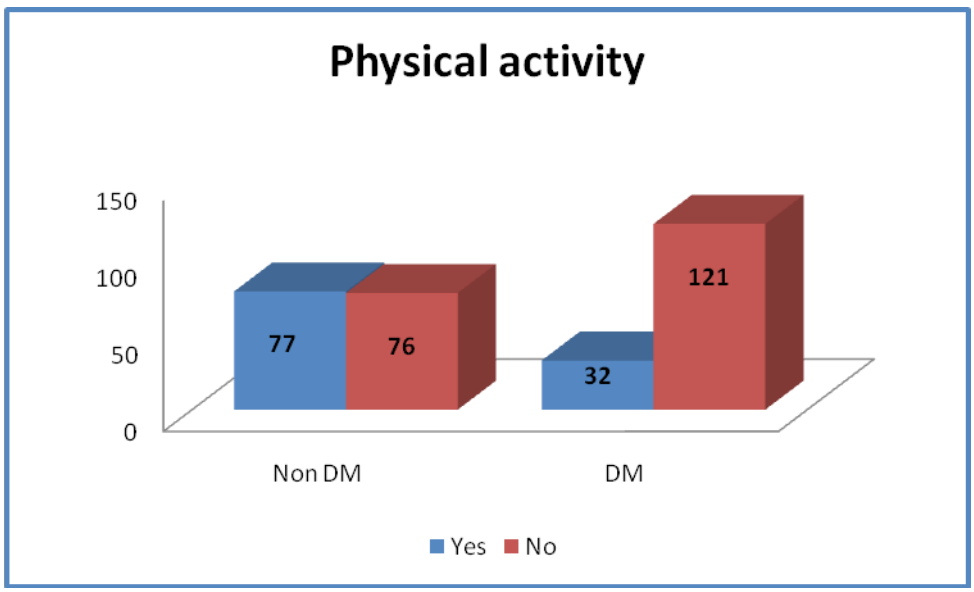
Physical activity:

Parameters assessed were hours in a day they were involved in some kind of activity which could be walking, gardening, participation in games or manual labor and hours spent was divided into 4 groups as not involved in any activity, less than 3 hrs in a day, 3 to 10 hrs in a day and more than 10hrs in a day like who were essentially engaged in heavy manual labor (Figure 9).



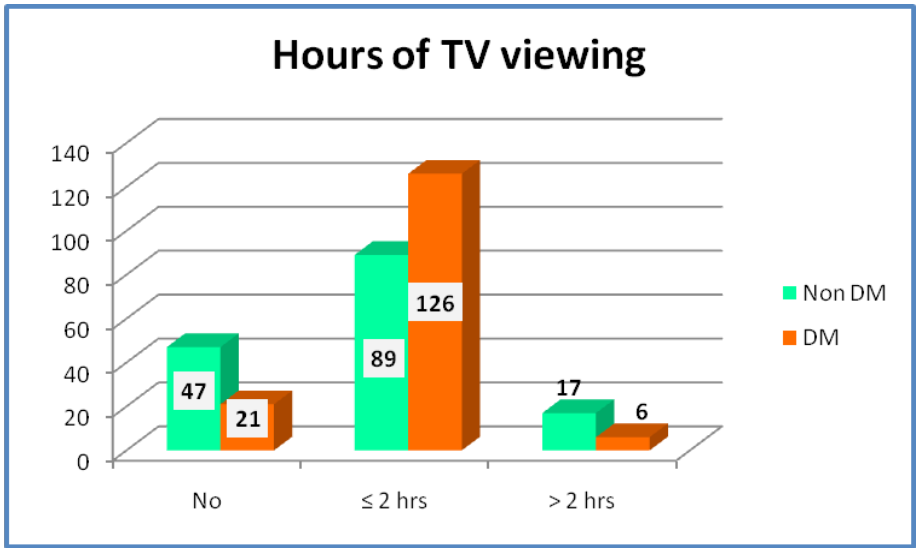
(Figure 9)

Among the controls 76(49.67%) were physically inactive and 77(50.33%) active and from cases 121(79.08%) were inactive and 32(20.92%) active (p = 0.00) (Figure 10). Among Diabetics, Mean TC/HDL (4.7 ± 1.2 Vs 4.06 ± 0.9) and mean LDL/HDL (2.8 ± 0.9 Vs 2.3 ± 0.7) were more for physically inactive persons (p = 0.005 & 0.002 respectively).TC, TG, LDL, HDL, VLDL & non HDL were not associated with physical activity (all p >0.05).



(Figure 10)

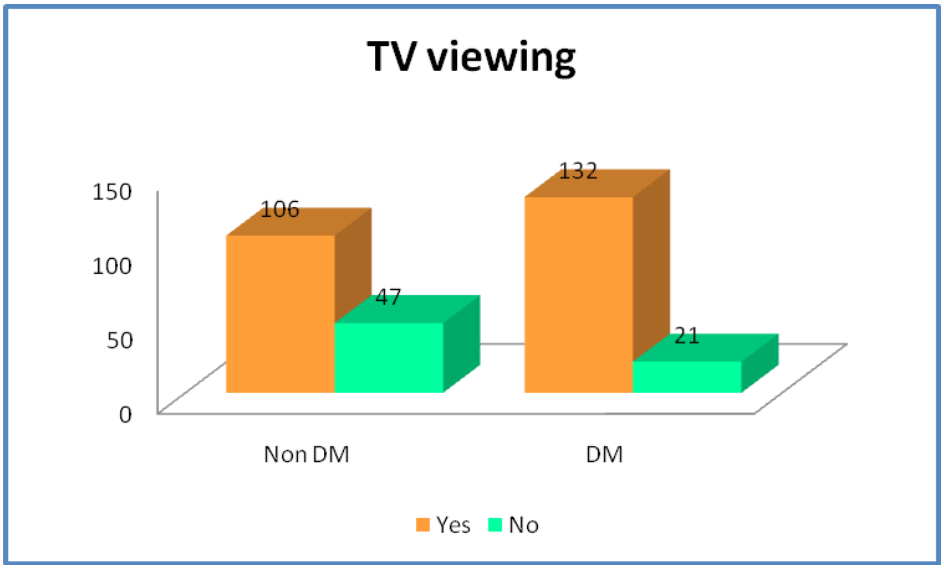
Also enquired about the hours they spent in front of television. Categorized into do not watch at all, to less than 2 hrs and to more than 2 hrs per day (Figure 11).



(Figure 11)

Among the controls 47(30.72%) did not watch TV at all and 106(69.28%) used to watch TV for some hours of the day. Among diabetics 21(13.73%) did not watch TV at all and 132(86.27%)

used to watch TV for some hours of the day ($p = 0.00$) (Figure 12). Among diabetics, mean TC/HDL was more for TV viewers (4.6 ± 1.1 Vs 4.02 ± 1.1) ($p = 0.019$). Other lipids were not associated with hours of TV viewing (all $p > 0.05$).

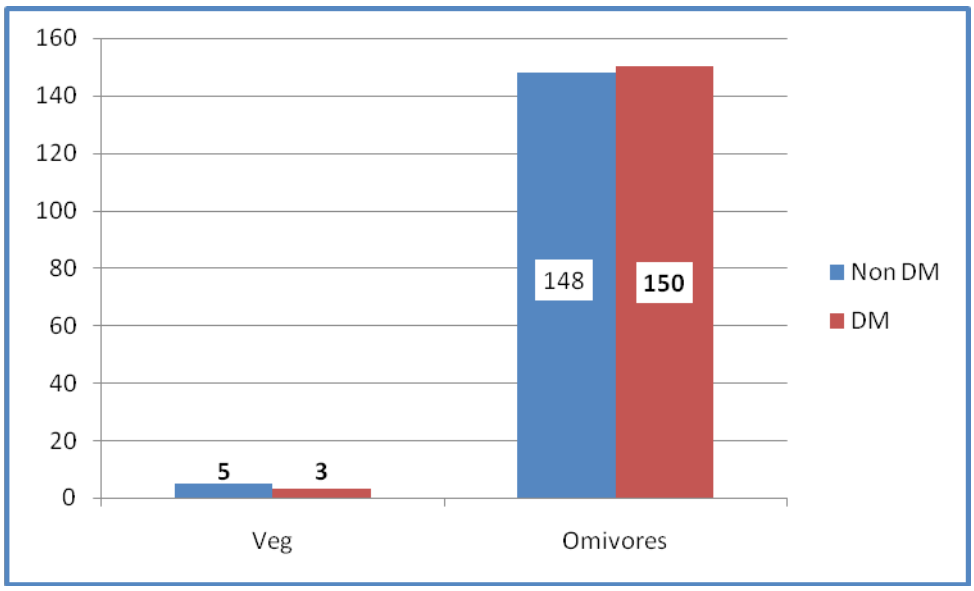


(Figure 12)

Diet history

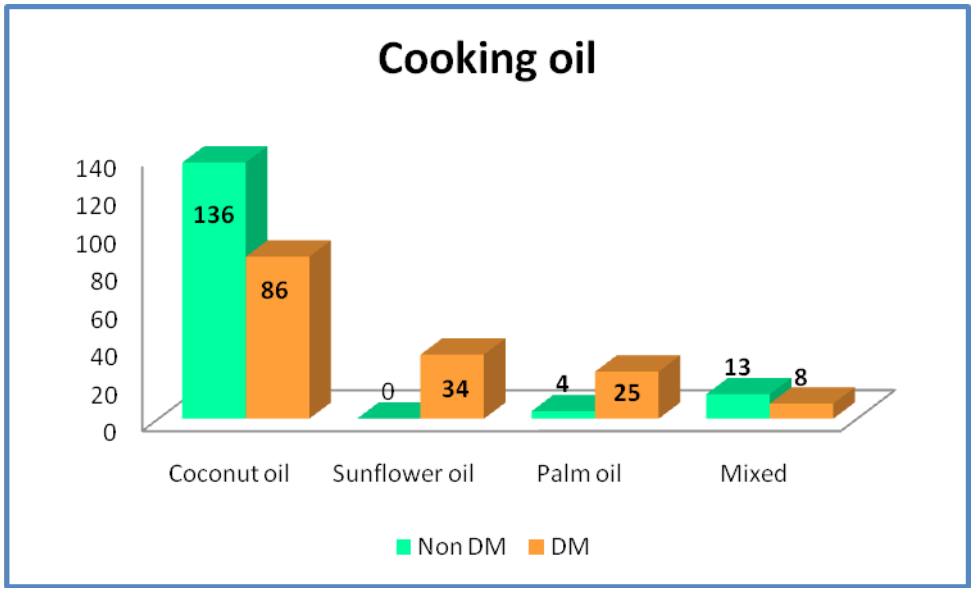
Detailed dietary history was taken in all the 306 studied. A three day diet recall method used and the total consumed calories, carbohydrates, proteins and fats were estimated with the help of a trained dietician and also asked for the cooking oil used. The oil currently in use was enquired about.

Among the diabetic patients 150(98.04%) were non-vegetarians (omnivores) and 3(1.6%) were vegetarians as against 148(96.73%) and 5(3.27%) among controls (p = 0.47) (Figure 13).



(Figure 13)

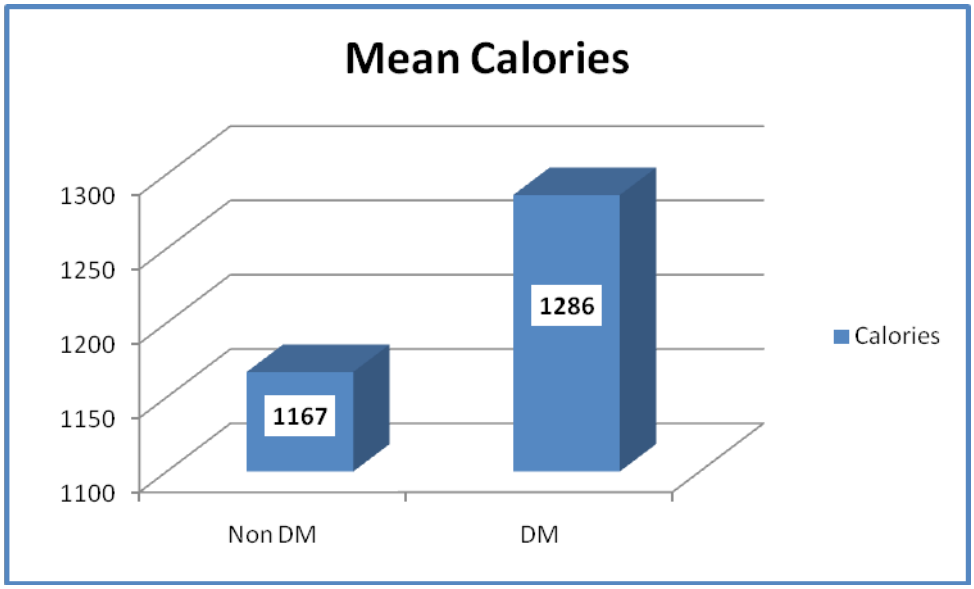
An enquiry was also made into the cooking oil currently in use. Among controls 136 (88.9%) use coconut oil, 4 (2.6%) use palm oil and 13 (18.5%) use mixed, while 86 (56.2%) use coconut oil, 34 (22.2%) use sun flower oil, 25 (16.3%) use palm oil and 8 (5.2%) use mixed among controls (p = 0.00) (Figure 14).



(Figure 14)

Calories consumed:

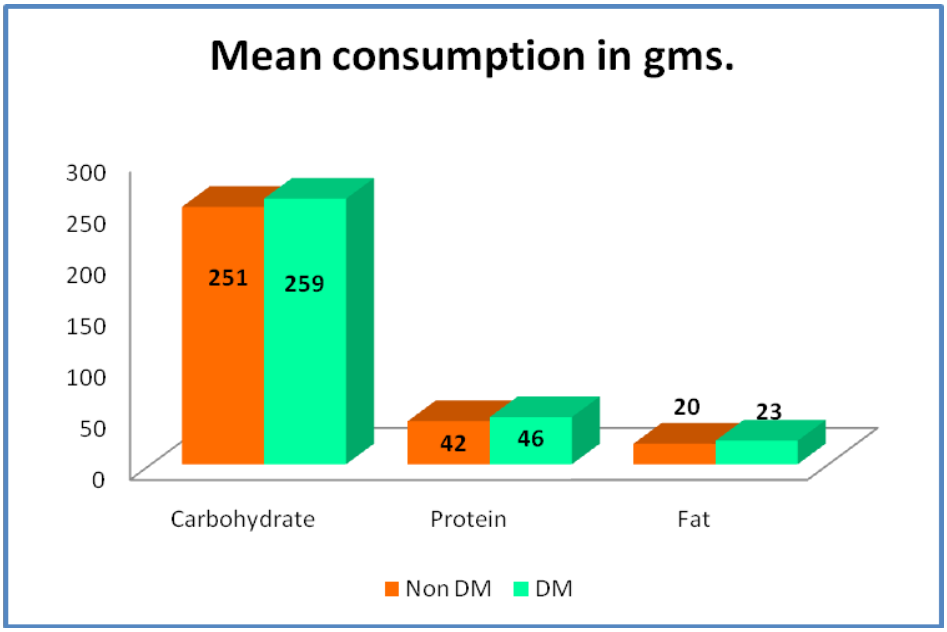
Among the diabetic patients mean caloric intake was 1285.96±222.35. Among the controls it was 1166.66±266.3 (p = 0.00) (Figure 15).



(Figure 15)

Carbohydrate, Protein and fat consumption:

Mean carbohydrate consumed among patients was 259.00±54.84 gm and among control was 250.92±57.32 gm (p = 0.21).Mean Protein consumption among patients was 46.41±17.15 gm and among control was 42.10±11.61 gm. (p = 0.01). Mean fat consumption among patients was 23.36 ± 6.35 and among control was 20.412± 6.94 (p = 0.00) (Figure 16).



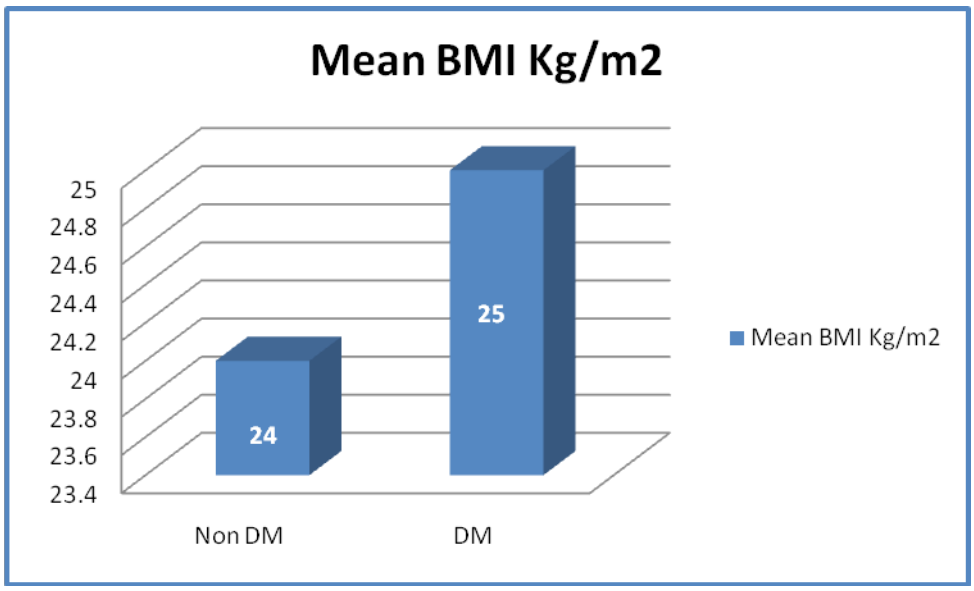
(Figure 16)

Physical characteristics:

The values assessed were Body Mass Index (BMI) and waist circumference.

Body Mass Index (BMI):

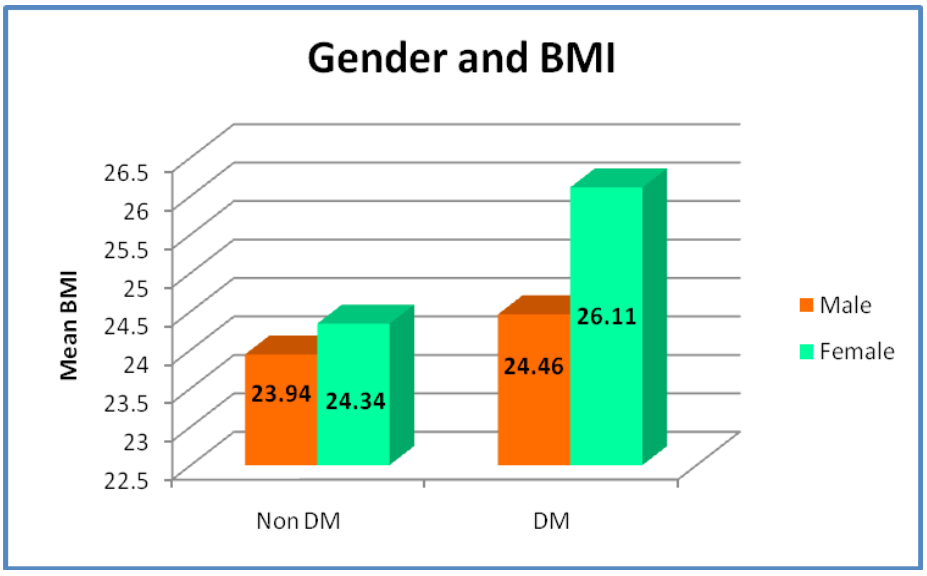
Among diabetic patients mean BMI was 25.18±3.89. Among controls it was 24.12 ±3.20 (p = 0.00) (Figure 17).



(Figure 17)

Association of Gender and BMI:

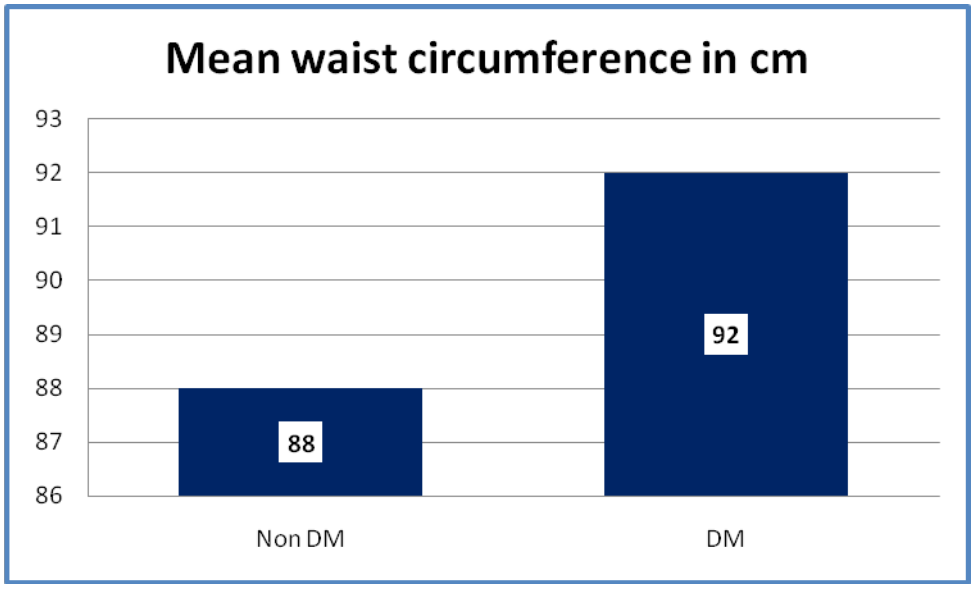
Mean BMI in diabetic and controls in both the genders were compared. Among Diabetics, mean BMI of males was 24.46±3.24 and of females was 26.11±4.45 (p = 0.009).Among controls the mean BMI of males was 23.94±2.8 and of females was 24.34±3.62 (p = 0.443).Among females when diabetic and non diabetic groups were compared mean BMI was 24.34±3.62 for controls and 26.11±4.45 for diabetics (p=0.013). While among males when diabetic and non diabetic groups were compared mean BMI was 23.94±2.8 for controls and 24.46±3.24 for diabetics (p=0.23) (Figure 18).



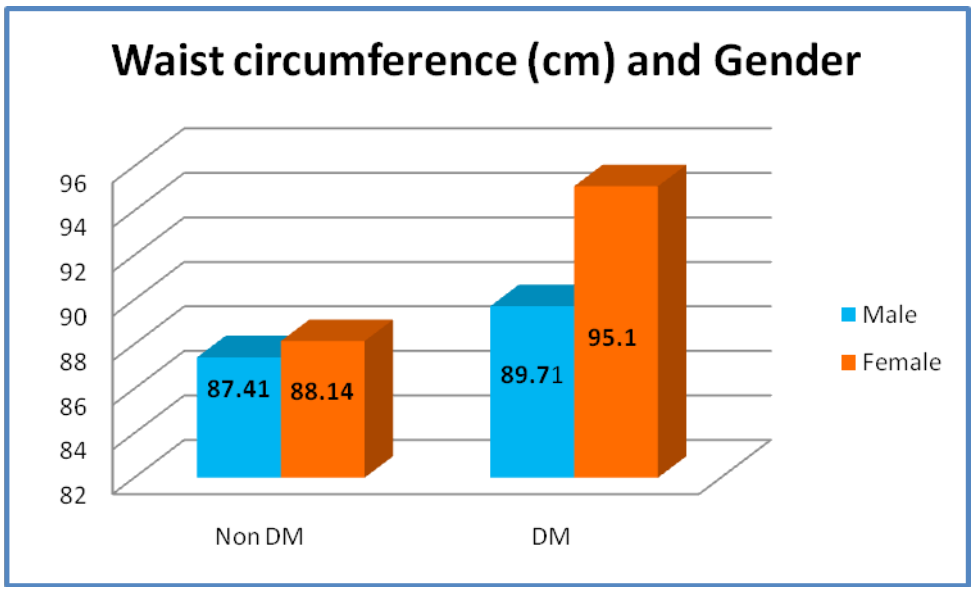
(Figure 18)

Waist circumference

Among diabetic patients mean waist circumference was 92.07±8.997 and among controls it was 87.73 ± 8.76 (p = 0.00) (Figure 19).



(Figure 19)



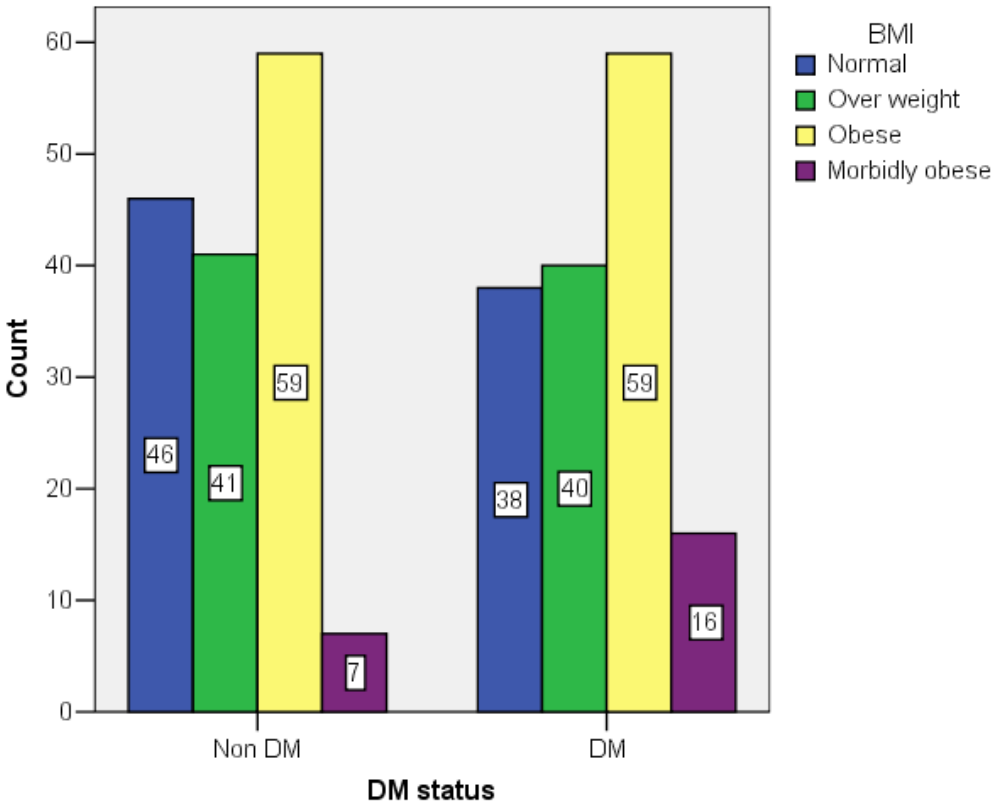
(Figure 20)

Among diabetic subjects mean waist circumference of males was 89.71±7.88 and of females was 95.1±9.48 (p = 0.009) and among controls mean waist circumference of males was 87.41±7.87 and of females was 88.14±9.84 (p = 0.61) [Figure 20]. Among diabetic

patients mean waist circumference of females was significantly higher than males.

