A STUDY ON ASSOCIATION BETWEEN ULTRASONOGRAPHIC VISCERAL FAT THICKNESS AND CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"A STUDY ON ASSOCIATION BETWEEN ULTRASONOGRAPHIC VISCERAL FAT THICKNESS AND CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS"** is the bonafide work of **Dr G.PREMKUMAR ,** in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015.**

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DECLARATION

I, **Dr.