Distribution of subjects and control based on BMI and waist circumference:

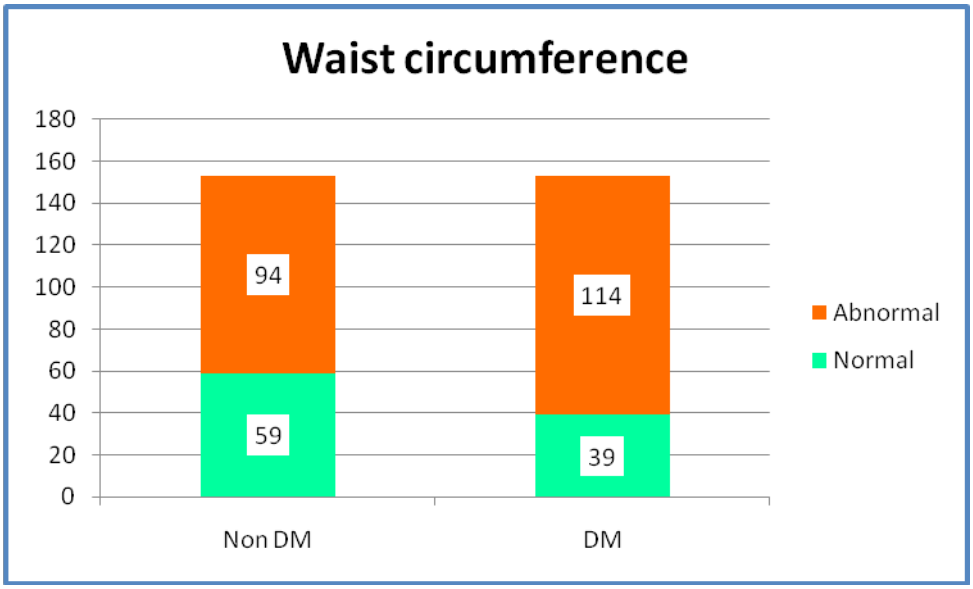
Among controls 46(30.1%) had normal BMI, 41(26.8%) were overweight, 59(38.6%) were obese and 7(4.5%) were morbidly obese. Among diabetics 38(24.8%) had normal BMI, 40(26.1%) were overweight, 59(38.6%) were obese and 16(10.5%) were morbidly obese (Figure 21).



(Figure 21)

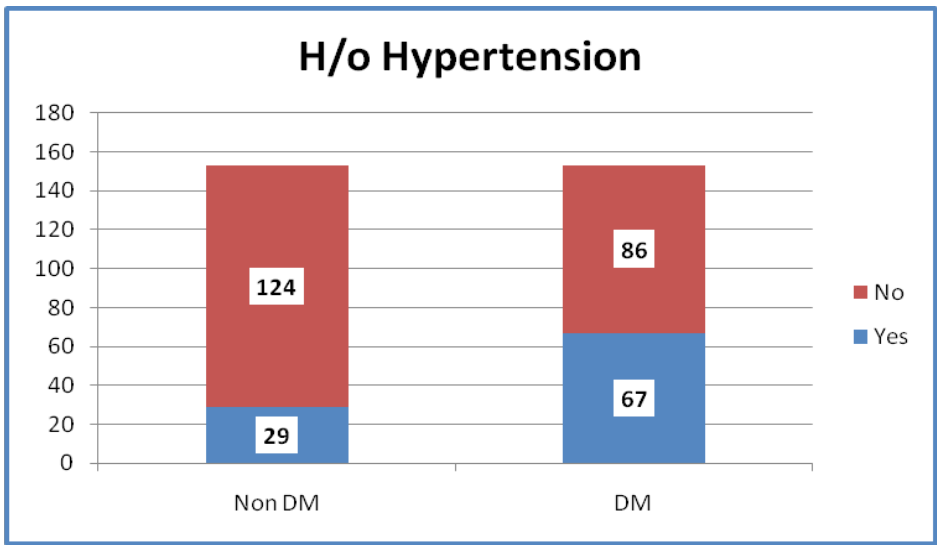
Waist circumference:

Among controls 59(38.6%) had normal and 94(61.4%) had abnormal values and among patients 39(25.5%) had normal and 114(74.5%) had abnormal waist circumference (Figure 22).



(Figure 22)

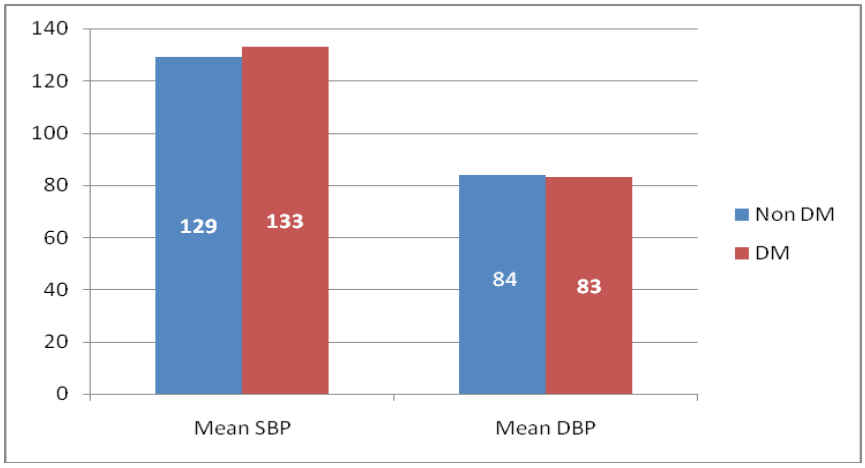
Hypertension was present in 29 (18.95%) among controls and in 67 (43.79%) among patients. 124 (81.05%) among controls and 86(56.21%) among patients were non-hypertensive (Figure 23).



(Figure 23)

Blood Pressure:

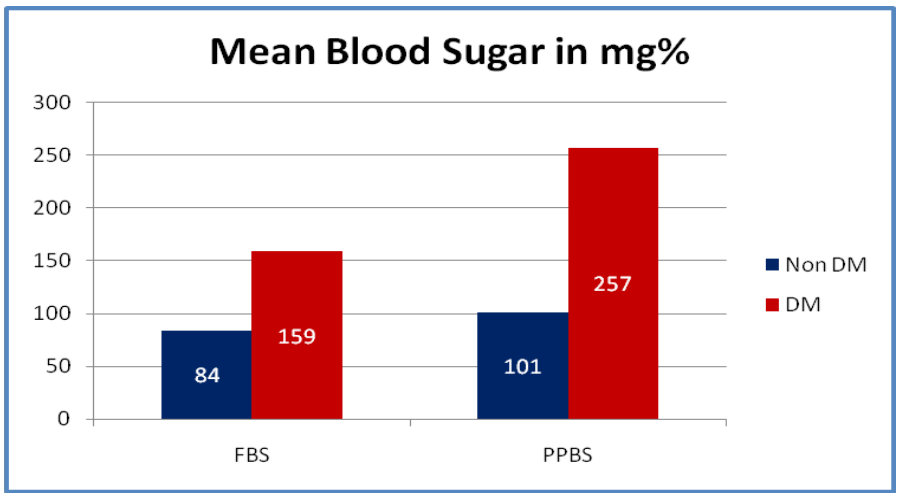
Mean blood pressure was 133±17.09 mm of Hg and 82.67± 9.44 mm of Hg among the patients. Among the controls it was 128±15.32 (p = 0.01) and 84.17±8.64 mm of Hg respectively (p = 0.15) [Figure 24]



(Figure 24)

Control of diabetes:

Mean Fasting Blood Sugar (FBS) among the control group was 83.65±8.69 as against 158.59±66.54mg% among the diabetic group [p = 0.00]. Mean Post-Prandial Blood Sugars (PPBS) among the controls were 101.20±14.20mg% and among the patients were 257.12± 99.50 mg% (p = 0.00) (Figure 25).

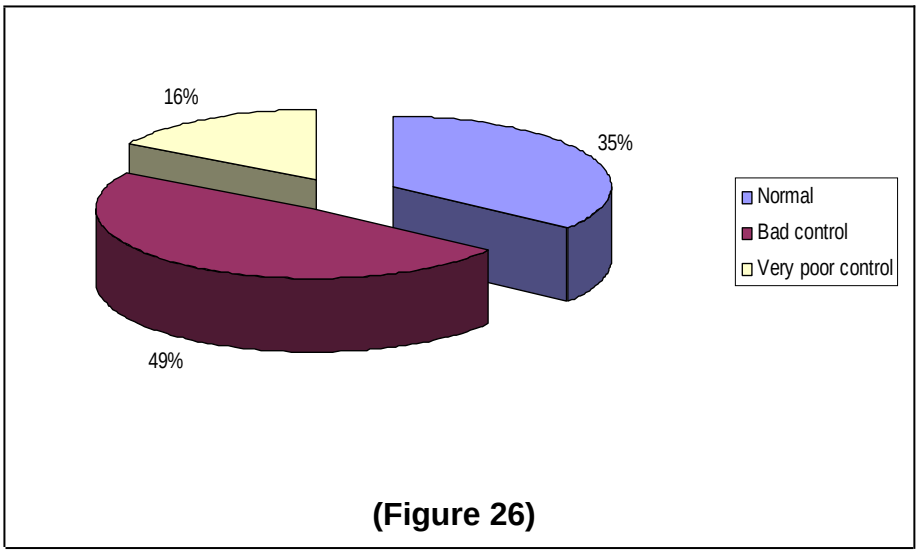


(Figure 25)

HbA_{1c} among patients and control:

HbA_{1c} was less than 7 in all among controls 153(100%). Among diabetic subjects 54(35.29%) were under good control (HbA1c <7); 74 (48.37%) were under bad control (HbA1c 7 to 10) and 25 (16.34%) were having very poor control with an HbA1c more than 10. (Figure 26). Mean HbA1c among control group was 5.02±0.49 % .Among diabetic subjects 54 had HbA1c of 5.96±0.55%; 74 had 8.26±0.87% and 25 had 11.64±1.48.

Distribution of Diabetic Patients based on Control of Diabetes



(Figure 26)

Detailed evaluation of the diabetic patients:

Family history of diabetes

Among diabetic patients 107 (69.93 %) gave a positive family history and 46(30.07%) did not give any family history.

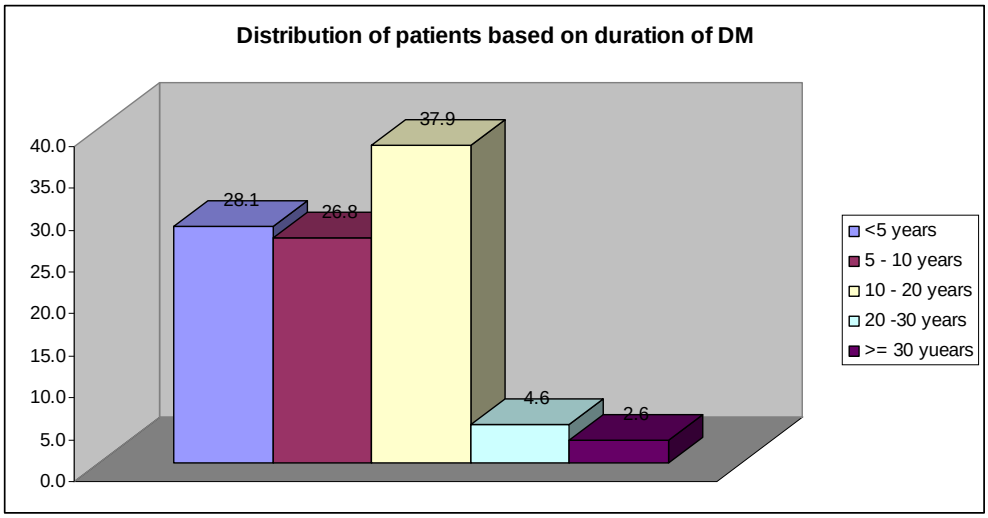
Among the diabetic group there were 153 patients. Duration of diabetes was divided between various groups into less than 5 years, 5-10 years, 10-20 years, 20-30 years and more than 30 years. Blood

sugar control was evaluated based on HbA1c and average blood glucose values.

Duration of diabetes: (Table 1 & Figure 27)

Duration of DM	No	%
< 5 years	43	28.1
5 – 10 years	41	26.8
10 – 20 years	58	37.9
20 – 30 years	7	4.6
> = 30 years	4	2.6

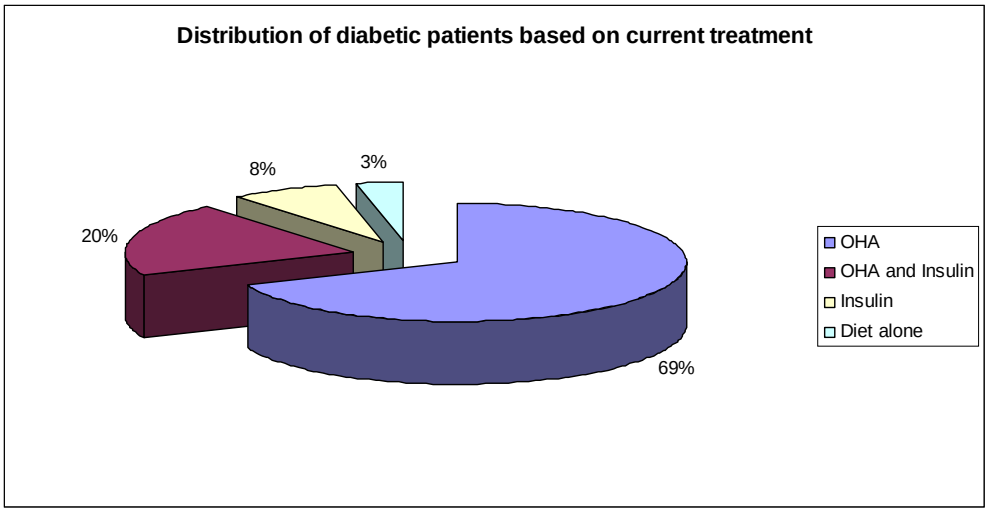
(Table 1)



(Figure 27)

Current treatment:

Of the 153 patients 7(4.58%) were on diet alone, 105(68.63%) were on diet and oral ant diabetic drug therapy, 30(19.60%) were on diet, oral ant diabetic drug therapy and Insulin and 11(7.12%) were on diet and Insulin therapy (Figure 28).



(Figure 28)

Lipid abnormalities in Type 2 Diabetes:

Lipid abnormalities were assessed in detail among diabetic subjects and non diabetic controls (Table 2).

	Cases Mean	Cases SD	Control Mean	Control SD	P value
TC	203.60	39.92	216.80	37.52	0.003
TG	136	67.12	127.35	60.69	0.24
HDL	46.24	10.16	51.58	14.24	0.00
LDL	120.92	30.69	140.08	31.81	0.00
VLDL	31.79	18.80	27.76	12.46	0.03
Non HDL	157.08	37.97	166.42	38.88	0.04
TC/HDL	4.56	1.13	4.49	1.40	0.65
LDL/HDL	2.73	0.89	2.95	1.07	0.04

(Table 2)

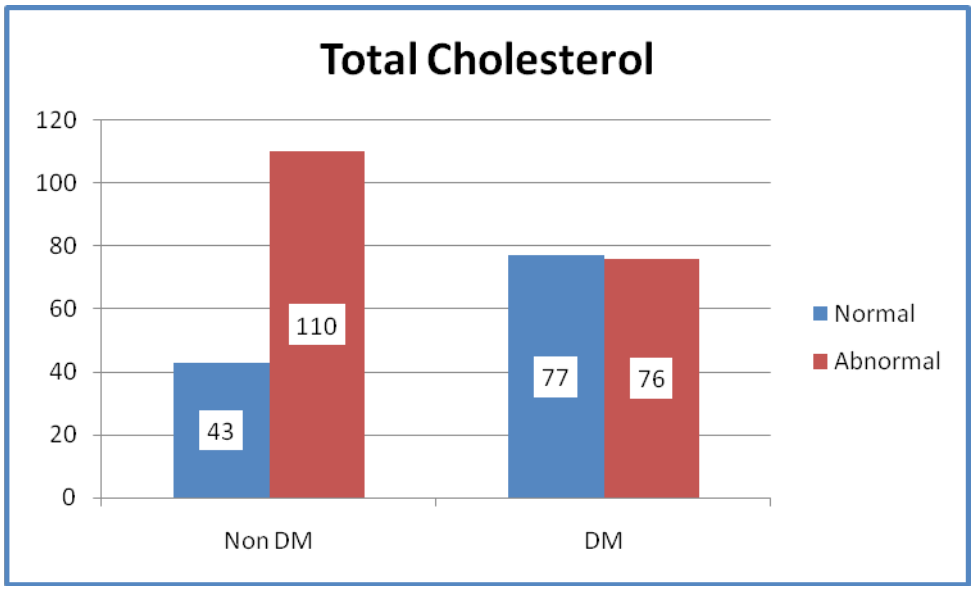
Mean values of Total cholesterol, Low Density Lipoprotein cholesterol (LDL), Non High Density lipoprotein (Non HDL) and LDL/HDL were higher for control group. Serum Triglycerides were higher among subjects with diabetes along with low High Density lipoprotein (HDL).

Total Cholesterol (mg %) (Table 3)

	Normal (<200)	Abnormal(≥200)
Control group	43 (28%)	110(72%)
Diabetic subjects	77(50%)	76(50%)

(Table 3)

Abnormal Total Cholesterol was more among controls (p = 0.00) (Figure 29)



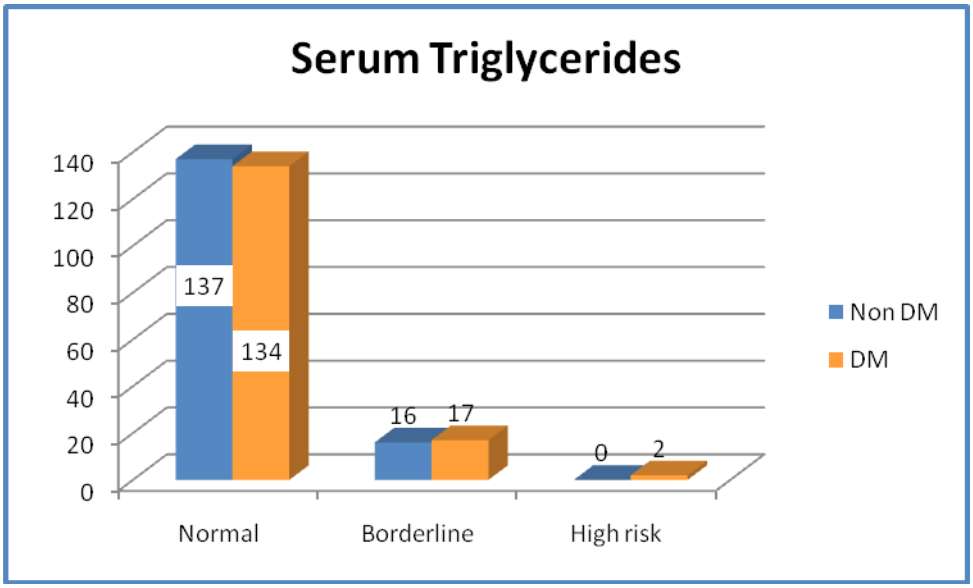
(Figure 29)

Serum Triglycerides (Table 4)

S.Triglycerides (mg%)	Normal (<200mg %)	Border line (200–399mg %)	High risk (≥ 400mg %)
Control group	137(90 %)	16 (10%)	0(0%)
Diabetic subjects	134(88%)	17(11%)	2(1%)

(Table 4)

Triglycerides were comparable among diabetics and controls. (Figure 30).



(Figure 30)

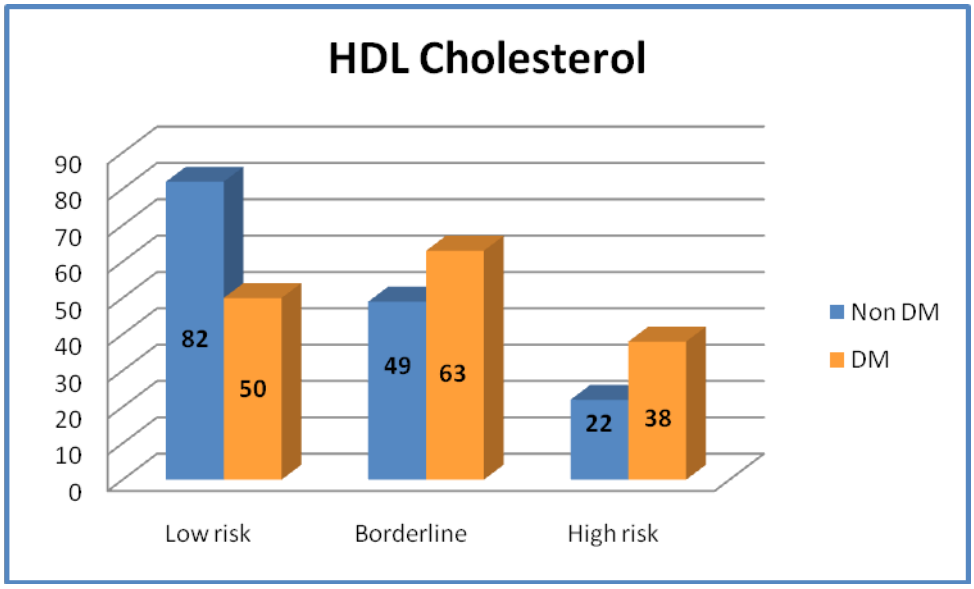
HDL Cholesterol:

This was considered of low risk if >45 mg% in men and > 55 mg % in women. Of borderline risk if 35-45 mg % in men and 45-55 mg % in women and of high risk if < 35 mg% in men and < 45 mg% in women (Table 5)

HDL Cholesterol (mg %)	Low risk	Border line	High risk
Control group	82 (54%)	49(32%)	22(14%)
Diabetic subjects	50(33%)	63(42%)	38(25%)

(Table 5)

High risk HDL was more among diabetics (p= 0.001) (Figure 31).

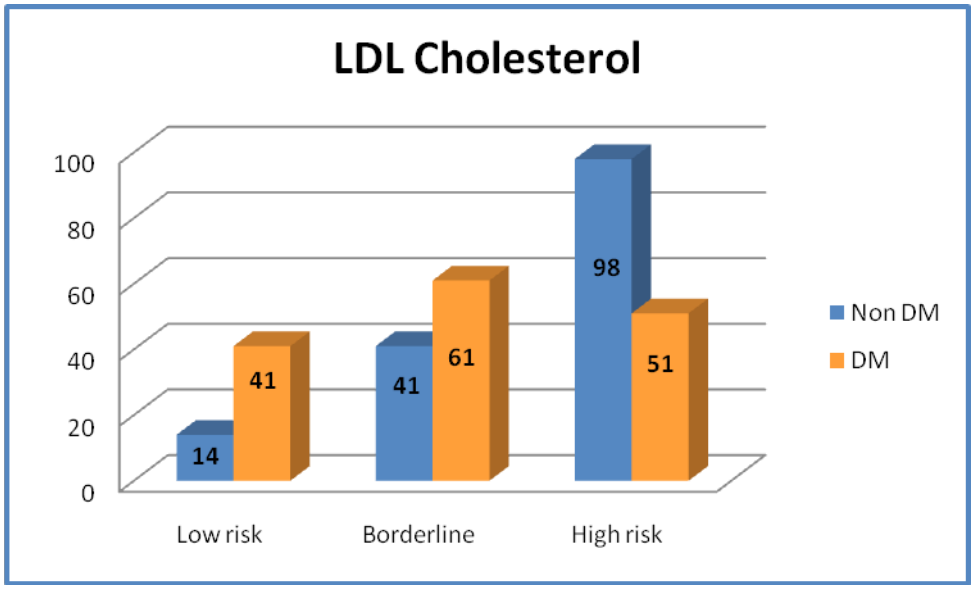


(Figure 31)

LDL Cholesterol (Table 6):

LDL Cholesterol (mg%)	Low risk (< 100 mg %)	Border line (100 –129 mg %)	High risk (≥ 130 mg %)
Control group	14(9 %)	41 (27%)	98(64%)
Diabetic subjects	41(27%)	61(40%)	51(33%)

High risk LDL was more among controls (p= 0.001) (Figure 32).



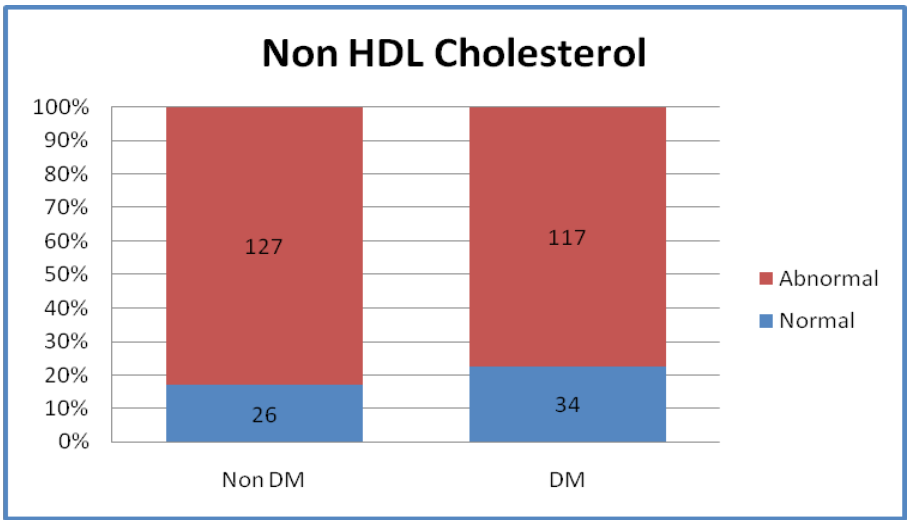
(Figure 32)

Non HDL cholesterol (Table 7)

Non HDL Cholesterol	Normal (<130mg %)	Abnormal (≥130 mg %)
Control	26(17%)	127(83%)
Diabetic subjects	34(23%)	117(77%)

(Table 7)

Non HDL was comparable among diabetics and controls (Figure 33).



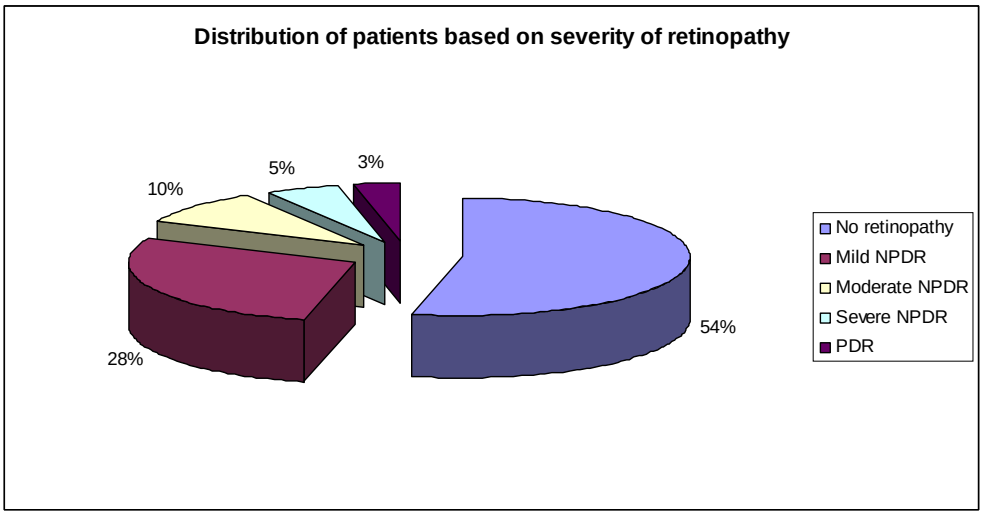
(Figure 33)

Complications

Micro vascular complications

Diabetic Retinopathy:

Of the 153 diabetic patients 82(53.6%) had no retinopathy. 43 (28.1%) had mild Non proliferative Diabetic Retinopathy (NPDR) and 15(9.8%) had moderate NPDR 8 (5.2%) had severe NPDR and 5(3.3%) had severe Proliferative Diabetic Retinopathy (PDR). (Figure 34).

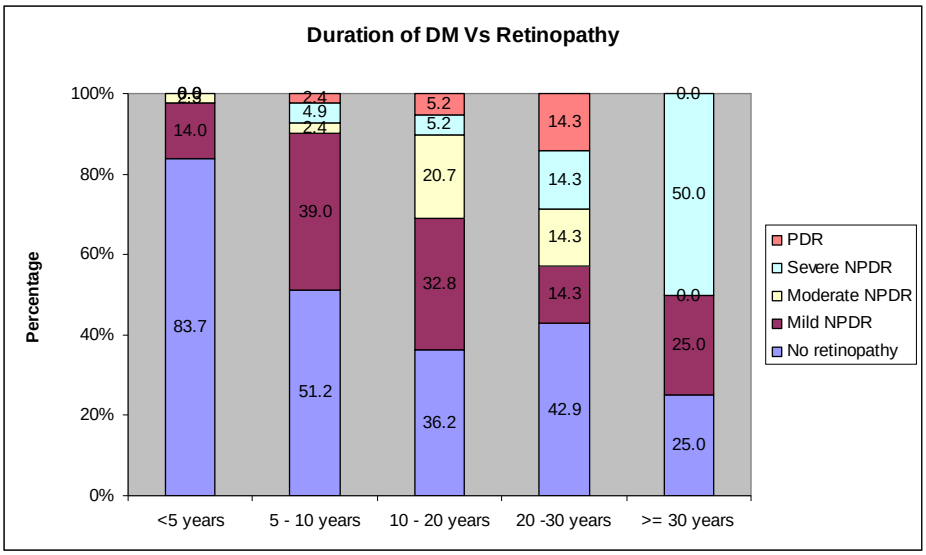


(Figure 34)

As duration of DM increases, severity of retinopathy also increases (correlation coefficient = 0.42, p = 0.00) (Figure 35 and Table 8).

Duration of Diabetes	No retino-pathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
<5 years	36(84%)	6 (14%)	1(2%)	0(0%)	0(0%)	43(100%)
5-10 years	21(51%)	16(39%)	1(2%)	2(5%)	1(2%)	41(100%)
10-20years	21(36%)	19(33%)	12(21%)	3(5%)	3(5%)	58(100%)
20-30years	3(43%)	1(14%)	1(14%)	1(14%)	1(14%)	7(100%)
≥30 years	1(25%)	1(25%)	0(0%)	2(50%)	0(0%)	4(100%)
Total	82(54%)	43(28%)	15(10%)	8(5%)	5(3%)	153(100%)

(Table 8)

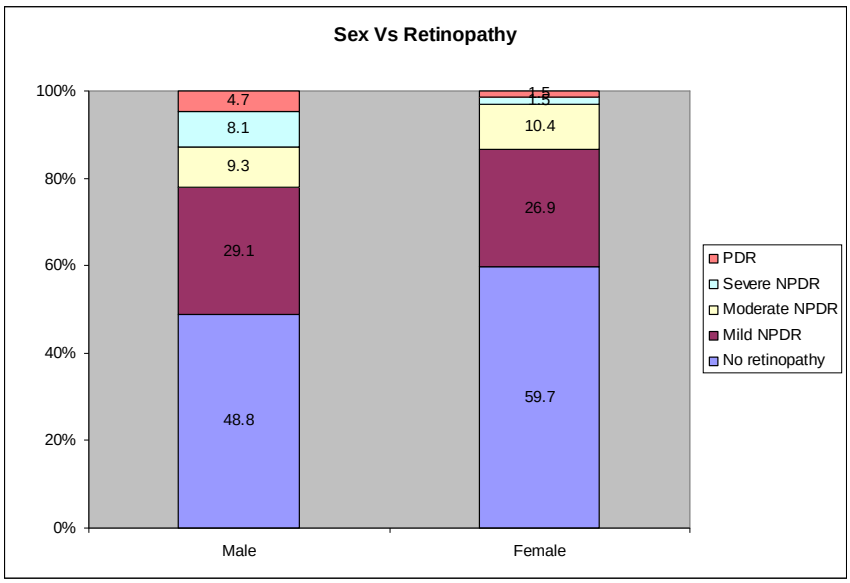


(Figure 35)

Gender with retinopathy (Table 9)

Retinopathy	Male	Female	Total
No retinopathy	42(49%)	40(60%)	82(54%)
Mild NPDR	25(29%)	18(27%)	43(28%)
Moderate NPDR	8(9%)	7(10%)	15(10%)
Severe NPDR	7(8%)	1(2%)	8(5%)
PDR	4(5%)	1(2%)	5(3%)
Total	86(100%)	67(100%)	153(100%)

(Table 9)



(Figure 36)

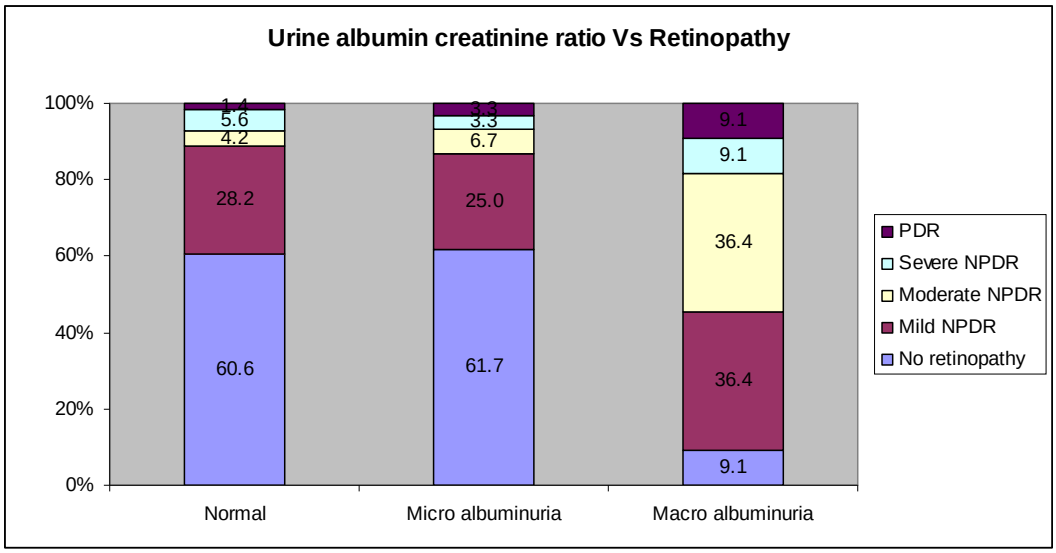
There is no significant association between sex and severity of retinopathy (Figure 36).

Correlation with Urine Albumin-Creatinine ratio and retinopathy: (Table 10).

Retinopathy	Normal	Micro albuminuria	Macro albuminuria	Total
No retinopathy	43(61%)	37(62%)	2(9.1%)	82(54%)
Mild NPDR	20(28%)	15(25%)	8(36.4%)	43(28%)
Moderate NPDR	3(4%)	4(7%)	8(36.4%)	15(10%)
Severe NPDR	4(7%)	2(3%)	2(9.1%)	8(5%)
PDR	1(1%)	2(3%)	2(9.1%)	5(3%)
Total	71(100%)	60(100%)	22(100%)	153(100%

(Table 10)

Severity of retinopathy increases with urine albumin creatinine ratio (correlation coefficient = 0.271, p = 0.001) (Figure 37).



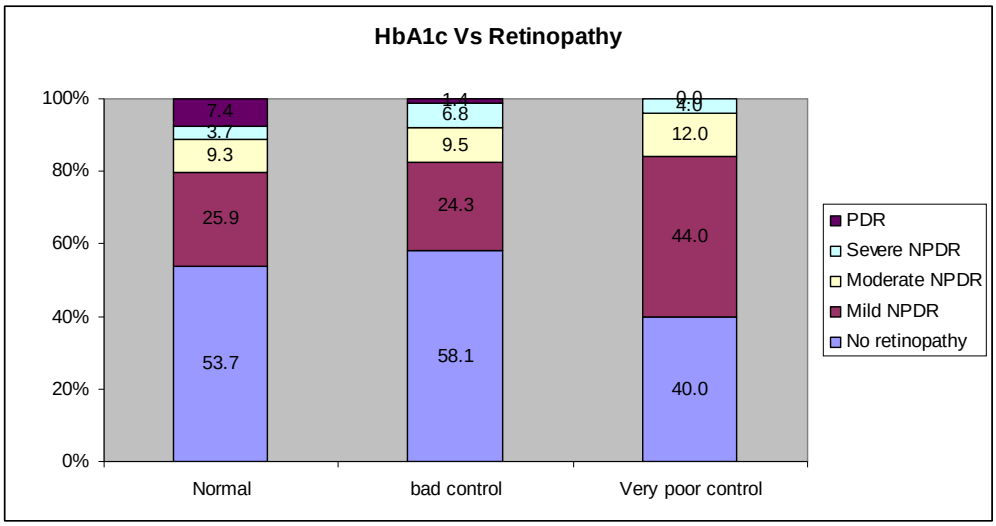
(Figure 37)

HbA1c and Retinopathy:

Diabetes was considered under good control if HbA1c is <7% and bad control if between 7-10% and very poor control if ≥10%...In the present study the severity of retinopathy was not associated with control of diabetes. (Table 11 & Figure 38)

Retinopathy	HbA1c			Total
	<7%	7-10%	≥10%	
No Retinopathy	29(54%)	43(58%)	10(40%)	82(54%)
Mild NPDR	14(26%)	18(24%)	11(44%)	43(28%)
Moderate NPDR	5(9%)	7(10%)	3(12%)	15(10) %)
Severe NPDR	2(4%)	5(7%)	1(4%)	8(5%)
PDR	4(8%)	1(1%)	0(0%)	5(3%)
Total	54(100%)	74(100%)	25(100%)	153(100%)

(Table 11)



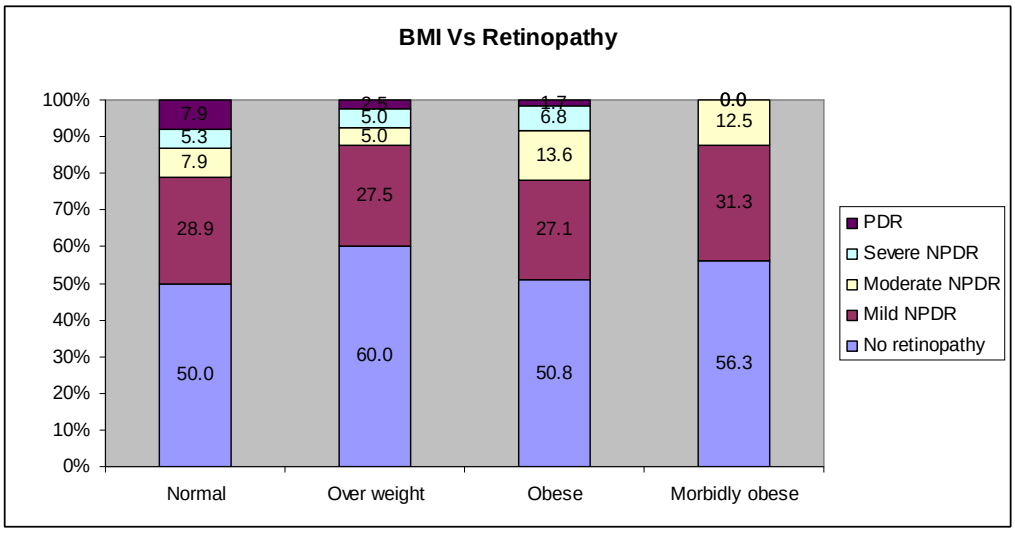
(Figure 38)

BMI and Retinopathy:

Severity of retinopathy was not associated with BMI. (Figure 43).BMI was categorized into <23=Normal; ≥23 -25-Overweight; ≥25-30= Obese and ≥30 as morbidly obese. (Figure 39 and Table 12).

Retinopathy	Normal	Over weight	Obese	Morbidly obese	Total
No Retinopathy	19(50%)	24(60%)	30(51%)	9(56%)	82(54%)
Mild NPDR	11(30%)	11(28%)	16(27%)	5(31%)	43(28%)
Moderate NPDR	3(8%)	2(5%)	8(14%)	2(13%)	15(10%)
Severe NPDR	2(5%)	2(5%)	4(7%)	0(0%)	8(5%)
PDR	3(8%)	1(3%)	1(2%)	0(0%)	5(3%)
Total	38(100%)	40(100%)	59(100%)	16(100%)	153(100%)

(Table 12)



(Figure 39)

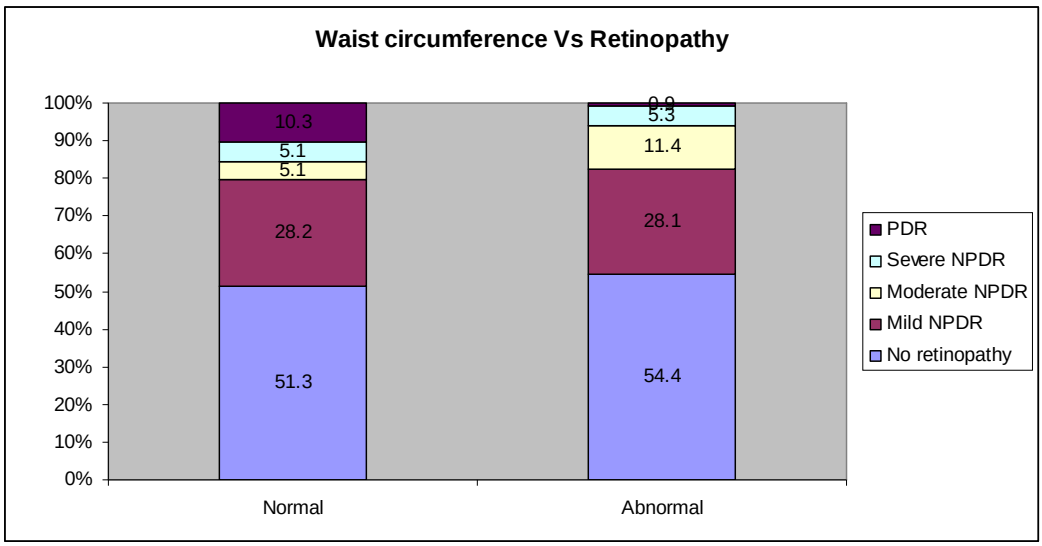
Waist circumference and retinopathy:

Waist circumference was considered abnormal if ≥90 cm. in males and ≥80 cm in females. Severity of retinopathy was not associated with waist circumference. (Figure 40 and Table 13).

Retinopathy	Normal waist circumference	Abnormal waist circumference	Total
No Retinopathy	20(51%)	62(54%)	82(54%)
Mild NPDR	11(28%)	32(28%)	43(28%)
Moderate NPDR	2(5%)	13(11%)	15(10%)

Severe NPDR	2(5%)	6(5%)	8(5%)
PDR	4(10%)	1(1%)	5(3%)
Total	39(100%)	114(100%)	153(100%)

(Table 13)



(Figure 40)

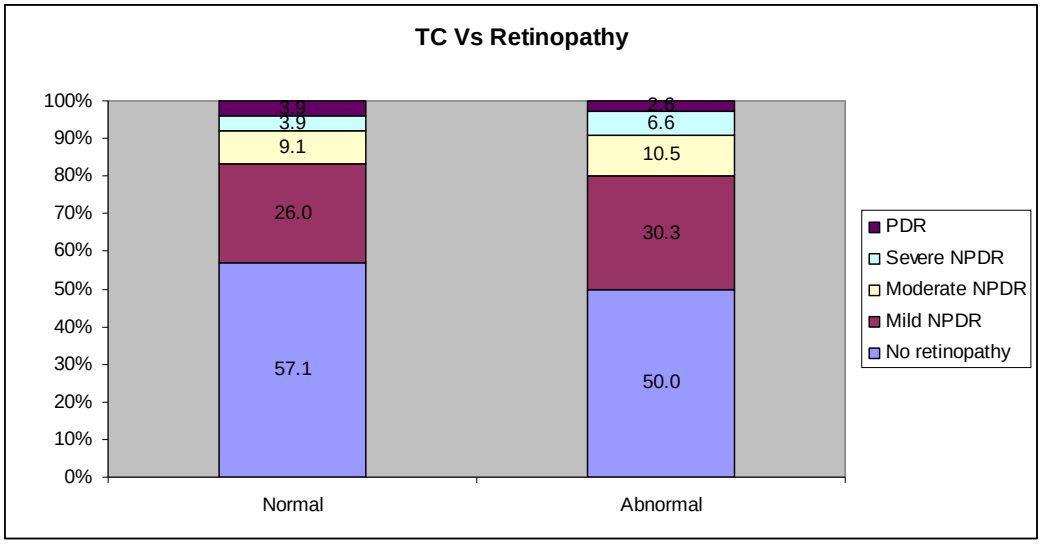
Serum Lipids and retinopathy:

Correlation of Serum Total Cholesterol and Retinopathy (Table 14)

Total Cholesterol	No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
Normal <200mg%	44(57%)	20(26%)	7(9%)	3(4%)	3(4%)	77(100%
Abnormal ≥200 mg%	38(50%)	23(30%)	8(11%)	5(7%)	2(3%)	76(100%)
Total	82(54%)	43(28%)	15(10%)	8(5%)	5(3%)	153(100%)

(Table 14)

Severity of retinopathy is not associated with total cholesterol (Figure 45).



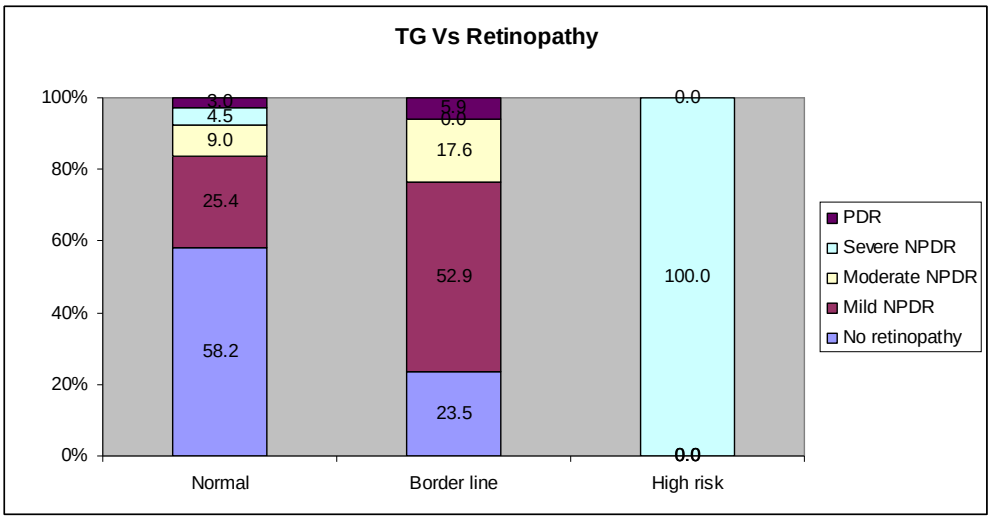
(Figure 45)

Correlation of Serum Triglycerides with Retinopathy (Table 15):

Serum TG	No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
Normal	78(58%)	34(25%)	12((9%)	6(5%)	4(3%)	134(100%)
Borderline	4(24%)	9(53%)	3(18%)	0(0%)	1(6%)	17(100%)
High Risk	0(0%)	0(0%)	0(0%)	2(100%)	0(0%)	2(100%)
Total	82(54%)	43(28%)	15(10%)	8(5%)	5(3%)	153(100%)

(Table 15)

Serum Triglycerides was considered normal if < 200 mg%, 200-399 mg% and > 400 mg% as high risk. The severity of retinopathy increased with Serum Triglycerides (correlation coefficient = 0.241, p = 0.00) (Figure 46).



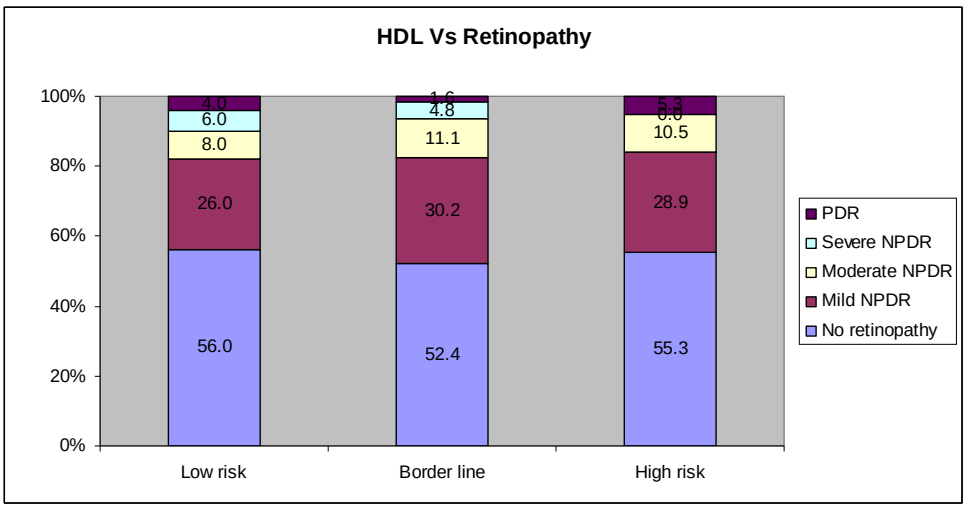
(Figure 46)

Serum HDL and Retinopathy:

Severity of retinopathy was not associated with HDL ((Figure 47 and Table 16).

Ser.HDL	No retinopathy	Mild NPDR	Mod. NPDR	Severe NPDR	PDR	Total
Low risk	28(56%)	13(26%)	4(8%)	3(6%)	2(4%)	50(100%)
Borderline	33(52%)	19(30%)	7(11%)	3(5%)	1(2%)	63(100%)
High Risk	21(53%)	11(30%)	4(11%)	0(0%)	2(5%)	38(100%)
Total	82(54%)	43(29%)	15(10%)	6(4%)	5(3%)	151(100%)

(Table 16)



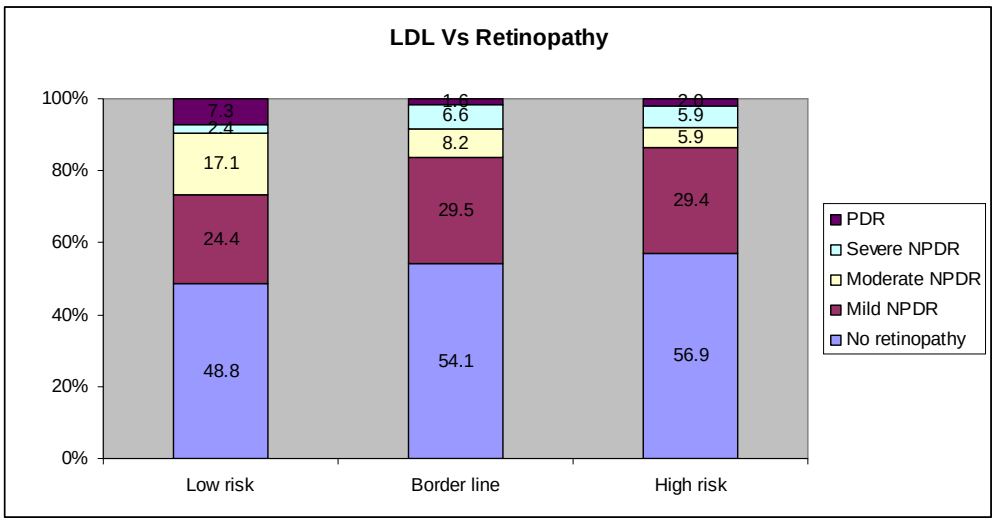
(Figure 47)

LDL and Retinopathy (Table 17)

Ser. LDL	No retinopathy	Mild NPDR	Mod. NPDR	Severe NPDR	PDR	Total
Low risk	20(49%)	10(24%)	7(17%)	1(2%)	3(7%)	41(100%)
Borderline	33(54%)	18(30%)	5(8%)	4(7%)	1(2%)	61(100%)
High Risk	29(57%)	15(29%)	3(6%)	3(6%)	1(2%)	51(100%)
Total	82(54%)	43(28%)	15(10%)	8(5%)	5(3%)	153(100%)

(Table 17)

Severity of retinopathy was not associated with LDL (Figure 48).



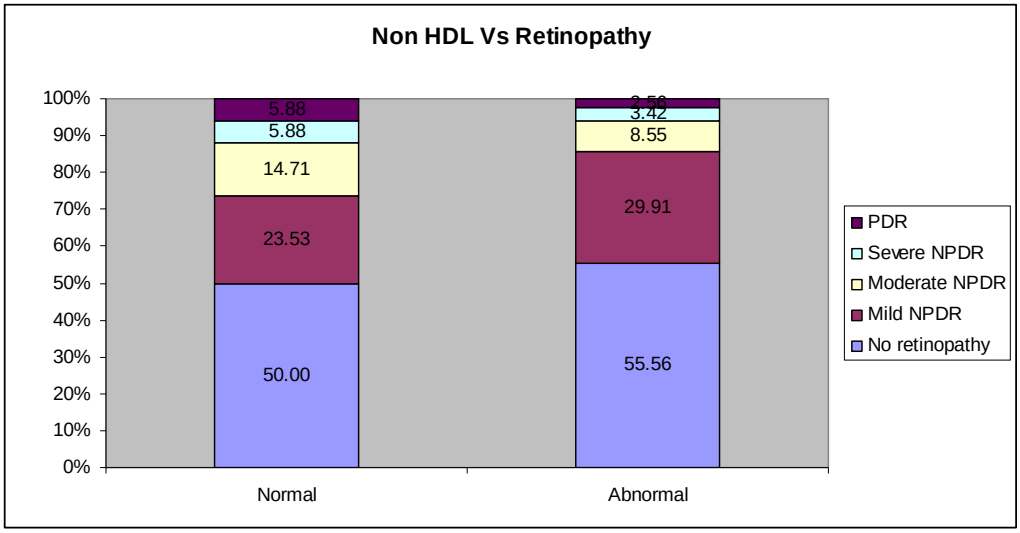
(Figure 48)

Non HDL Cholesterol and Retinopathy (Table 18)

Non HDL	No retinopathy	Mild NPDR	Mod. NPDR	Severe NPDR	PDR	Total
Normal	17(50%)	8(24%)	5(15%)	2(6%)	2(6%)	34(100%)
Abnormal	65(56%0	35(30%)	10(9%)	4(3%)	3(3%)	117(100%)
Total	82(54%)	43(29%)	15(10%)	6(4%)	5(3%)	151(100%)

(Table 18)

Severity of retinopathy is not associated with non HDL. (Figure 49).



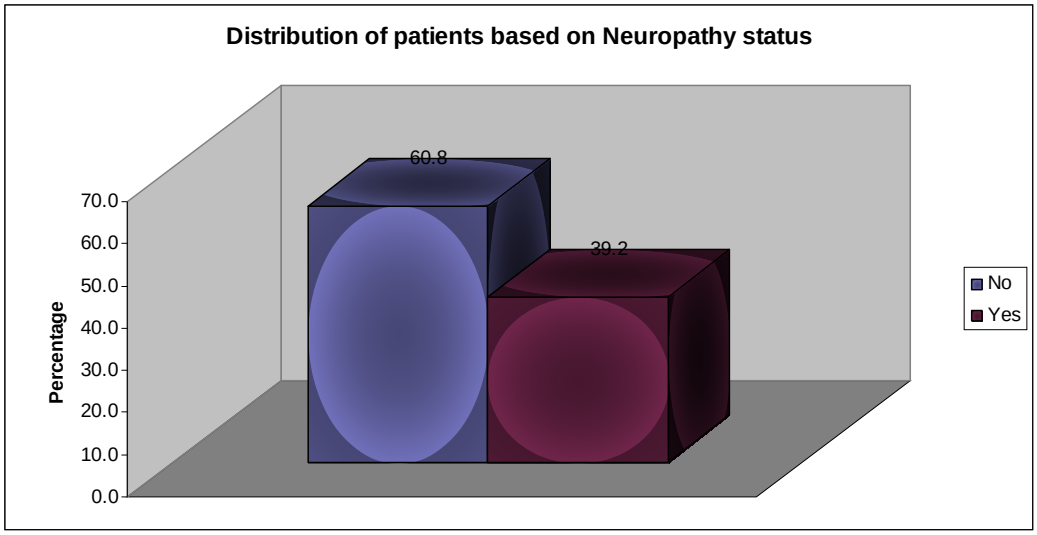
(Figure 49)

Retinopathy is not associated with gender, BMI and waist -circumference.

In binary logistic regression, after adjusting the effect of duration of Diabetes mellitus and urine albumin creatinine ratio only serum Triglyceride was found to be associated with retinopathy (exp (β) = 210, p = 0.012) or Serum Triglyceride is found to be the only risk factor for retinopathy among the serum lipid parameters. HbA_{1c} is not associated with Retinopathy

Diabetic neuropathy:

Of the 153 patients neuropathy was present in 60(39.2%) patients and there were no features of neuropathy in 93(60.8%). Neuropathy was correlated with only PPBS. (Coefficient = 0.334, p = 0.00) (Figure 50).

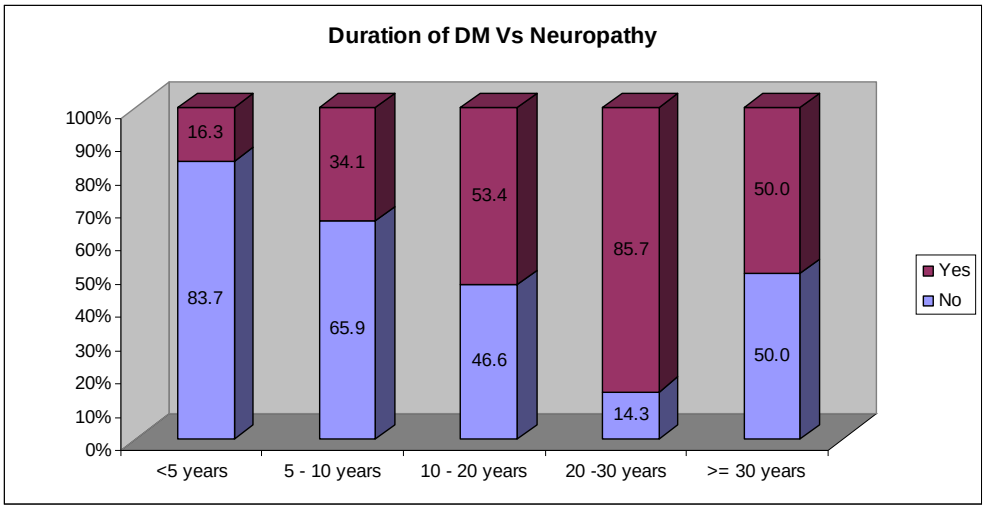


(Figure 50)

Duration of Diabetes and Neuropathy (Table 19):

Duration of diabetes	Neuropathy		Total
	Absent	Present	
<5 years	36(84%)	7(16%)	43(100%)
5-10 years	27(66%)	14(34%)	41(100%)
10-20 years	27(47%)	31(53%)	58(100%)
20-30 years	1(14%)	6(86%)	7(100%)
≥ 30 years	2(50%)	2(50%)	4(100%)
Total	93(61%)	60(39%)	153(100%)

The chance for neuropathy increases with increase in duration of Diabetes mellitus. (Correlation coefficient = 0.359, p = 0.00) (Figure 51).

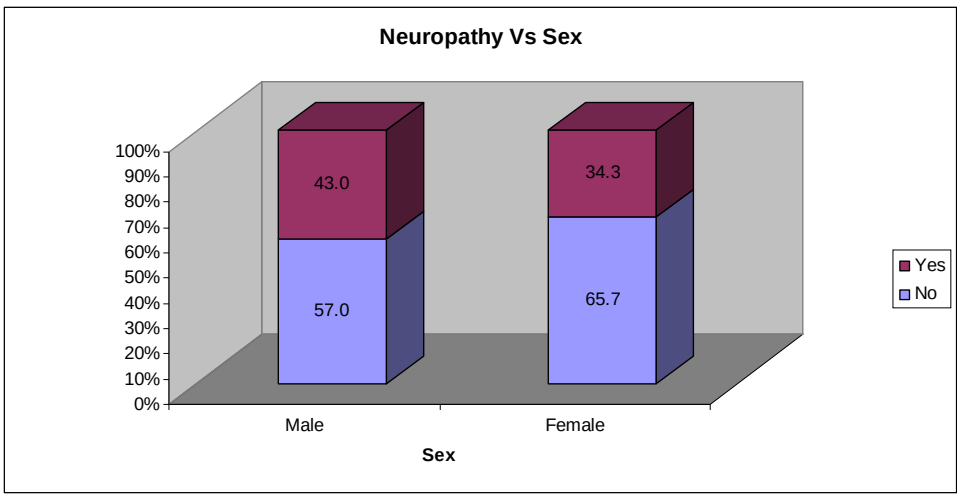


(Figure 51)

Gender and Neuropathy (Table 20):

Gender	Neuropathy		Total
	Absent	Present	
Male	49(57%)	37(43%)	86(100)
Female	44(66%)	23(34%)	67(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 20)



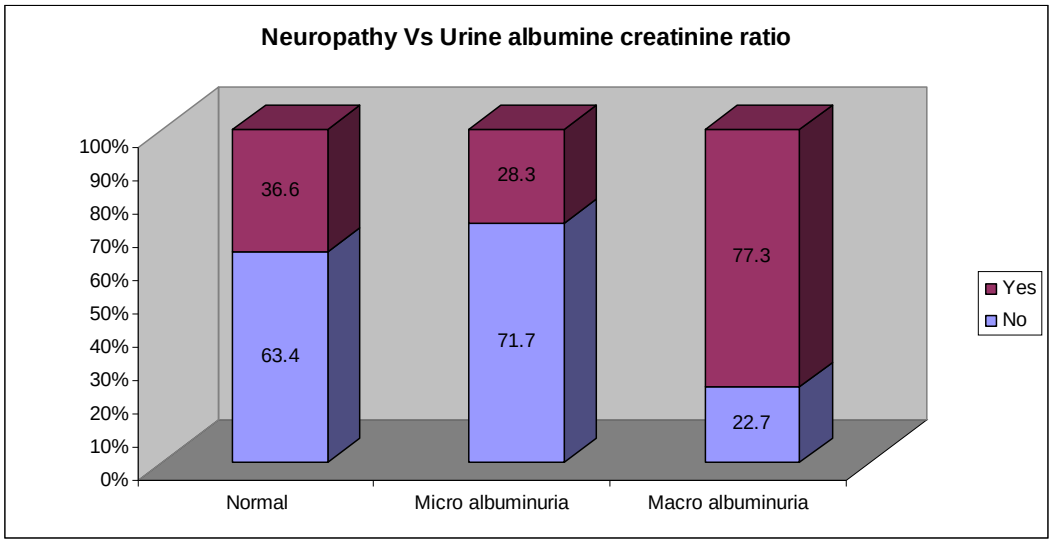
(Figure 52)

Neuropathy is not associated with gender (Figure 52).

Neuropathy and Urine Albumin-Creatinine Ratio (Table 21):

Urine Alb/Creat.	Neuropathy		Total
	Absent	Present	
Normal	45(63%)	26(37%)	71(100%)
Microalbuminuria	43(72%)	17(28%)	60(100%)
Macroalbuminuria	5(23%)	17(77%)	22(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 21)



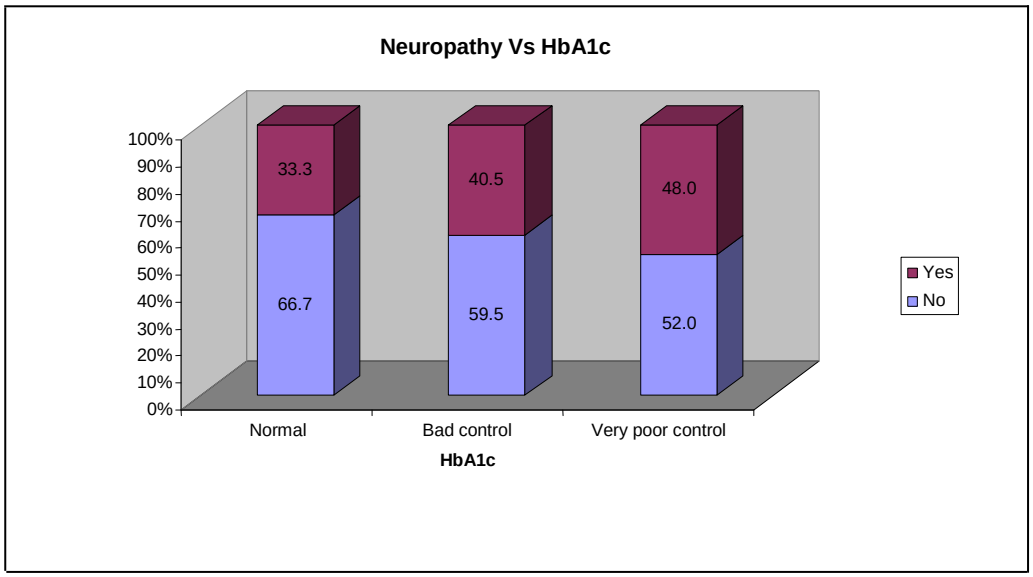
(Figure 53)

The chance for neuropathy increases with urine albumin creatinine ratio (Correlation coefficient = 0.24, p = 0.04) (Figure 53).

Neuropathy and HbA1c (Table 22):

HbA1c	Neuropathy		Total
	Absent	Present	
Good control	36(67%)	18(33%)	54(100%)
Bad control	44(60%)	30(41%)	74(100%)
Very poor control	13(52%)	12(48%)	25(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 22)



(Figure 54)

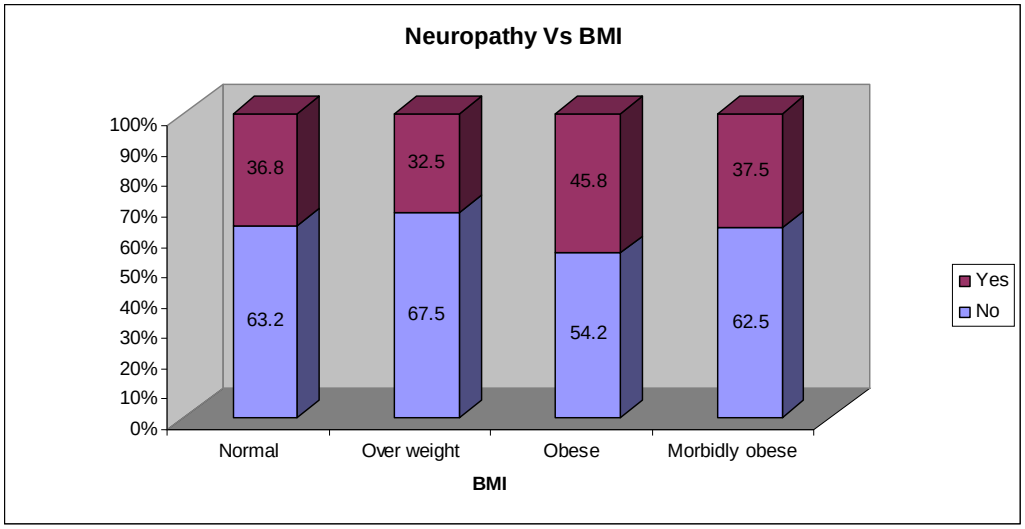
Neuropathy is not associated with control of diabetes. (Figure 54).

BMI and Neuropathy (Table 23):

BMI in Diabetics	Neuropathy		Total
	Absent	Present	
Normal	24(63%)	14(37%)	38(100%)
Overweight	27(68%)	13(33%)	40(100%)
Obese	32(54%)	27(46%)	59(100%)
Morbidly obese	10(63%)	6(38%)	16(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 23)

Neuropathy is not associated with BMI. (Figure 55).

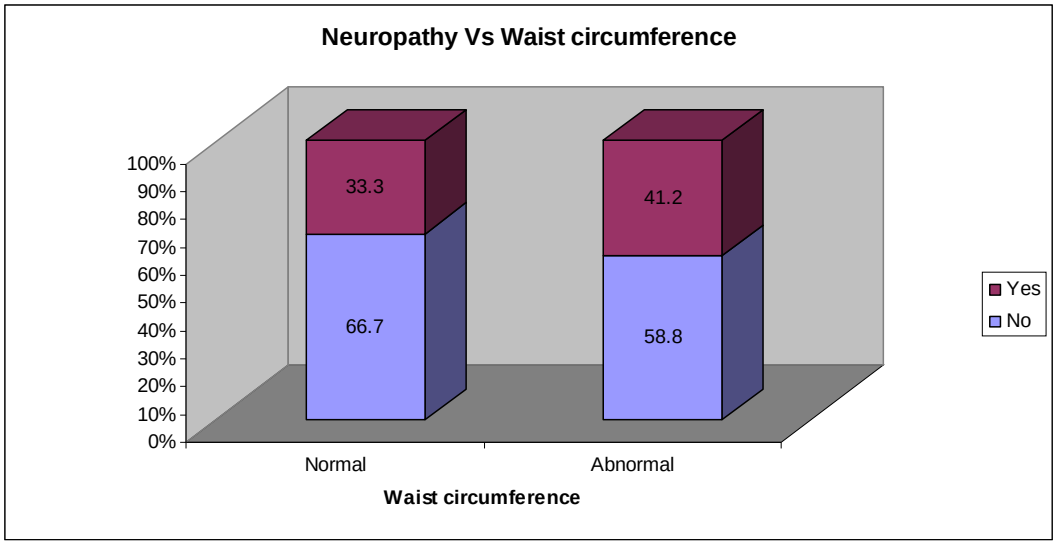


(Figure 55)

Neuropathy and waist circumference (Table 24):

Waist circumference	Neuropathy		Total
	Absent	Present	
Normal	26(67%)	13(33%)	39(100%)
Abnormal	67(59%)	47(41%)	114(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 24)



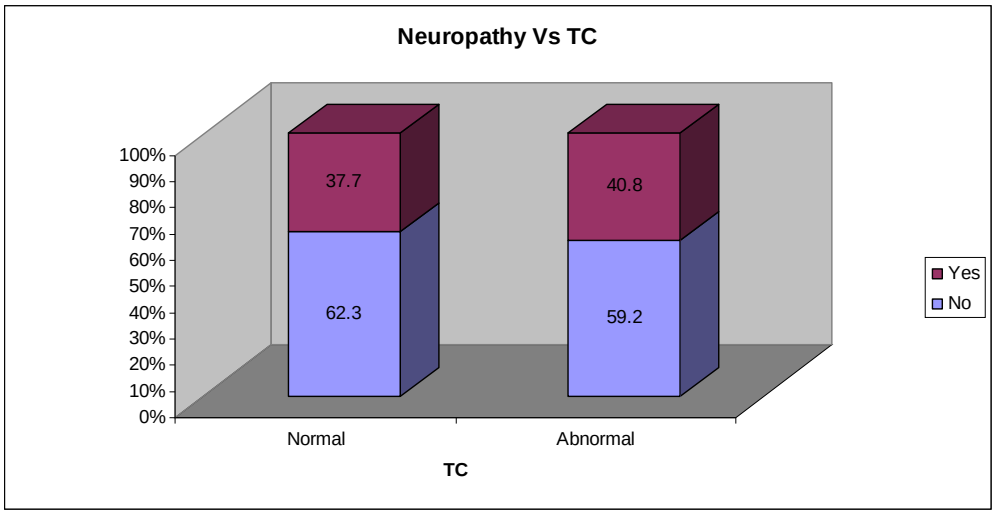
(Figure 56)

Neuropathy is not associated with waist circumference. (Figure 56).

Neuropathy and Total Cholesterol (Table 25):

Total Cholesterol	Neuropathy		Total
	Absent	Present	
Normal	48(62%)	29(38%)	77(100%)
Abnormal	45(59%)	31(41%)	76(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 25)



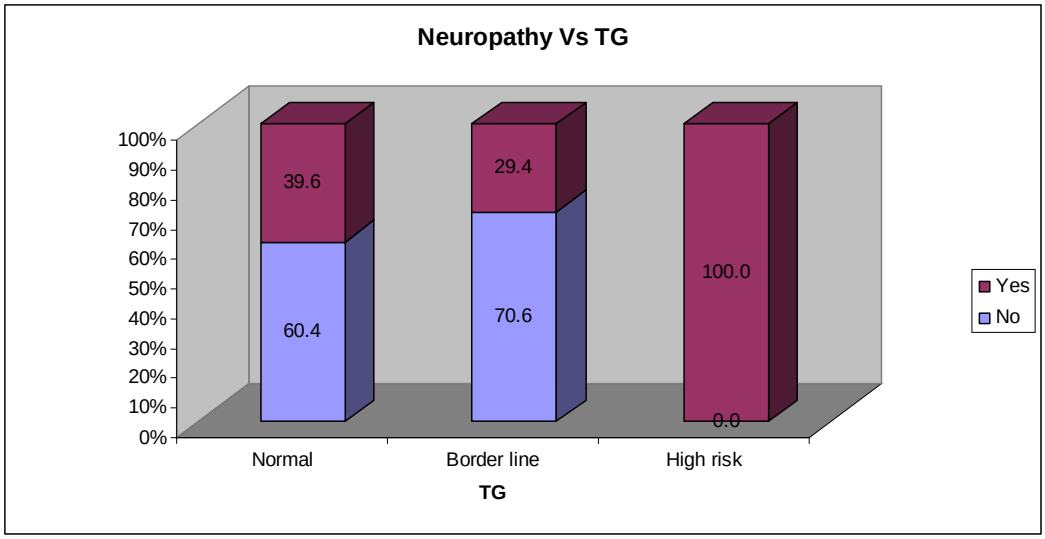
(Figure 57)

Neuropathy is not associated with total cholesterol. (Figure 57).

Serum Triglycerides and Neuropathy (Table 26):

S.Triglycerides	Neuropathy		Total
	Absent	Present	
Normal	81(60%)	53(40%)	134(100%)
Borderline risk	12(71%)	5(29%)	17(100%)
High risk	0(0%)	2(100%)	2(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 26)



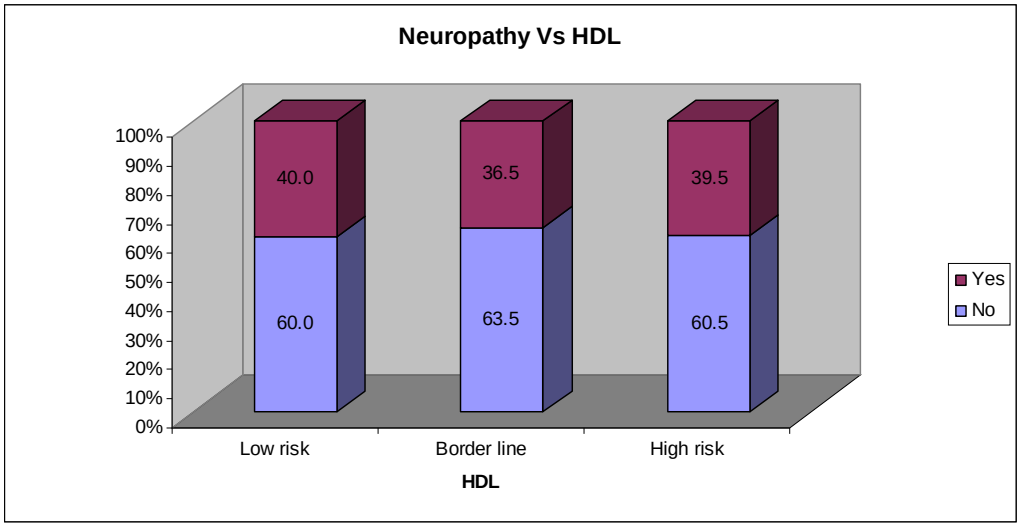
(Figure 58)

Neuropathy is not associated with Serum Triglycerides. (Figure 58).

Neuropathy and HDL Cholesterol (Table 27):

HDL	Neuropathy		Total
	Absent	Present	
Low risk	30(60%)	20(40%)	50(100%)
Borderline risk	40(64%)	23(37%)	63(100%)
High risk	23(61%)	15(40%)	38(100%)
Total	93(62%)	58(38%)	151(100%)

(Table 27)



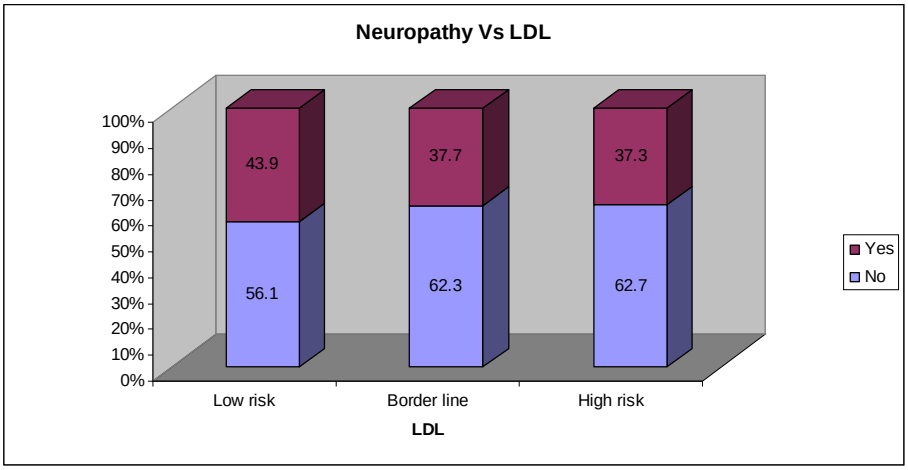
(Figure 59)

Neuropathy is not associated with HDL (Figure 59).

Neuropathy and LDL Cholesterol (Table 28):

LDL	Neuropathy		Total
	Absent	Present	
Low risk	23(56%)	18(44%)	41(100%)
Borderline risk	38(62%)	23(38%)	61(100%)
High risk	32(62%)	19(37%)	51(100%)
Total	93(61%)	60(39%)	153(100%)

(Table 28)



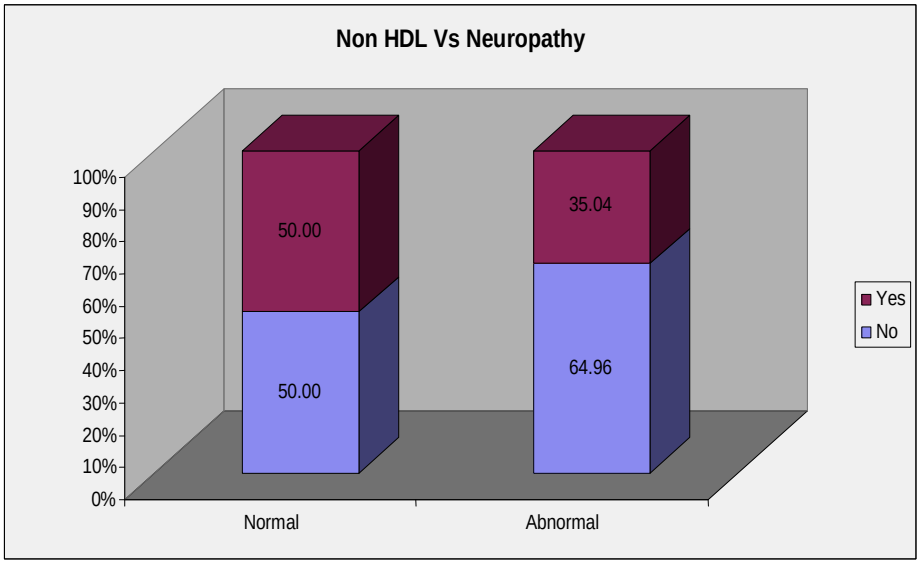
(Figure 60)

Neuropathy is not associated with LDL (Figure 60).

Neuropathy and Non HDL Cholesterol (Table 29):

Non HDL	Neuropathy		Total
	Absent	Present	
Normal	17(50%)	17(50%)	34(100%)
Abnormal	76(65%)	41(35%)	117(100%)
Total	93(62%)	58(38%)	151(100%)

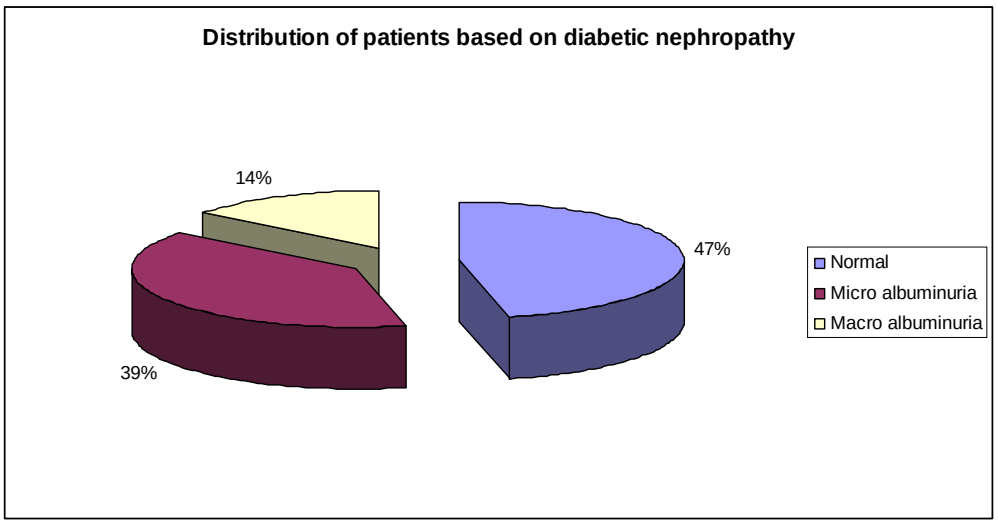
(Table 29)



(Figure 61)

Diabetic Nephropathy

The parameter used was urine albumin creatinine ratio.71 (46.4%) were having normoalbuminuria, 60(39.2%) had microalbuminuria and 22(14.4%) had macroalbuminuria (Figure 62).



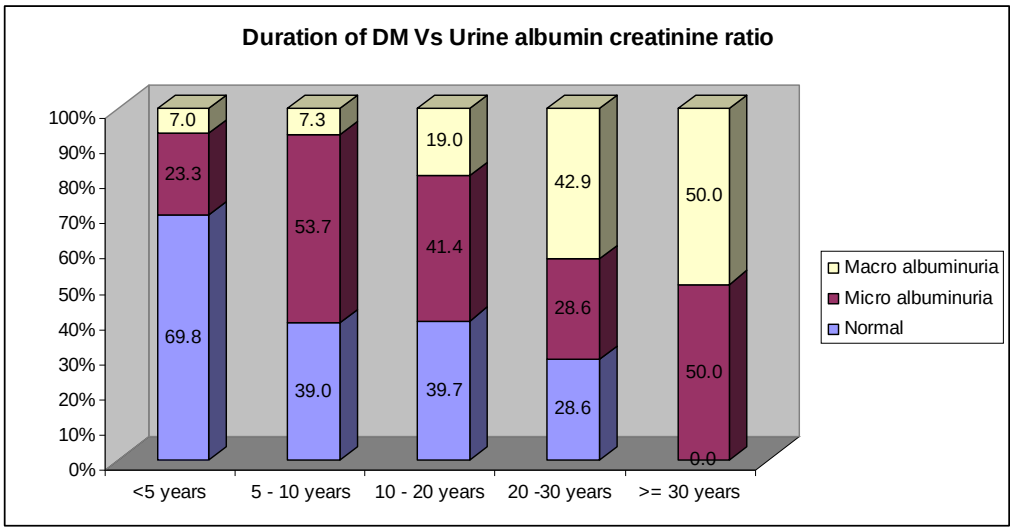
(Figure 62)

Duration of diabetes and Diabetic nephropathy (Table 30):

Duration of diabetes	Normal	Micro-albuminuria	Macro-albuminuria	Total
< 5 years	30 (70%)	10 (23%)	3 (7%)	43 (100%)

5 – 10 years	16 (39%)	22 (54%)	3 (7%)	41 (100%)
10 – 20 years	23(40%)	24 (41%)	11 (19%)	58 (100%)
20 – 30 years	2 (29%)	2 (29%)	3 (43%)	7 (100%)
≥ 30 years	0 (0%)	2 (50%)	2 (50%)	4 (100%)
Total	71(46%)	60(39%)	22(14%)	153(100%)

(Table 30)



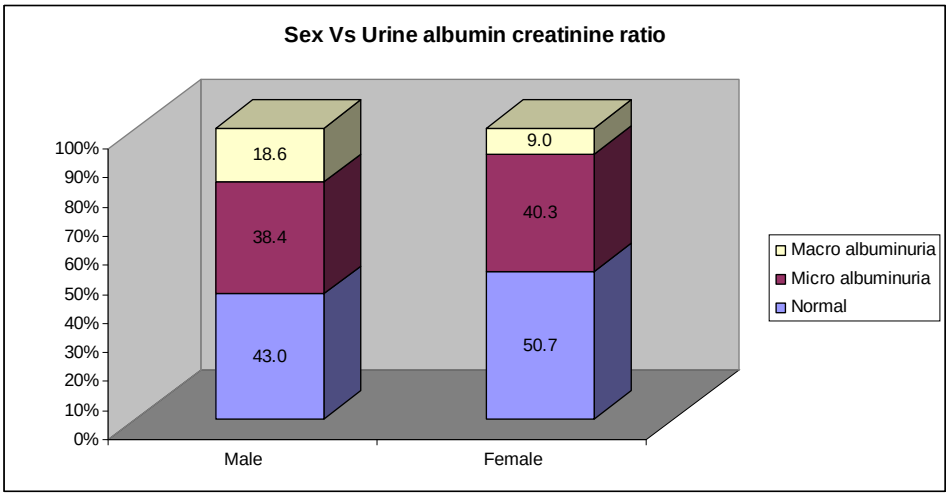
(Figure 63)

Urine albumin creatinine ratio increases with increase in duration of DM (correlation coefficient = 0.310, p = 0.00). (Figure 63.)

Gender and Nephropathy in diabetic subjects (Table 31):

Gender	Normal	Micro albuminuria	Macro albuminuria	Total
Male	37 (43%)	33 (38%)	16 (19%)	86 (100%)
Female	34 (51%)	27 (40%)	6 (9%)	67 (100%)
Total	71 (46%)	60 (39%)	22 (14%)	153 (100%)

(Table 31)



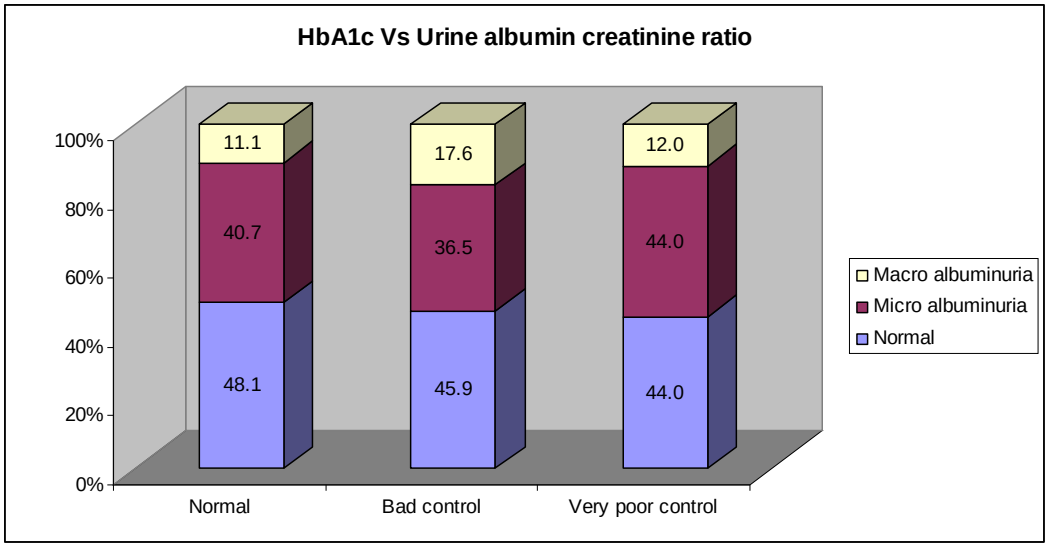
(Figure 64)

Diabetic nephropathy is not associated with gender(Figure 64).

HbA1c and urine albumin-creatinine ratio (Table 32):

HbA1c	Normal	Micro albuminuria	Macro albuminuria	Total
≤ 7%	26 (48%)	22 (41%)	6 (11%)	54(100%)
> 7 - 10%	34 (46%)	27 (37%)	13 (18%)	74(100%)
≥ 10%	11 (44%)	11 (44%)	3 (12%)	25(100%)
Total	71 (46%)	60 (39%)	22 (14%)	153(100%)

(Table 32)



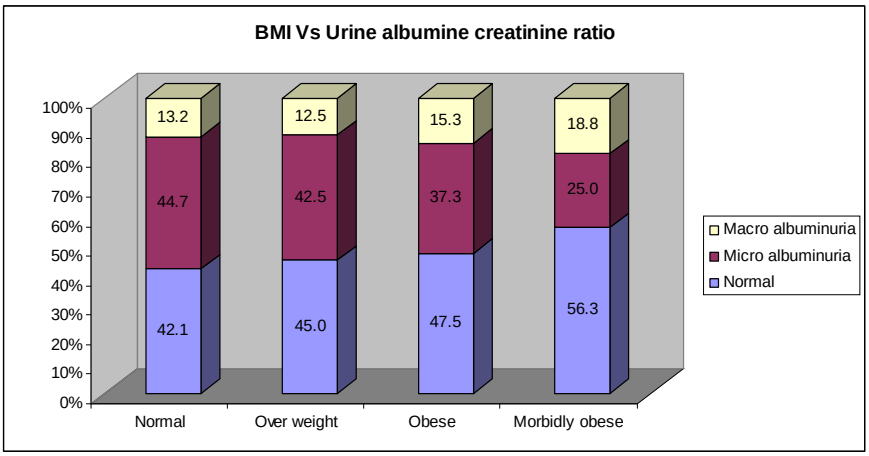
(Figure 65)

Diabetic nephropathy is not associated with control of diabetes (Figure 65).

BMI and Urine Albumin Creatinine Ratio (Table 33):

BMI	Normal	Micro albuminuria	Macro albuminuria	Total
Normal	16(42%)	17(45%)	5 (13%)	38(100%)
Over weight	18(45%)	17(43%)	5(12%)	40(100%)
Obese	28(48%)	22(37%)	9(15%)	59(100%)
Morbidly obese	9(56%)	4(25%)	3(19%)	16(100%)
Total	71(47%)	60(39%)	22(14%)	153(100%)

(Table 33)



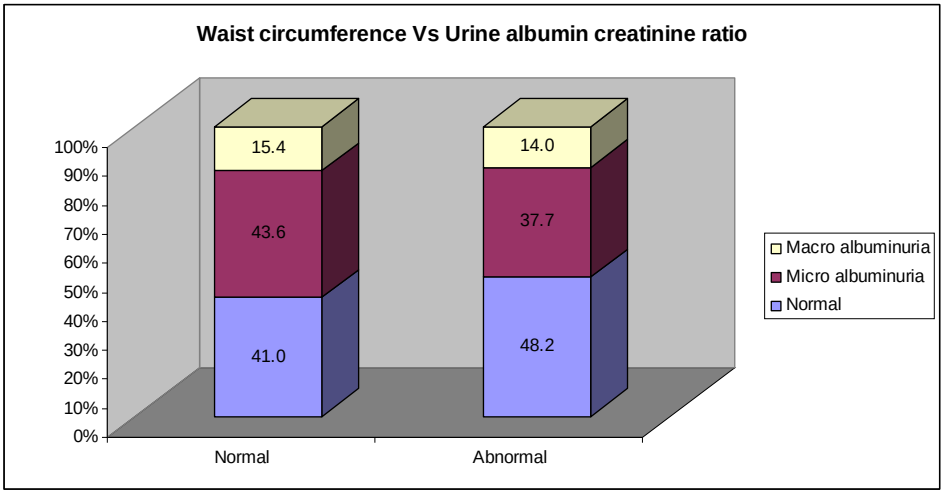
(Figure 66)

Diabetic nephropathy is not associated with BMI (Figure 66).

Diabetic nephropathy and waist circumference (Table 34):

Waist circumference	Normal	Micro albuminuria	Macro albuminuria	Total
Normal	16 (41%)	17 (44%)	6 (15%)	39(100%)
Abnormal	55 (48%)	43 (38%)	16 (14%)	114(100%)
Total	71 (46%)	60 (39%)	22 (15%)	153(100%)

(Table 34)



(Figure 67)

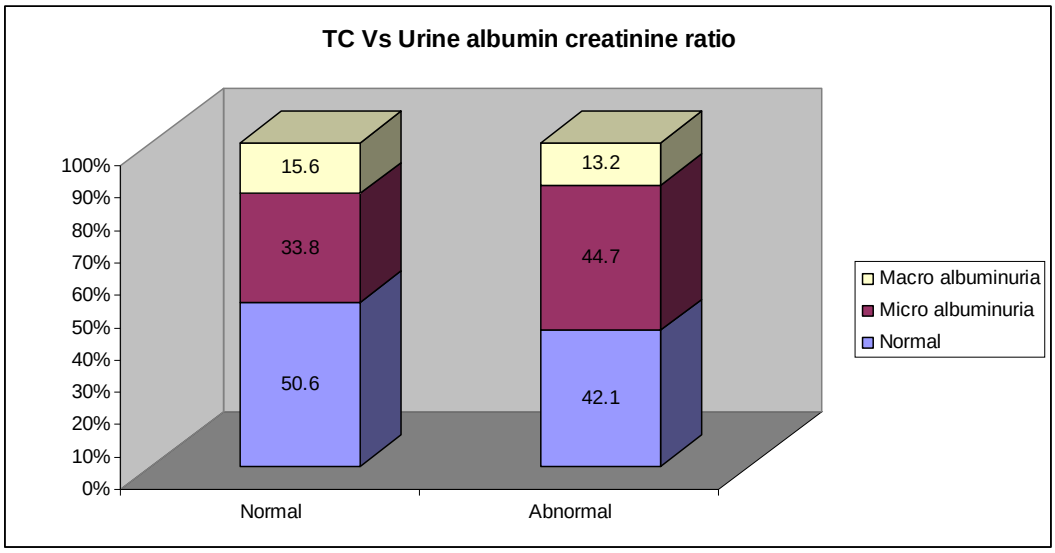
Diabetic nephropathy is not associated with waist circumference (Figure 67).

Diabetic nephropathy and Serum Lipid Profile:

Urine Albumin Creatinine Ratio and Serum Cholesterol (Table 35):

Total Cholesterol	Normal	Micro albuminuria	Macro albuminuria	Total
Normal	39(51%)	26(34%)	12(15%)	77(100%)
Abnormal	32(42%)	34(45%)	10(13%)	76(100%)
Total	71(47%)	60(39%)	22(14%)	153(100%)

(Table 35)



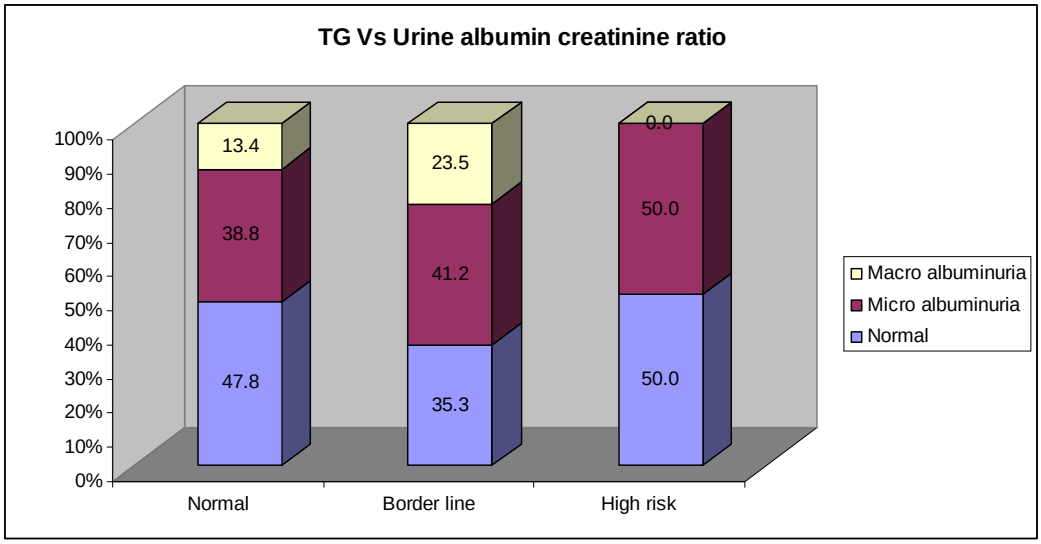
(Figure 68)

Diabetic nephropathy is not associated with TC (Figure 68)

Serum Triglycerides and urine albumin creatinine ratio (Table 36)

S.Triglycerides	Normal	Micro-albuminuria	Macro-albuminuria	Total
Low risk	64(48%)	52(39%)	18(13%)	134(100%)
Borderline	6(35%)	7(41%)	4(24%)	17(100%)
High risk	1(50%)	1(50%)	0(0%)	2(100%)
Total	71(47%)	60(39%)	22(14%)	153(100%)

(Table 36)



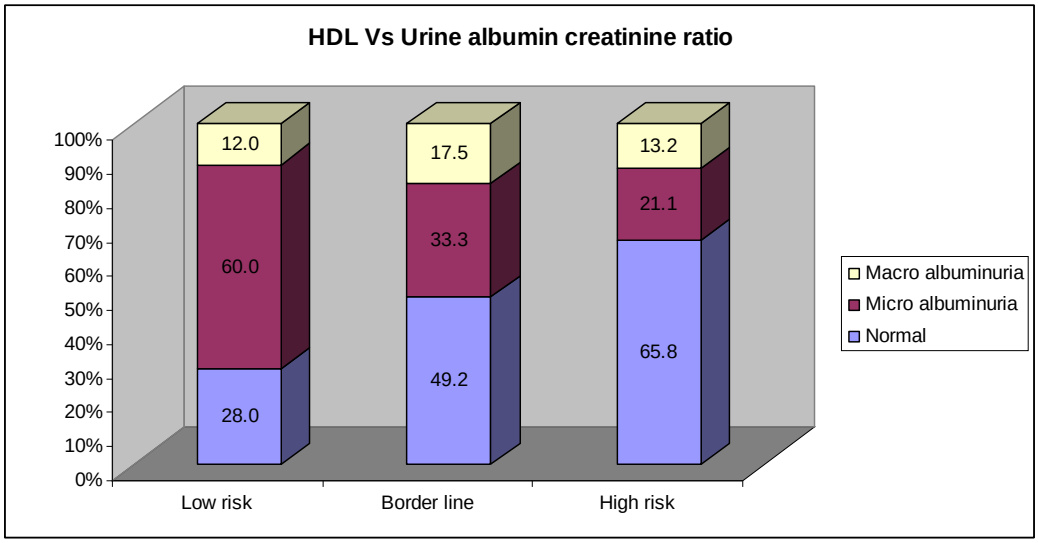
(Figure 69)

Diabetic nephropathy is not associated with TG (Figure 69).

Serum HDL and Urine albumin creatinine ratio: (Table 37)

HDL	Normal	Micro-albuminuria	Macro-albuminuria	Total
Low risk	14(28%)	30(60%)	6(12%)	50(100%)
Borderline	31(49%)	21(33%)	11(18%)	63(100%)
High risk	25(66%)	8(21%)	5(13%)	38(100%)
Total	70(46%)	59(39%)	22(15%)	151(100%)

(Table 37)



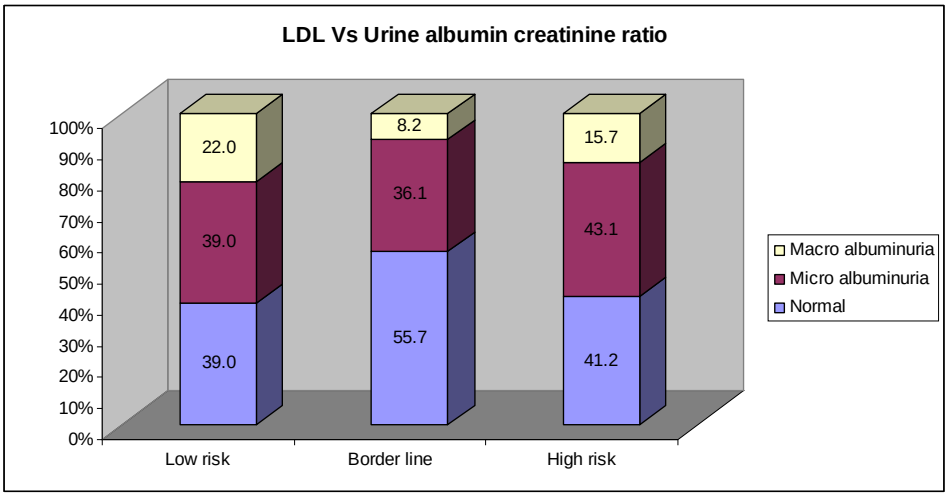
(Figure 70)

The risk for diabetic nephropathy decreases with HDL (p =0.005) (Figure 70). The present study showed an inverse correlation with HDL cholesterol.

Serum LDL and Urine albumin creatinine ratio (Table 38):

LDL	Normal	Micro-albuminuria	Macro-albuminuria	Total
Low risk	16(39%)	16(39%)	9(22%)	41(100%)
Borderline	34(56%)	22(36%)	5(8%)	61(100%)
High risk	21(41%)	22(43%)	8(16%)	51(100%)
Total	71(46%)	60(39%)	22(14%)	153(100%)

(Table 38)



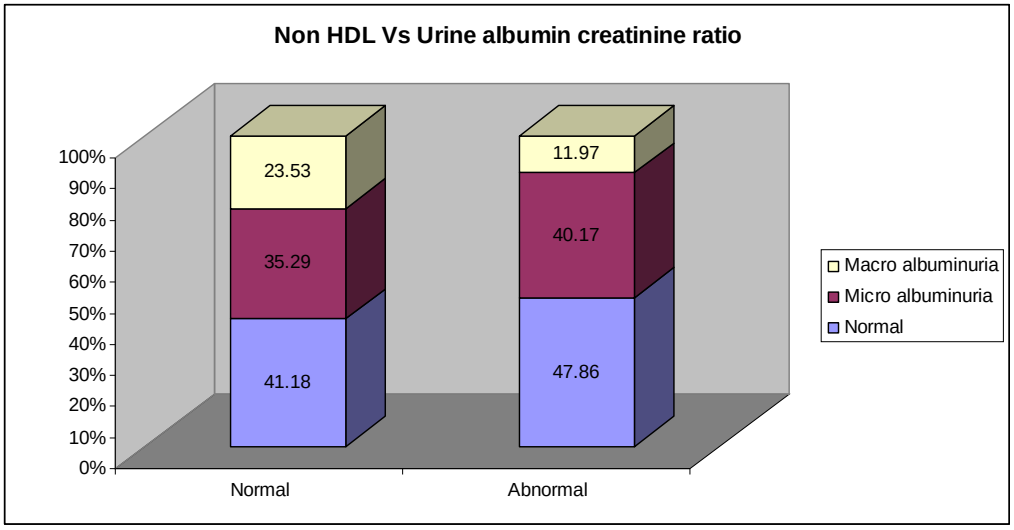
(Figure 71)

Diabetic nephropathy is not associated with LDL (Figure 71).

Non HDL Cholesterol and Urine Albumin Creatinine Ratio (Table 39):

Non HDL	Normal	Micro-albuminuria	Macro-albuminuria	Total
Normal	14(41%)	12(35%)	8(24%)	34(100%)
Abnormal	56(48%)	47(40%)	14(12%)	117(100%)
Total	70(46%)	59(39%)	22(15%)	151(100%)

(Table 39)



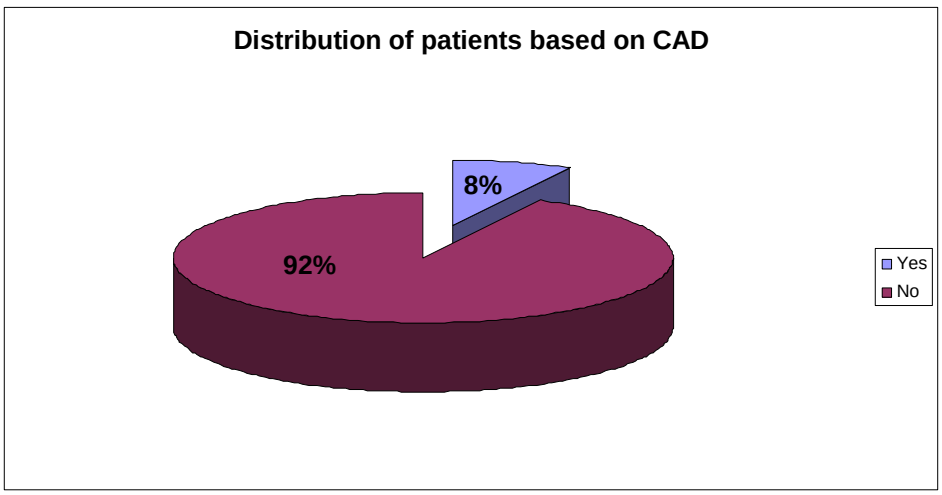
(Figure 72)

Diabetic nephropathy is not associated with non HDL(Figure 72)

Macrovascular complications:

Coronary Artery Disease (CAD):

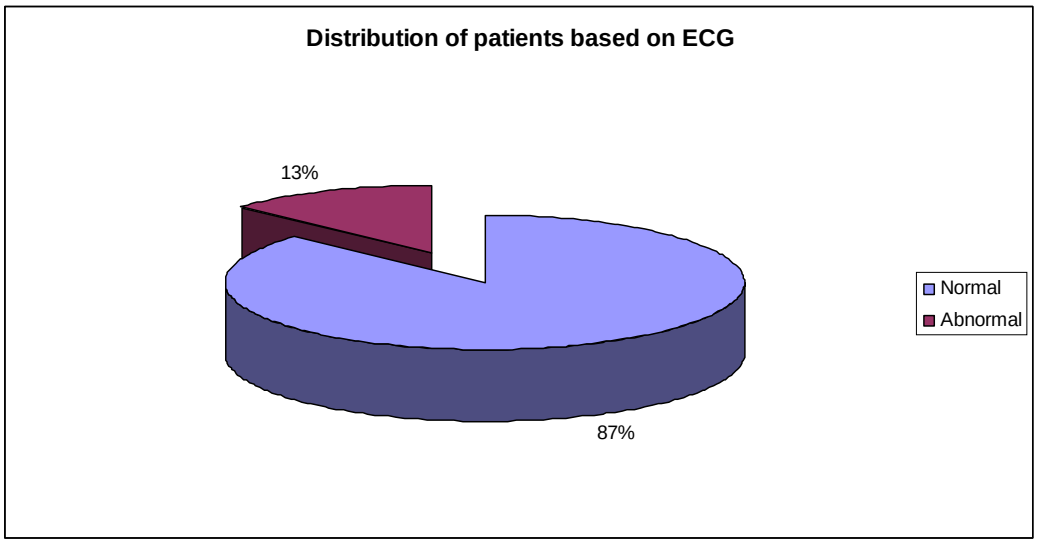
As the patients on Statins were excluded the majority of the cases did not show features of CAD from history or from ECG. Of the 153 diabetics gave history of CAD in 12(7.84%) and 141(92.16%) gave no history of CAD. (Figure 73).



(Figure 73)

ECG:

As those patients on lipid lowering drugs were excluded from the study those who were having abnormal ECGs were less.Of the 153 patients 133(86.93%) were having normal ECG and 20(13.07%) with abnormal ECG.The ECG changes were mainly ST-T changes only (Figure 74).



(Figure 74)

Control of diabetes:

Mean HbA1c among control group was 5.02±0.49 % .Among diabetic subjects 54 had HbA1c of 5.96±0.55%; 74 had 8.26±0.87% and 25 had 11.64±1.48. HbA_{1c} was less than 7 in all among controls 153(100%). Among diabetic subjects 54(35.29%) were under good control (HbA1c <7); 74 (48.37%) were under bad control (HbA1c 7 to 10) and 25 (16.34%) were having very poor control with an HbA1c more than 10 (Table 40).

HbA1c	No	Mean	SD
Control group	153	5.02	0.49
Diabetic Good control	54	5.96	0.55
Diabetic Bad control	74	8.26	0.87
Diabetic very poor control	25	11.64	1.48

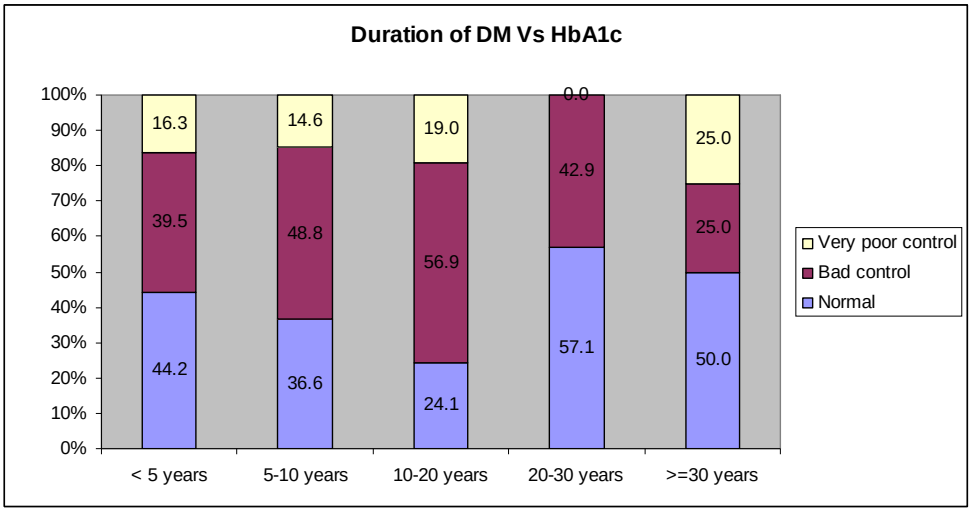
(Table 40)

Duration of Diabetes and HbA1c (Table 41):

Duration of diabetes	Good control	Bad control	Very poor control	Total
< 5 years	19(44%)	17(40%)	7(16%)	43(100%)
5 – 10 years	15(37%)	20(49%)	6(15%)	41(100%)
10 – 20 years	14(24%)	33(57%)	11(19%)	58(100%)
20 – 30 years	4(57%)	3(43%)	0(0%)	7(100%)
≥ 30 years	2(50%)	1(25%)	1(25%)	4(100%)
Total	54(35%)	74(48%)	25(16%)	153(100%)

(Table 41)

Control of diabetes is not associated with duration of DM (Figure 75)



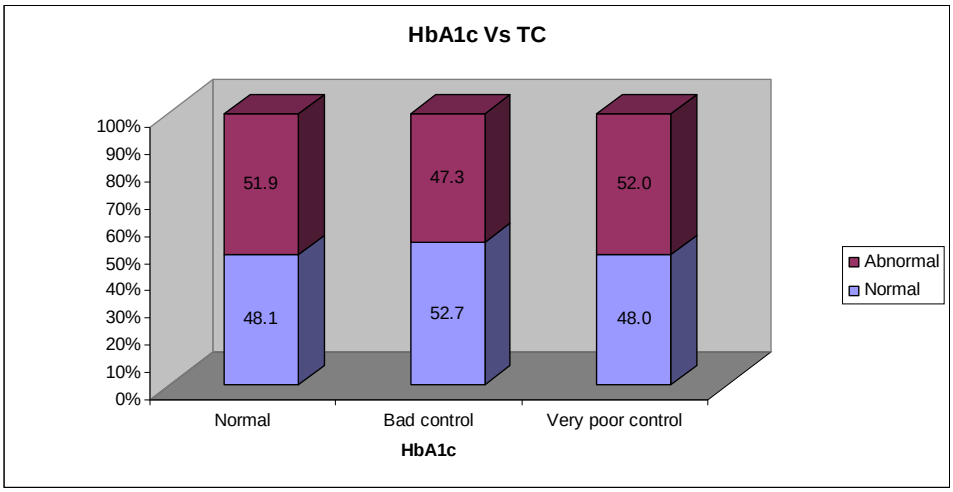
(Figure 75)

HbA1c and Serum Total Cholesterol:

HbA1c	Normal	Abnormal	Total
Good control	26(48%)	28(52%)	54(100%)
Bad control	39(53%)	35(47%)	74(100%)
Very poor control	12(48%)	13(52%)	25(100%)
Total	77(50%)	76(50%)	153(100%)

(Table 42)

Total cholesterol is not associated with control of diabetes among diabetes patients (Figure 76).

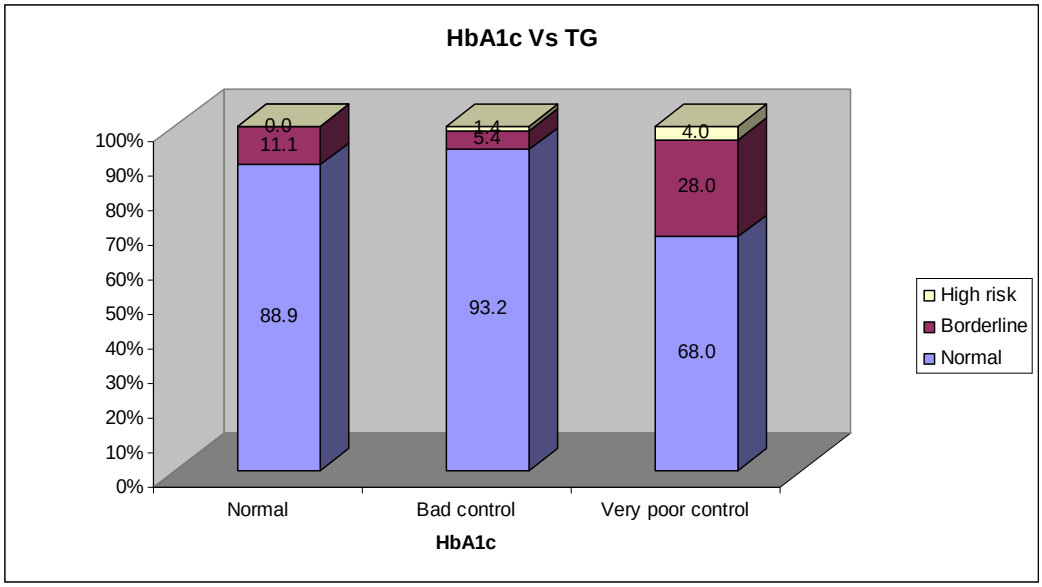


(Figure 76)

HbA1c and Serum Triglycerides (Table 43):

HbA1c	Low risk	Borderline	High risk	Total
Good control	48(89%)	6(11%)	0(0%)	54(100%)
Bad control	69(93%)	4(5%)	1(1%)	74(100%)
Very poor control	17(68%)	7(28%)	1(4%)	25(100%)
Total	134(88%)	17(11%)	2(1%)	153(100%)

(Table 43)



(Figure 77)

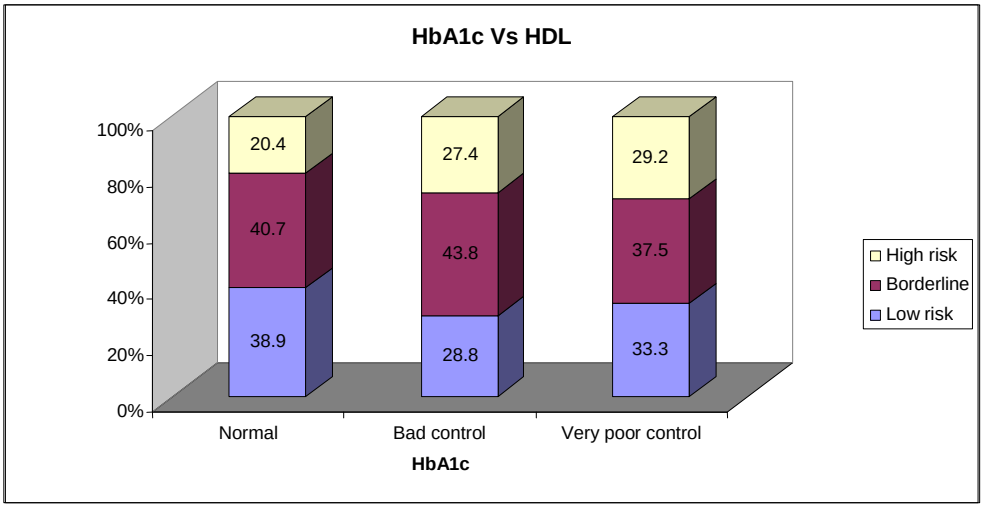
Serum Triglycerides were associated with control of diabetes among diabetes patients. The Serum Triglyceride level increased with HbA1c and a significantly high value for serum Triglyceride was observed in the very poorly controlled diabetic subjects. (r = 0.233, p = 0.004) (Figure 77).

Control of Diabetes (HbA1c) and HDL Cholesterol:

HbA1c	Low risk	Borderline	High risk	Total
Good control	21(39%)	20(37%)	13(24%)	54(100%)
Bad control	21(29%)	32(44%)	20(27%)	73(100%)
Very poor control	8(33%)	9(38%)	7(29%)	24(100%)
Total	50(33%)	61(40%)	40(27%)	151(100%)

(Table 44)

a

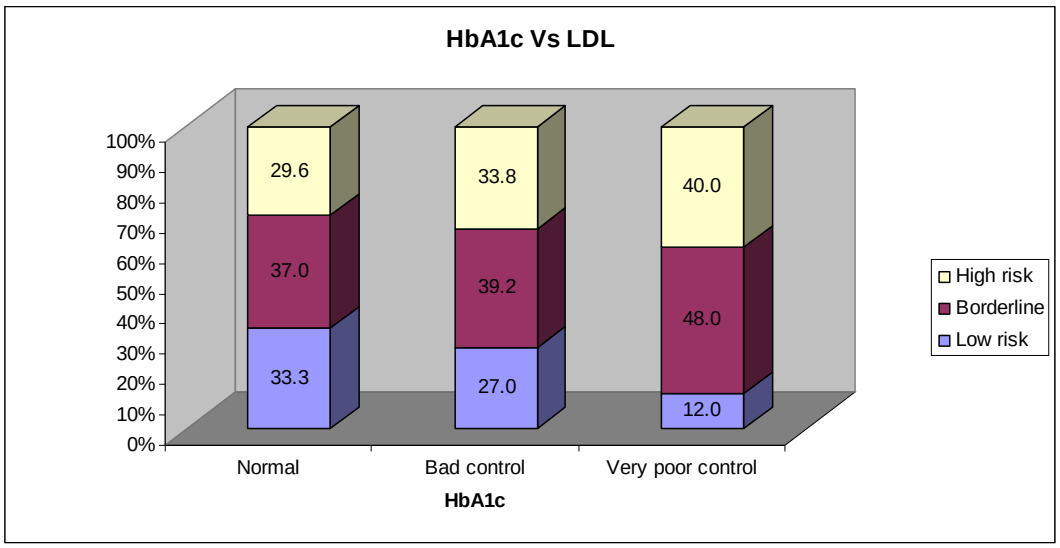


(Figure 78)

HbA1c and LDL Cholesterol (Table 45):

HbA1c	Low risk	Borderline	High risk	Total
Good control	18 (33%)	20 (37%)	16 (30%)	54(100%)
Bad control	20 (27%)	29 (39%)	25 (34%)	74(100%)
Very poor control	3 (12%)	12 (48%)	10 (40%)	25(100%)
Total	41 (27%)	61 (40%)	51 (33%)	153(100%)

(Table 45)



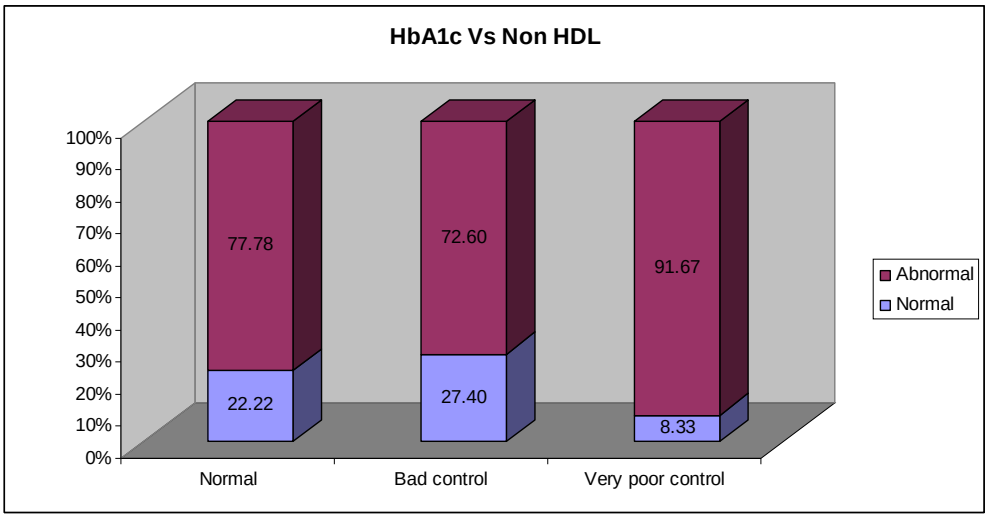
(Figure 79)

LDL cholesterol is not associated with control of diabetes among diabetes subjects (Figure 79).

HbA1c and Non HDL Cholesterol (Table 46):

HbA1c	Non HDL Normal	Non HDL Abnormal	Total
Good control	12 (22%)	42 (78%)	54 (100%)
Bad control	20 (27%)	53 (73%)	73 (100%)
Very poor control	2 (8%)	22 (92%)	24 (100%)
Total	34 (23%)	117 (77%)	151(100%)

(Table 46)



(Figure 80)

Non HDL cholesterol is not associated with control of diabetes among diabetes patients (Figure 80)

Control of Diabetes and Serum Lipid Profile (Table 47):

Lipid parameters	HbA1c	No	Mean	SD	P value
Total Cholesterol	Good	54	203.80	38.35	0.12
	Bad	74	198.68	38.65	
	Very poor	25	217.76	44.94	
Serum Triglycerides	Good	54	125.13	51.44	0.009
	Bad	74	131.47	65.28	
	Very poor	25	172.88	89.35	
HDL Cholesterol	Good	54	46.00	9.08	0.83
	Bad	73	46.71	10.82	
	Very poor	24	45.33	10.72	
LDL Cholesterol	Good	54	116.91	31.44	0.16
	Bad	74	120.44	29.99	
	Very poor	25	130.97	30.08	

Non HDL Cholesterol	Good	54	157.48	36.94	0.29
	Bad	73	151.01	36.08	
	Very poor	24	174.63	41.77	

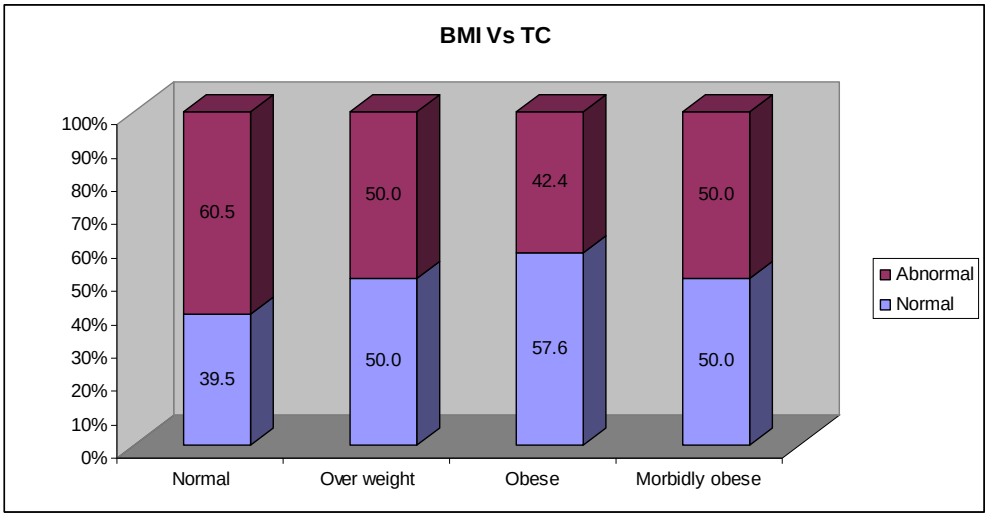
(Table 47)

A significantly high value of serum Triglyceride is observed in very poorly controlled diabetes.

BMI and Total Cholesterol (Table 48):

BMI in diabetics	Normal	Abnormal	Total
Normal	15(40%)	23(61%)	38(100%)
Overweight	20(50%)	20(50%)	40(100%)
Obese	34(58%)	25(42%)	59(100%)
Morbidly obese	8(50%)	8(50%)	16(100%)
Total	77(50%)	76(50%)	153(100%)

(Table 48)



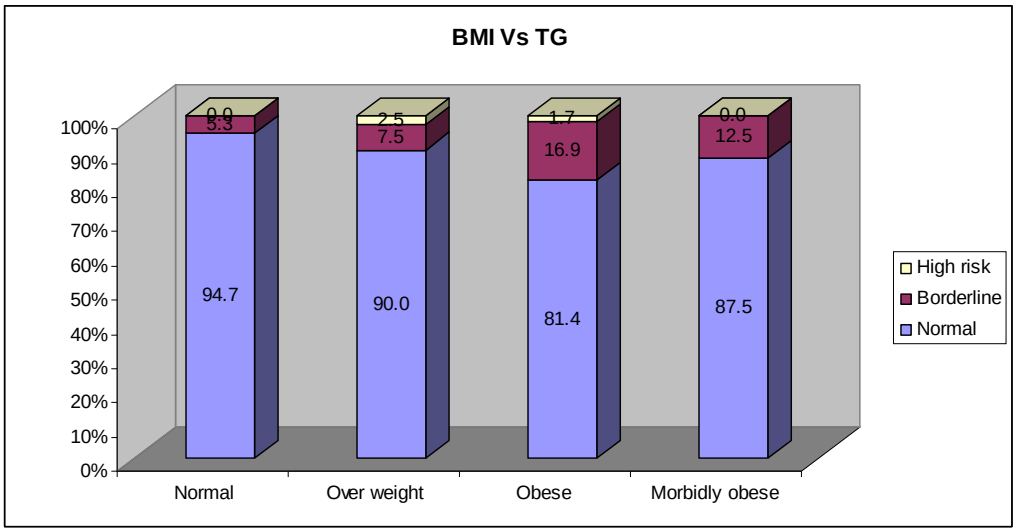
(Figure 81)

Total cholesterol is not associated with BMI among diabetes patients (Figure 81).

BMI and Serum Triglycerides (Table 49):

BMI in diabetics	Normal	Borderline	High risk	Total
Normal	36(95%)	2(5%)	0(0%)	38(100%)
Overweight	36(90%)	3(8%)	1(3%)	40(100%)
Obese	48(81%)	10(17%)	1(2%)	59(100%)
Morbidly obese	14(86%)	2(13%)	0(0%)	16(100%0
Total	134(88%)	17(11%)	2(1%)	153(100%)

(Table 49)



(Figure 82)

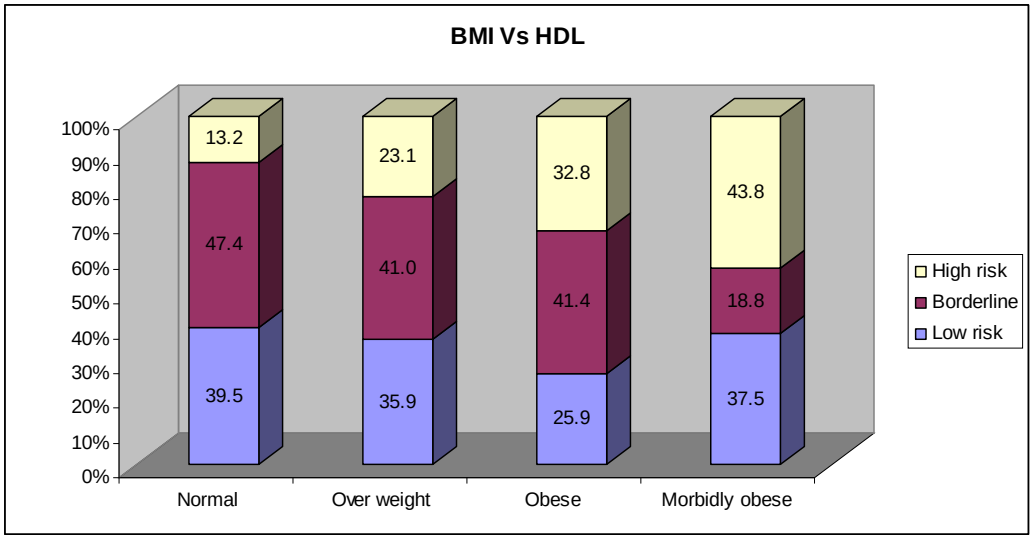
Serum Triglyceride is associated with BMI among diabetes patients. Value of TG increases with increase in BMI (r = 0.177, p = 0.029) (Figure 82).

BMI and HDL Cholesterol (Table 50):

BMI in diabetics	Low risk	Borderline	High risk	Total
Normal	15(40%)	18(48%)	5(13%)	38(100%)
Overweight	14(36%)	16(41%)	9(23%)	39(100%)
Obese	15(26%)	24(41%)	19(33%)	58(100%)
Morbidly obese	6(38%)	3(19%)	7(44%)	16(100%)
Total	50(33%)	61(40%)	40(27%)	151(100%)

(Table 50)

HDL cholesterol is not associated with BMI among diabetes patients (Figure 83).



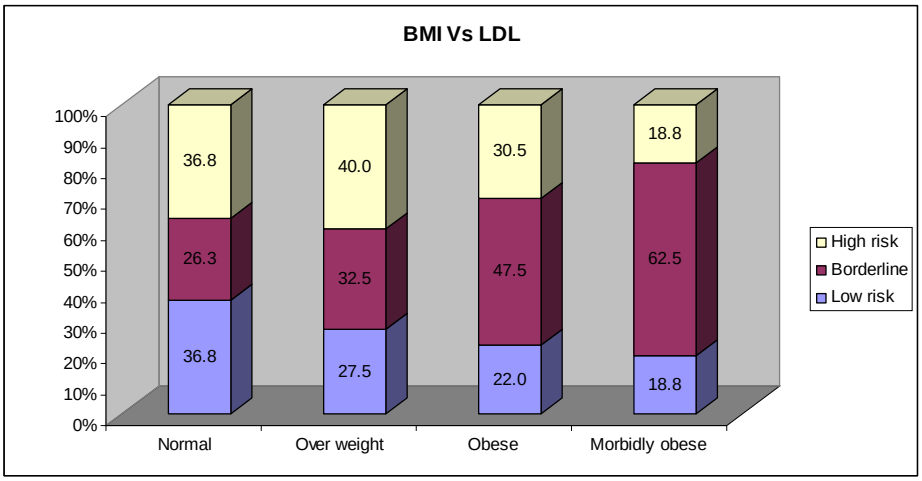
(Figure 83)

BMI and LDL Cholesterol (Table 51):

BMI in diabetics	Low risk	Borderline	High risk	Total
Normal	14(37%)	10(26%)	14(37%)	38(100%)
Overweight	11(28%)	13(33%)	16(40%)	40(100%)
Obese	13(22%)	28(48%)	18(31%)	59(100%)
Morbidly obese	3(19%)	10(63%)	3(19%)	16(100%)
Total	41(27%)	61(40%)	51(33%)	153(100%)

(Table 51)

LDL cholesterol is not associated with BMI among diabetes patients (Figure 84).

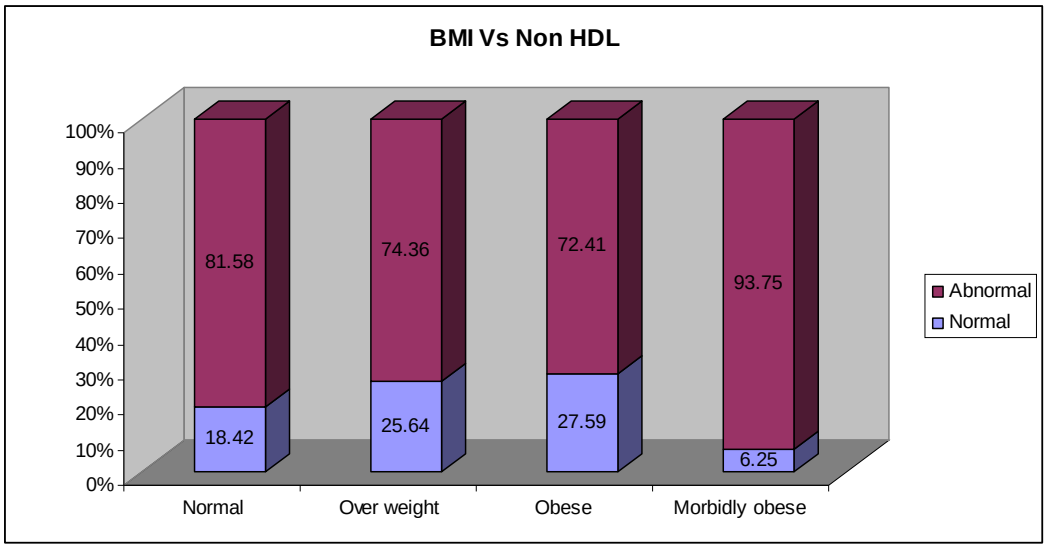


(Figure 84)

BMI and Non HDL Cholesterol (Table 52):

BMI in Diabetics	Non HDL Normal	Non HDL abnormal	Total
Normal	7(18%)	31(82%)	38(100%0
Overweight	10(26%)	29(74%)	39(100%)
Obese	16(28%)	42(72%)	58100%)
Morbidly obese	1(6%)	15(94%)	16(100%)
Total	34(22%)	117(77%)	151(100%)

(Table 52)



(Figure 85)

Non HDL cholesterol is not associated with BMI among diabetes patients (Figure 85).

Among diabetic patients only Serum Triglyceride was found to be correlated with HbA1c and BMI. After controlling the effect of BMI in Binary logistic regression Serum Triglycerides were associated only with HbA1c ($p = 0.016$). None of the lipids were associated with waist circumference or duration of Diabetes mellitus.

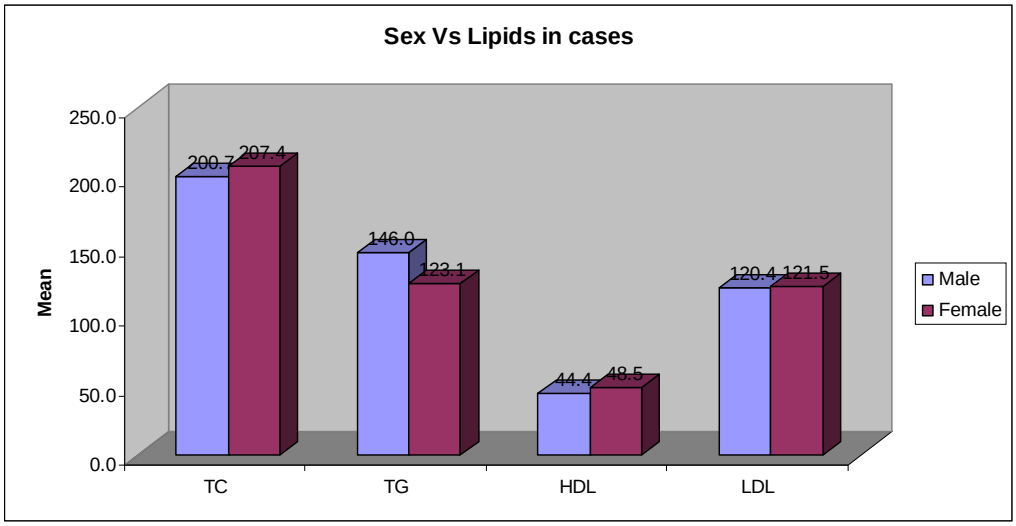
Among controls lipids were not correlated with HbA1c, BMI or waist circumference.

Mean Lipid values in mg/100 ml based on gender in both groups (Table 53):

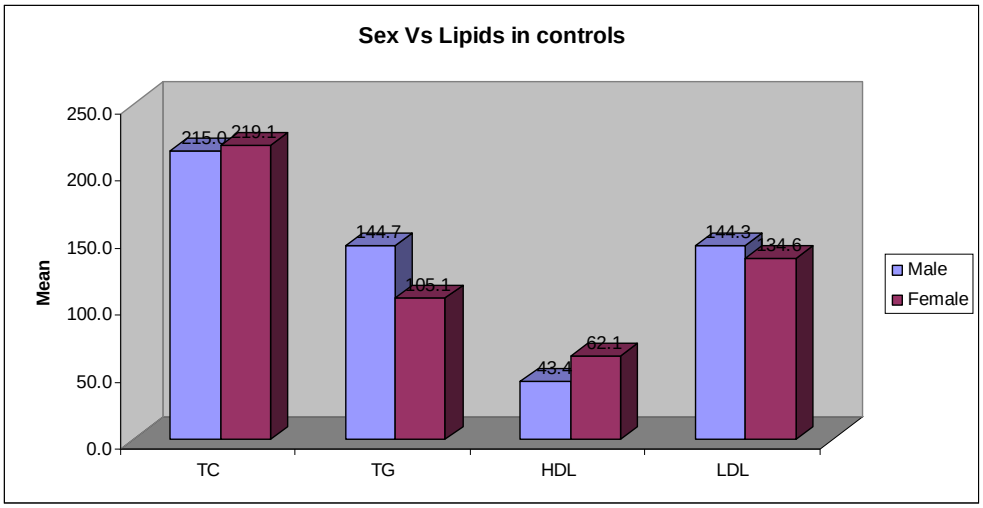
Group	TC	TG	HDL	LDL
Case male	200.7	146	44.4	120.4
Case female	207.4	123.1	48.5	121.5
Control male	215	144.7	43.4	144.3
Control female	219.1	105.1	62.1	134.6

(Table 53)

Both among cases and controls, females have better values for Serum Triglycerides, HDL cholesterol and LDL cholesterol (p = 0.036, 0.025, 0.014 and p = 0.00, 0.00, 0.00 resp.).(Figures 86 and 87). Gender is correlated with Triglyceride, HDL and VLDL. (p value <0.05). Males have got high values for Triglyceride and VLDL and low values for HDL.

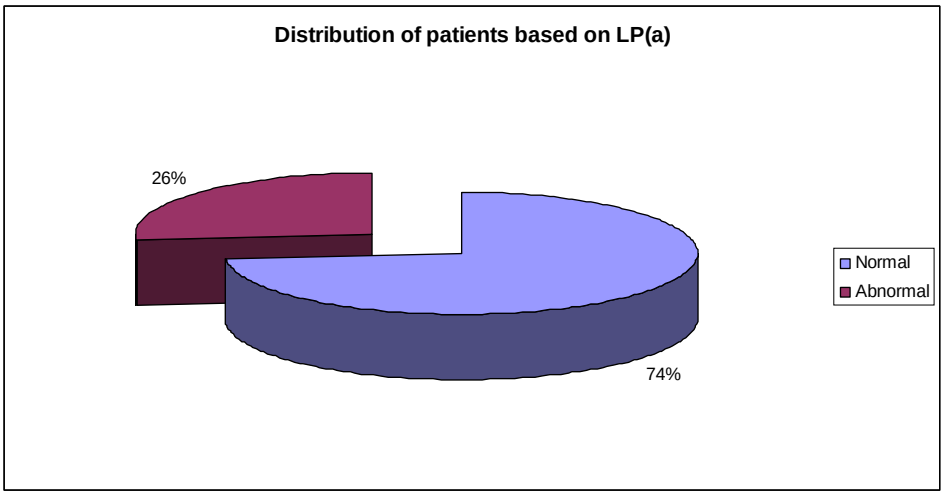


(Figure 86)



(Figure 87)

Lipoprotein (a) or Lp (a) was done in 144 cases. Lp (a) is a low density lipoprotein like particle containing apolipoprotein B100 disulphide-linked to one large glycoprotein called apolipoprotein (a).High Lipoprotein (a) concentration represents an indicator of risk for cardiovascular diseases, especially when the serum LDL cholesterol or Apo B are elevated. The quantification of Lp (a) in serum or plasma is important for identification of individuals at risk for developing atherosclerosis. Normal range in serum is up to 30 mg/dl. Lp (a) was normal in 74% and abnormal in 26 %.(Figure 88).



(Figure 88)

Lp (a) & microvasular complications:

Mean Lp (a) score was not significantly different in patients with and without Neuropathy (p = 0.93) & Retinopathy (p = 0.22) .

Lp(a) and diabetic nephropathy:

Alb/Cr.ratio	No	Mean	SD	p value
Normal	66	17.92	16.43	0.03
Micro	58	26.09	19.98	
Macro	20	30.35	36.93	

(Table 54)

Mean Lp(a) score of micro albuminuria and macro albuminuria groups were significantly higher compared to normal group, p=0.038 and p=0.026 respectively.

Apo B:

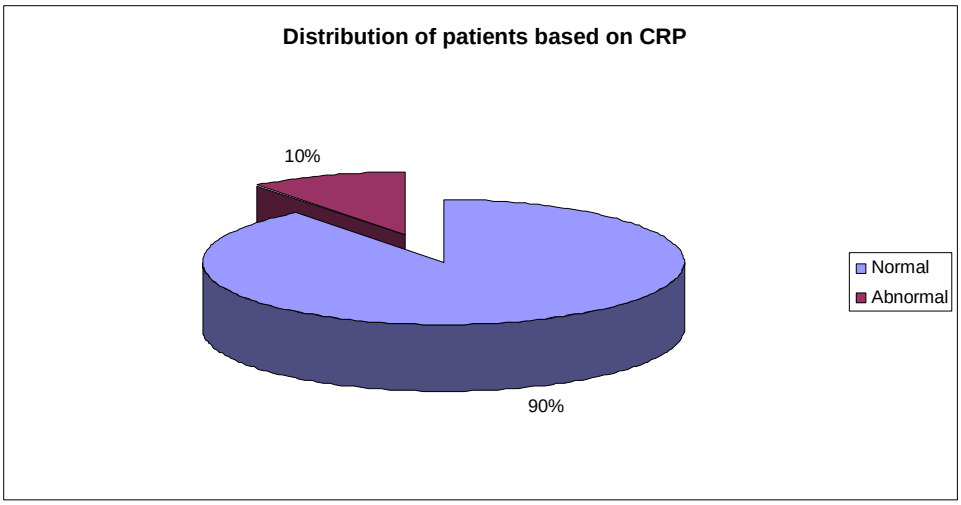
Apo B is the major structural apolipoprotein in VLDL, LDL and lipoproteins and chylomicron. Apo B exists in two forms: Apo B 100 and Apo B 48. Apo B 100, the most important component of LDL is synthesized in the liver and excreted in plasma as part of VLDL. Apo B 48 is the most important component of chylomicrons is synthesized in the intestine. Changes in the serum concentrations of Apo A1 and Apo B are are similar to those for HDL and LDL respectively. Apo B was estimated in 62 diabetic patients and 8 non diabetic control persons. The association between Apo B and Non HDL cholesterol was looked into. Normal value was taken as 69 to 105 mg/dl. There was significant correlation between apo B & non HDL. Value of apo B increased with increase in non HDL (r=0.412402, p = 0.00). Among diabetics there was no statistically significant correlation between waist circumference and Apo B (r=0.135, p=0.29).

Apo B and microvascular complications:

Mean Apo B score was not significantly different in patients with and without Neuropathy (p = 0.53), Retinopathy (p = 0.38) and Nephropathy (p = 0.26).

CRP- Ultrasensitive:

CRP- ultrasensitive is an acute phase protein present in normal serum, which increases significantly after most forms of tissue injuries, bacterial and virus infections, inflammation and malignant neoplasia.CRP may also be useful in detecting atherosclerotic process and providing important prognostic information about patients with asymptomatic heart disease, unstable angina and myocardial infarction.CRP concentration in serum rise long before traditional symptoms of heart and vascular diseases are noticed. Below 3mg/L is considered normal. Quantitative estimation of CRP- ultrasensitive was estimated in 62 diabetic patients and qualitative estimation of CRP was done in 91 patients. 16 (10.5%) had abnormal CRP and 137 (89.5%) had normal CRP (Figure 89).



(Figure 89)

Among diabetics, CRP was not associated with waist circumference (p =0.65) and physical activity (p =0.871). Mean VLDL value was

significantly higher in patients with abnormal CRP (42.4 ± 28.5 Vs 30.8 ± 17.3) (p = 0.029). Other lipids and CRP were not associated (all p > 0.05). Lp (a), Apo B and HbA1c were not associated with CRP (all p > 0.05).

CRP and microvascular complications:

CRP was not associated with Neuropathy (p = 0.13), Retinopathy (p = 0.56) and Nephropathy (p = 0.16).

DISCUSSION

DISCUSSION

Although the advanced lesions of atherosclerosis are seen in adult life, it has been well established that fatty streaks are present in the aorta by the age of 10 years and in the coronary arteries by the age of 20 years. So the mainstay of management for prevention of risk factor development is through behavioral means which should begin in childhood itself. Diabetes mellitus is a major risk factor for rapid progression of atherosclerosis apart from other causes like

familial hypercholesterolemia and physical inactivity. In adults with diabetes, the risk of atherosclerotic cardiovascular disease morbidity and mortality is greatly increased. The metabolic syndrome and type 2 diabetes mellitus are both becoming more prevalent, and both increase the risk of cardiovascular disease

Lipid concentrations are strongly related to the risk of macro vascular disease (coronary heart disease, stroke, and peripheral vascular disease) in adults with diabetes. Treatment with HMG-glutaryl CoA enzyme reductase inhibitors (statins), which lower low-density lipoprotein cholesterol (LDL-C) levels, prevents primary and secondary coronary events in adults with type 1 and type 2 diabetes.[124,125,126]

The present study included a total of 153 subjects having diabetes and was compared to an age and gender matched control group. Subjects were selected from patients having diabetes of varying duration and those who have not received any lipid lowering drugs or Glitazones. Seriously ill patients, those having hypothyroidism including subclinical hypothyroidism, renal or hepatic diseases or with familial hypercholesterolemia were excluded.

Control group included persons having no significant illnesses including diabetes and there is no history suggestive of familial hypercholesterolemia The subjects and controls were enrolled from the same socio-cultural and religious backgrounds including dietary habits.

Those having hypertension were not excluded. Samples were taken for blood sugars, HbA_{1c} as well as Fasting Serum Lipid

Profile after a complete history taking and detailed physical examination.

The age group ranged between 26 years and 85 years with mean age of 53.93 ±10.66 among both the groups. 70% belonged to the age group of 40 – 64 years, 20% ≥65 years and 10% ≤39 years. There were 86(56.2%) males and 67 (43.8%) females among both the groups. There were Hindus, Muslims and Christians among both the groups in the same distribution as in the society of the groups studied.

The detailed enquiry was made into the habits and divided into non users, previous users and current users for both smoking and alcoholism and the data showed the two groups were comparable as the distribution was equal among the the groups. . In a study from rural southern India the prevalence of life-time use, use in the past year and hazardous use of alcohol was 46.7%, 34.8% and 14.2%, respectively[128].As the prevalence in Kerala is equally high or more, history of alcoholism was reviewed in detail and problem drinkers using CAGE questionnaire with score ≥ 2[129],[130] were excluded. Smoking and Alcohol use were matched among the groups. However the present study had only 8 (5.23%) among the diabetic group and 15 (9.8%) among the control group as current alcohol users**.** Majority were non-users of Alcohol (never consumed alcohol) [(140(91.50%) among cases and 130(84.97%) among the non-diabetic controls (p = 0.20)]

Socioeconomic background was assessed based on the assessment done at presentation. There were 93(61%) from the APL

category and 60(39%) from the BPL category in the controls as against 143 (93%) from the APL and 10 (7%) from the BPL categories in the diabetic patients (p = 0.00).So definitely the diabetic group belonged to the moderately higher socio-economic group than the non-diabetic age and gender matched controls. None of the cases or controls was from the extremes of socio-economic status but belonged to a moderate income and with comparable access to amenities of daily living.

Achievable reductions in the risk of NIDDM by favorably altering the modifiable determinants of NIDDM were estimated to be 50%-75% for obesity and 30%-50% for physical activity[131]. In the present study physical activity and the hours of TV viewing were taken to compare the life style as a whole. Among the controls 76(49.67%) were physically inactive and 77(50.33%) active and from subjects 121(79.08%) were inactive and 32(20.92%) active (p = 0.00). Among the controls 47(30.72%) did not watch TV at all and 106(69.28%) used to watch TV for some hours of the day. Among diabetics 21(13.73%) did not watch TV at all and 132(86.27%) used to watch TV for some hours of the day (p = 0.00).The habits were followed on individual basis and was not modified by any interventions other than the overall regular advices given on diet and life-style changes. Physical inactivity and hours of Television viewing were higher in the diabetic group compared to non diabetic group. This highlighted the effect of lifestyle especially physical inactivity which plays a major role in disease predisposition especially in an ethnically predisposed group as in Indians and there is adequate scope for intervention.

In their study by K. Waller et al showed Leisure-time physical activity protects from type 2 diabetes after taking familial and genetic effects into account[132]. It was a 28 year follow up study in twins. Prospective observational studies consistently show a markedly reduced risk for type 2 diabetes among physically active or fit individuals as compared with their inactive or unfit counterparts. In the Nurses' Health Study, moderate-intensity exercise and more vigorous activity resulted in comparable reductions in diabetes incidence, given equivalent total exercise energy expenditures[133]. In the Women's Health Study, participants who reported walking 2 to 3 hours/week were 34% less likely to develop diabetes over a 7-year follow-up than those who reported not walking[134]. In the Iowa Women's Health Study, which tracked >34 000 participants aged 55 to 69 years for 12 years, women engaging in moderate-intensity exercise at least once/week, 2 to 4 times/week, and >4 times/week were 10%, 14%, and 27% less likely, respectively, to develop diabetes than women engaging in such exercise less than once/week[135]. In a cohort of 4369 middle-aged Finnish women and men followed for 9.4 years, individuals who walked or cycled to work for at least 30 minutes/day experienced a 36% reduction in risk of diabetes compared with their peers who did not engage in these activities[136]. All of these estimates reflect adjustment for the effects of BMI and potential confounders.

A detailed diet history was taken in both the subjects and controls based on a three days dietary re-call method and were calculated by a qualified dietician. Despite the public health significance

of type 2 diabetes, relatively little is understood about the role of diet in the development of this disease. Epidemiologic studies and controlled clinical trials consistently have demonstrated cardio-protective benefits of dietary patterns high in vegetables, fruits, legumes, whole grains, fiber, fish, lean meats and poultry, and low-fat dairy products.[137],[138]. In a prospective cohort study of 35988 older Iowa women initially free of diabetes, during 6 y of follow-up, 1141 incident cases of diabetes were reported. These data supported a protective role for grains (particularly whole grains), cereal fiber, and dietary magnesium in the development of diabetes in older women[139]. In the present study, groups were comparable based on age, gender, religion and in the habits of smoking and alcoholism. But the groups were not very closely comparable on the economic background.

Among the diabetic patients 150(98.04%) were non-vegetarians (omnivores) and 3(1.6%) were vegetarians as against 148(96.73%) and 5(3.27%) among controls (p = 0.47), the difference was not statistically significant. An enquiry was made into the cooking oil used but the use was not consistent and the oil currently in use only could be documented.

Among the diabetic subjects mean caloric intake was 1285.96±222.35 and among the controls it was 1166.66±266.3 (p = 0.00). Mean carbohydrate consumed among subjects was 259.00±54.84 and among control was 250.92±57.32 (p = 0.21). Mean Protein consumption among subjects was 46.21±17.15 and among control was 42.10±11.61 (p = 0.01). Mean Fat consumption among

subjects was 23.36 ± 6.35 and among control was 20.412± 6.94 (p = 0.00). . Mean calorie, carbohydrate, protein and fat intakes were higher in the diabetic group. In the study on diet of second-generation Japanese-American men with and without non-insulin-dependent diabetes Christine H Tsunehara et al showed that Kilocalorie intake was very similar for the three diagnostic groups (NGT, IGT & DM). However, the proportions of protein, fat, and carbohydrate calories differed significantly among the groups. Pair-wise tests indicated that the DM men ate significantly higher proportions of protein (P < 0.001) and fat (P < 0.05) calories and a lower proportion of carbohydrate calories (P < 0.0 1) than both the NGT and IGT men. The NGT and lGT men did not differ significantly from each other in these proportional intakes nor in any of the other nutrient variables[140]. Abhimanyu Garg et al in their study have shown that in NIDDM patients, high-carbohydrate diets compared with high—monounsaturated-fat diets caused persistent deterioration of glycemic control and accentuation of hyperinsulinemia, as well as increased plasma triglyceride and very-low-density lipoprotein cholesterol levels, which may not be desirable[141].

Physical characteristics: The increase in body mass index and waist circumference was expected in the diabetes group since obesity is a known risk factor of diabetes.

Body Mass Index and waist circumference were studied among subjects and the controls. The mean BMI was high in the diabetic group compared to controls ((p = 0.00).It was high among females than

males in the diabetic group (p = 0.009) and also in the analysis between diabetic females to control group females (p=0.013).

Of 5 lifestyle variables—obesity, physical inactivity, poor diet, current smoking, and alcohol abstinence—examined in the Nurses' Health Study, excess body weight was by far the most important predictor of the onset of type 2 diabetes[142]. The risk of developing diabetes over 16 years of follow-up was nearly 40-fold higher for women with BMI ≥35 and 20-fold higher for women with BMI 30.0 to 34.9, as compared with women with BMI ≤23.

Waist circumference: Among the diabetic patients mean waist circumference was 92.07±8.997. Among the controls it was 87.73 ± 8.76 (p = 0.00). Among diabetic patients mean waist circumference of males was 89.71±7.88 and of females was 95.1±9.48 (p = 0.009) and among controls mean waist circumference of males was 87.41±7.87 and of females was 88.14±9.84 (p = 0.61). Among diabetic patients mean waist circumference of females was higher than males and this was true on comparing females with and without diabetes. Based on waist circumference groups were divided into normal and abnormal. In males ≥90 cm and in females ≥ 80 cm considered abnormal. Among controls 59 had normal and 94 had abnormal values and among patients 39 had normal and 114 had abnormal waist circumference. When both genders are included waist circumference was abnormal more in diabetic subjects than in controls. In an original article by Vijay K Panikar et al in an Inter-Generation Comparison of Type-2 Diabetes

in 73 Indian Families, comparison between diabetics and non diabetics in the 2nd generation showed that the incidence of metabolic syndrome as per ATPIII criteria was significantly higher among the diabetics at 62.63% as against 28.45% in the non diabetics. BMI, W/H ratio and lipid profile individually did not show any significant differences between the diabetics and non diabetics[143]

As hypertensives were not excluded, among controls hypertension was present in 18.95% among controls and 43.79% among subjects. Mean blood pressure was 133±17.09 mm of Hg and 82.67± 9.44 mm of Hg among the subjects. Among the controls it was 128±15.32 ($p = 0.01$) and 84.17±8.64 mm of Hg respectively ($p = 0.15$). In a tertiary care hospital-based study of conventional risk factors including lipid profile in proven coronary artery disease in the subgroup analysis of those with coronary artery disease, the commonest associated conventional risk factor in diabetics was hypertensionError: Reference source not found.

The subjects included 153 diabetics. Among diabetic patients 107 (69.93 %) gave a positive family history and 46(30.07%) did not give any family history of diabetes. The diabetic control was poor in the diabetic patients. Mean FBS was 158.59±66.54mg% and PPBS was 257.12± 99.50 mg%.HbA1c was less than 7 in all among controls 153(100%). Among diabetic subjects 54(35.29%) were under good control (HbA1c <7); 74 (48.37%) were under bad control (HbA1c 7 to 10) and 25 (16.34%) were having very poor control with an HbA1c more than 10.

Control of Diabetes:

Mean HbA1c among control group was 5.02±0.49 % (<7 % in control)..Among diabetic subjects 54 (35.29%) had HbA1c of 5.96±0.55%; 74(48.37%) had 8.26±0.87% and 25 (16.34%) had 11.64±1.48. The control of diabetes was not correlated with the duration of Diabetes.

Lipid Profile among the diabetic subjects and non diabetic controls:

Mean values of Total cholesterol, Low Density Lipoprotein cholesterol (LDL), Non High Density lipoprotein (Non HDL) and LDL/HDL were higher for control group. Serum Triglycerides were higher among subjects with diabetes along with low High Density lipoprotein (HDL). In a tertiary care hospital-based study of conventional risk factors including lipid profile in proven coronary artery disease, in the subgroup analysis of those with coronary artery disease, diabetics had significantly lower total cholesterol [174+/-41.1 mg/dl v. 180.4+/-42.4 mg/dl (p<0.001)] and low-density lipoprotein cholesterol levels [105.8+/-34 mg/dl v. 111.5+/-35.8 mg/dl (p<0.001)] than non-diabetics, whereas triglyceride and high-density lipoprotein cholesterol levels were not significantly different, triglycerides being equally high in both [186.2+/-95.5 mg/dl v. 192.5+/-95.2 mg/dl (p=ns)], and high-density lipoprotein equally low in both [30.9+/-9.3 mg/dl v. 30.5+/-9 mg/dl (p=ns)][144].

BMI, waist circumference and Lipid parameters:

Serum Triglyceride (TG) is associated with BMI among diabetes patients. Value of Triglycerides increased with increase in BMI ($r = 0.177$, $p = 0.029$). Among diabetic patients only TG was found to be correlated with HbA1c and BMI. After controlling the effect of BMI in Binary logistic regression, TG was associated only with HbA1c ($p = 0.016$). None of the lipids were associated with waist circumference or duration of Diabetes mellitus.

Among controls lipids were not correlated with HbA1c, BMI or waist circumference. In the study by A Chehreiet al in non-diabetic and normotensive people, WC and W/Ht were correlated with TC / HDL-C[145]. The present study did not show an association between waist circumference and lipid levels in the subjects and control group. It is suggested that the simultaneous interpretation of waist girth and fasting TG levels may contribute to a better identification of individuals characterized by the simultaneous presence of hyperinsulinemia, hyperapo B, and the small, dense LDL phenotype who are at increased risk of CHD. This “hypertriglyceridemic waist” concept may prove to be a helpful approach for the cost-effective screening of the population. In a study by Lemieux et al[146] it seems that apo B levels are very sensitive to an increase in waist girth resulting from an accumulation of visceral adipose tissue. Analyses on sensitivity and specificity revealed that 90 cm of waist circumference was the critical cutoff point in screening for the nontraditional lipid triad, which included elevated apo B concentrations. In the above study by Lemieux et al, all subjects were

sedentary but healthy nonsmoking volunteers and were not under treatment for CHD, diabetes, dyslipidemias, or endocrine disorders (matching the control group of present study).But in the present study among the diabetic group there was no statistically significant correlation between waist circumference and Apo B

In an epidemiological study by Gupta et al on Body-mass index, waist-size, waist-hip ratio and cardiovascular risk factors in urban Indian subjects showed a continuous positive relationship of all markers of obesity (body-mass index, waist size and waist hip ratio) with major coronary risk factors- hypertension, diabetes and metabolic syndrome while WHR also correlates with lipid abnormalities. With increasing BMI, waist-size and WHR, prevalence of hypertension, diabetes, and metabolic syndrome increased significantly (p for trend <0.05).WHR increase also correlated significantly with prevalence of high total and LDL cholesterol and triglycerides ($p < 0.05$)[147].

In a study which compared the value of body fat mass (%FM) to indirect measures of general (body mass index (BMI)) and central adiposity (waist circumference (WC); waist-to-height ratio (WC/ ht)) for the prediction of overweight- and obesity-related metabolic risk in a study population with a high prevalence of metabolic syndrome concluded that at the population level, measurement of body FM has no advantage over BMI and WC in the prediction of obesity-related metabolic risk[148].

Gender and lipid parameters:

Both among cases and controls, females have better values for TG, HDL and LDL (p = 0.036, 0.025, 0.014 and p = 0.00, 0.00, 0.00 resp.).

Gender is correlated with Triglyceride, HDL and VLDL. (p value <0.05). Males have got high values for Triglyceride and VLDL and low values for HDL.

In the study by Bosy-Westphal A etal when compared with BMI and WC, % fat mass showed weaker associations with metabolic risk factors, except for CRP and Systolic BP in men. In women, HDL-C and HOMA-IR showed the closest correlations with BMI. For all other risk factors, WC or WC/ht was the best predictors in both sexes. Differences in the strength of correlations between an obesity index and different risk factors exceeded the differences observed between all obesity indices within one risk factor. In stepwise multiple regression analyses, WC/Ht was the main predictor of metabolic risk in both sexes combinedError: Reference source not found.

In a study conducted in apparently healthy men and women, South Asian men had significantly higher values for total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), total cholesterol: high-density lipoprotein-cholesterol (HDL-C) and CRP, and significantly lower values of HDL-C. South Asian women had significantly higher values for TG, TC: HDL-C and CRP and significantly lower values of HDL-C, glucose, systolic BP and diastolic BP[149]. The relationship between BMI or WC and risk factors

was such that men and women of South Asian descent present with a more adverse risk profile than those of European descent at the same BMI and/or WC.

Lipid parameters and the control of diabetes:

In patients with uncontrolled type 2 diabetes mellitus and hyperinsulinemia, triglycerides are elevated for several reasons. (1) LPL is less effective in the insulin-resistant state. (2) Overproduction of VLDL by the liver is common in patients with diabetes who are often overweight. (3) Diabetes mellitus is one of the conditions that leads to incomplete metabolism of VLDL, causing increased remnant VLDL or IDL observed in dysbetalipoproteinemia. In the present study also Triglyceride is associated with control of diabetes among diabetes patients.

Value of Triglyceride increased with HbA1c and a significantly high value for Triglyceride is observed in the cases with poor diabetic control ($r = 0.233$, $p = 0.004$).But the Total Cholesterol, HDL, LDL and Non HDL Cholesterol are not associated with control of diabetes among diabetes patients.

Micro vascular complications:

Retinopathy:

Of the 153 diabetic patients 82(53.6%) had no retinopathy.43 (28.1%) had mild NPDR and 15(9.8%) had moderate NPDR 8(5.2%) had severe NPDR and 5(3.3%) had severe PDR. As the duration of Diabetes Mellitus increased, severity of retinopathy also

increased (correlation coefficient = 0.42, p = 0.00). Severity of retinopathy increased with urine albumin-creatinine ratio (correlation coefficient = 0.271, p = 0.001) which speaks for the diabetic nephropathy. Previous studies have shown that the presence of diabetic retinopathy strongly suggests that diabetic nephropathy is the cause of persistent macroalbuminuria in non-insulin dependent diabetic patients[150]. In the present study the severity of retinopathy was not associated with the control of diabetes or with BMI or waist circumference. Severity of retinopathy was not associated with total cholesterol, HDL, LDL and non HDL Cholesterol. Severity of retinopathy increased with TG (correlation coefficient = 0.241(p = 0.00). In binary logistic regression after adjusting the effect of duration of Diabetes mellitus and urine albumin creatinine ratio only Triglyceride was found to be associated with retinopathy (exp (β) = .210, p = 0.012) or Serum Triglyceride is found to be the only risk factor for retinopathy in the present study. Rema et al also in her study showed a significant association of serum triglycerides with DR and LDL-cholesterol with DME.[151] In the study by Pradeepa R et al DR was associated with nephropathy after adjusting for age, gender, hemoglobin A1c, systolic blood pressure, serum triglycerides, and duration of diabetes (OR = 2.140, 95% confidence interval = 1.261-3.632, P = 0.005)[152].

Diabetic Neuropathy:

Of the 153 patients, neuropathy was present in 60(39.2%) patients and there were no features of neuropathy in

93(60.8%). This is the prevalence in the hospital based population. The risk factors most consistently associated with polyneuropathy in type 2 diabetic patients at the population level were increasing age, duration of diabetes, height, and poor glycemic control evidenced by A1C as well as presence of retinopathy and nephropathy.[153],[154],[155] In the present study neuropathy was correlated with Post- prandial blood sugar (Coefficient = 0.334, p = 0.00). But the neuropathy was not associated with the control of diabetes (based on HbA1c). The chance for neuropathy increased with increase in duration of Diabetes mellitus (Correlation coefficient = 0.359, p = 0.00). The chance for neuropathy also increased with urine albumin creatinine ratio (Correlation coefficient = 0.24, p = 0.04). It was not found to be associated with the gender. Neuropathy was not found to be associated with total cholesterol, Serum triglycerides, LDL, HDL and non HDL Cholesterol. The neuropathy was assessed with clinical examination as well with minimum methods including testing for sensations, Vibration perception using 128 Hz tuning fork, monofilament as well as ankle jerks. Hence cases having early or minimal neuropathy may be missed in our study.

In the present study neuropathy was not associated with BMI or waist circumference. In an original article by Dan Ziegler et al in Diabetes care in the diabetic group polyneuropathy was associated with age, waist circumference, and peripheral arterial disease (PAD) (all $P < 0.05$)[156].In another study older age, poor glycemic control, longer duration of diabetes, elevated cholesterol levels, current smoking, obesity defined by body mass index, large waist

circumference, elevated triglycerides and hypertension but not gender, were significant risk factors for diabetic neuropathy in both the univariate and multivariate analysis ($p < 0.05$)[157].

Diabetic nephropathy:

The parameter used was urine albumin creatinine ratio.71 (46.4%) were having normoalbuminuria and 60(39.2%) had microalbuminuria and 22(14.4%) had macroalbuminuria. As expected, in this study also the Urine albumin creatinine ratio increased with increase in duration of Diabetes mellitus (correlation coefficient = 0.310, $p = 0.00$).Diabetic nephropathy was not associated with gender, waist circumference or BMI in this study. In this group of patients Diabetic nephropathy was not associated with control of diabetes.Lipid parameters were not correlated with diabetic nephropathy. In the present study an observation which could not be explained or expected was diabetic nephropathy showed an inverse correlation with HDL Cholesterol.

Clinical study on the correlation between hyperlipidemia and renal dysfunction in patients with diabetic nephropathy is difficult due to the complex interrelation between serum lipid, blood glucose, and proteinuria. In studies on patients with type 2 diabetes, baseline level of serum cholesterol was also found to be the independent risk factor for the development of diabetic nephropathy[158],[159]. However, conflicting results were found between the effects of serum lipid on the progression of renal function in type 2 diabetes[160],[161].

In a prospective, long-term follow-up study conducted on 574 patients, aged 40 to 60 years, with recent onset of type 2 diabetes mellitus; levels of total cholesterol, mean blood pressure, and hemoglobin A1c were the main factors associated with the decrease in renal function and with the increase in albuminuria. The patients who progressed to nephropathy had significantly higher initial plasma values of hemoglobinA1c, total cholesterol, low-density lipoprotein cholesterol, and triglycerides and lower values of HDL than those who maintained normal UAE. Also, the initial mean blood pressure was significantly higher in the patients who developed nephropathy[162]. Their data indicated that the progression of diabetic nephropathy is truly multifactorial. The list of risk factors included (in a declining order of significance) elevated levels of plasma total cholesterol, small increments in mean blood pressure, hyperglycemia, high BMI, low levels of HDL, high levels of low-density lipoprotein, cigarette smoking, a low socioeconomic class, and male sex.

In another study, the trends of increased serum cholesterol and decreased high-density lipoprotein in diabetics and diabetic nephropathy patients were noted as compared with controls but they were not significant as expected. The low-density lipoprotein cholesterol was significantly higher in diabetics when compared with diabetic nephropathy and control subjects.

Chinese patients with type 2 diabetes mellitus and normoalbuminuria during a 4(1/2)-year period, it was shown that

diabetic nephropathy can be delayed by tight simultaneous achievement of multiple ADA-recommended targets (HbA(1c)), less than 7%; systolic blood pressure, less than 130 mm Hg; diastolic blood pressure, less than 80 mm Hg; low-density lipoprotein cholesterol, less than 100 mg/dL; triglycerides, less than 150 mg/dL; and high-density lipoprotein cholesterol, greater than 40 mg/dL for men and greater than 50 mg/dL for women). This multifactorial intervention should be started in patients with diabetes and normoalbuminuria[163].

The study by Tsutomu Hirano showed that Triglyceride (TG) levels were significantly increased in type 2 diabetic patients with microalbuminuria and overt proteinuria. Glycemic control or insulin resistance were not associated with TG levels[**164**].

Macrovascular complications:

Could not be assessed in detail as no investigations other than ECG could be done in all the cases. As the patients on Statins were excluded, the majority of the cases did not show features of CAD from history or from ECG. Of the 153 diabetics gave history of CAD in 12(7.84%) and 141(92.16%) gave no history of CAD. Of the 153 patients 133(86.93%) were having normal ECG and 20(13.07%) with abnormal ECG.The ECG changes were ST -T changes only.

The mixed dyslipidemia (or "lipid quartet"): Hypertriglyceridemia, low high-density lipoprotein cholesterol levels, a

preponderance of small, dense low-density lipoprotein particles and an accumulation of cholesterol-rich remnant particles (e.g. high levels of apolipoprotein B)--emerged as the greatest "competitor" of low-density lipoprotein-cholesterol among lipid risk factors for cardiovascular disease.A very high prevalence rates of coronary artery disease have been reported among Indians.

In a study by Mohan.V et al multivariate regression analysis revealed age (odds ratio 1.06; $p < 0.001$), male sex (odds ratio 1.7; $p < 0.001$), hypercholesterolemia (odds ratio 1.26; $p = 0.07$) and high low-density lipoprotein levels (odds ratio 1.22; $p = 0.043$) to be strongly associated with coronary artery disease. Among South Indian type 2 diabetic subjects, serum isolated hypercholesterolemia and high low-density lipoprotein cholesterol but not isolated hypertriglyceridemia appear to be associated with coronary artery disease.[165]

Lp (a) was abnormal in 74% and normal in 26% among diabetic subjects but however the clinical implication of this finding is not known. Some reports on serum Lp (a) levels in subjects with type 2 DM show that Lp (a) levels are higher in this group of patients compared with non diabetic healthy controls[166], [167]. Multiple studies have demonstrated that elevated serum lipoprotein (a) [Lp(a)] levels are independent predictors for coronary artery disease (CAD) in subjects without diabetes mellitus (DM). However, their contribution in patients with DM is controversial and still requires clarification. J. Pedreño et al in their study concluded that serum Lp(a) levels are increased in patients with angiographically documented CAD, but there

were no significant differences between diabetic and non-diabetic patients, which indicates that elevated Lp(a) levels are specifically associated with CAD but not with type-2 DM[168].

In another study the authors concluded that Lp(a) levels are increased in type 2 diabetic patients. The elevated Lp(a) levels do not reflect the glycemic status and are also independent of increase in LDL:HDL ratio suggesting different metabolic pathways and the genetic connection for LDL and Lp(a)[169].

In the present study Type 2 diabetic patients with nephropathy had significantly higher Lp(a) levels compared to those without nephropathy ($p = 0.03$). The Lp(a) levels were similar in patients with or without retinopathy and neuropathy. There appears to be no association between Lp(a) and retinopathy or neuropathy.The similar observations were made by Manoj Lakhotia et al in their study also[170]. H Kapelrud et al in their study showed that serum concentrations of Lp(a) lipoprotein were twice as high in insulin dependent diabetic patients with microalbuminuria as in those without microalbuminuria[171]. Increased concentrations of Lp(a) lipoprotein might partly explain the increased morbidity and mortality from cardiovascular disease observed among patients with diabetic nephropathy.

Apo B:

Heterogeneity of LDL particle cholesterol content is increased in type 2 diabetes because insulin resistance drives VLDL cholesterol production, leading to depletion of LDL cholesterol via the action of cholesterol ester transfer protein (CETP)[172]. CETP exchanges triglycerides for cholesterol on LDL particles, which are remodeled by lipases to produce cholesterol-poor, small, dense LDL particlesError: Reference source not found,[173]. Because there is one apoB per LDL particle, regardless of density, apo B detects the presence of these atherogenic particles, in contrast to LDL cholesterol, and thus may be better suited to guide lipid-lowering therapy, particularly in insulin resistance and type 2 diabetes. Patients with type 2 diabetes tend to have increased circulating LDL particles but normal concentrations of LDL cholesterol because their particles have low cholesterol content[174]. Despite elevated triglycerides and low HDL cholesterol, this normal LDL cholesterol has led to under appreciation of the risk associated with dyslipidemia in diabetes. Indeed, in type 2 diabetic subjects, Apo B and non-HDL cholesterol were favored over LDL cholesterol as predictors of CHD risk in the Health Professional's Follow-Up Study[175].

Non HDL cholesterol is considered as a surrogate marker of Apo B which can be easily derived in clinical practice and this is a cheaper test compared to Apo B. In this study also there was a significant correlation between Apo B & non HDL. Value of Apo B increased with increase in non HDL ($r = 0.412402$, $p = 0.00$). An important question that often arises is the benefit of ordering more advanced lipoprotein profiles. The main reason for the quandary, as

pointed out in the article by Lau and Smith, is that calculated low-density lipoprotein (LDL) cholesterol, measured by standard technologies, or non–high-density lipoprotein (non-HDL) cholesterol, are less predictive of ischemic cardiovascular risk than are Apo-lipoprotein B (Apo B) and nuclear magnetic resonance (NMR)–measured LDL particles in numerous studies. This is especially true in the presence of high triglycerides, or low-HDL cholesterol. Although Apo B levels and the number of NMR-measured LDL particles may be more predictive, no clinical trials comparing the use of these goals versus LDL cholesterol or non-HDL cholesterol goals have been performed. For those who can interpret the results, their use may be justified occasionally to confirm lipid goal attainment in those with mixed dyslipidemias and particularly in patients already at standard lipid goals in the presence of progressive coronary heart disease.Error: Reference source not found, Error: Reference source not found

In the present study, among diabetics there was no statistically significant correlation between waist circumference and Apo B and there was no association between Apo B and microvascular complications (nephropathy, retinopathy or neuropathy). I S Okosun et al in their article showed that after adjusting for age and triglyceride or insulin, waist circumference was also positively correlated with CVD risk factors including, ApoB, LDL-C, plasma glucose and fasting insulin, and inversely correlated with ApoAI and HDL-C in Blacks and Whites ($P<0.05$)[176].

C - reactive protein (CRP):

CRP may be useful in detecting atherosclerotic process and providing important prognostic information about patients with asymptomatic heart disease, unstable angina and myocardial infarction. CRP concentration in serum rise long before traditional symptoms of heart and vascular diseases are noticed. Support for a role of CRP in the pathogenesis of atherosclerosis comes largely from epidemiologic studies that have consistently observed an association between elevated plasma CRP levels and cardiovascular events[177],[178],[179].The statistical strength of such associations is at least as robust as that of established risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia Error: Reference source not found.In the study by Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi et al concluded that the serum CRP combined with the blood pressure, blood lipids, body weight and insulin indicators has important clinical significance for early diagnosis, prevention, treatment and prognosis of T2DM complication with vascular lesions[180]. In the present study among diabetic subjects 16 (10.5%) had abnormal CRP and 137 (89.5%) had normal CRP. Anubha Mahajan et al in urban north Indians in their study showed that median hs CRP levels were significantly higher in both diabetic men and women as compared to their non-diabetic counterparts (P_0.0001) Error: Reference source not found.

C-reactive protein, a marker of chronic, low-grade inflammation, is strongly associated with current central adiposity, and has been linked

to elevated risk of cardiovascular disease. But in the present study among diabetics, CRP was not associated with waist circumference (p =0.65) or physical activity (p =0.871). Rutherford JN et al also shown that waist circumference was a strong predictor of elevated CRP[181]. They also stated that women who reduced their waist circumference between 1994 and 2005 had greatly reduced risk (6.2%), suggesting that even long-term inflammatory burden can be reversed by weight loss. Fatma G. Huffman et al in their study on Waist Circumference and BMI in Relation to Serum High Sensitivity C-Reactive Protein (hs-CRP) in Cuban Americans with and without Type 2 Diabetes concluded that Hs-CRP did not vary by the diabetes status, but was strongly associated with both waist circumference and BMI[182]. Mean VLDL value was significantly higher in patients with abnormal CRP (p = 0.029). Other lipids and CRP were not associated (all p > 0.05). Lp (a), Apo B and HbA1c were not associated with CRP (all p > 0.05). Xiao-Ying Li et al suggested that in Chinese, plasma glucose, especially 2-h postload, is associated with biological markers of cardiovascular disease, such as serum CRP concentration and microalbuminuria[183]. But in the present study CRP was not associated with Neuropathy (p = 0.13), Retinopathy (p = 0.56) or Nephropathy (p = 0.16).

CONCLUSIONS

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- **Physical inactivity and hours of Television viewing were higher in the diabetic group compared to non diabetic group.**

- **Mean calorie, carbohydrate, protein and fat intakes were higher in the diabetic group.**

- **Mean BMI was higher in the diabetic group.**

- **Mean BMI and waist circumference was higher in females in the diabetic group compared to males. More over females in the diabetic group had higher BMI and waist circumference compared to the females in the non diabetic group.**

- **The need for a healthy lifestyle including diet, exercise and healthy habits should be stressed to all families, especially those who are a high risk for cardiovascular disease.**

- **Mean values of Total cholesterol, Low Density Lipoprotein cholesterol (LDL), Non High Density lipoprotein (Non HDL) and LDL/HDL were higher for control group. Serum Triglycerides were higher among subjects with diabetes along with low High Density lipoprotein (HDL). Gender is correlated with Triglyceride, HDL and VLDL. (p value <0.05). Males have got high values for Triglyceride and VLDL and low values for HDL**

- **TG is associated with BMI among diabetes patients. Value of TG increased with increase in BMI.**

- **A significantly high value in TG is observed in very poor control of diabetes. Value of Triglyceride increased with HbA1c and a significantly high value for Triglyceride is observed in the cases with poor diabetic control.**

- **There was a significant correlation between Apo B & non HDL cholesterol. Non HDL cholesterol is considered as a surrogate marker of Apo B which can be easily derived in clinical practice and this is a cheaper test compared to Apo B. Hence in resource poor situations where we cannot go for direct LDL cholesterol measurement especially in the context of high serum Triglycerides we can go for non HDL cholesterol**

estimation. This is especially of use in patients with mixed dyslipidemias.

- **Severity of retinopathy increased with increase in Serum TG.**

- **Neuropathy was correlated with Post- prandial blood sugar, duration of diabetes and urine albumin creatinine ratio. Neuropathy was not found to be associated with total cholesterol, Serum triglycerides, LDL, HDL and non HDL Cholesterol.**

- **Lipid parameters were not correlated with diabetic nephropathy**

LIMITATIONS OF THE STUDY

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Included self-reporting of eating patterns.

Duration of diabetes was assessed from the history and records available with the patient. As the patients on Statins were excluded the study may not be the true representation though many of

our patients are not put on statins before a CAD event happened. So the patients with CAD included those with not clinically detected CADs.

This is purely an observational study and so the benefits of interventions could not be assessed.

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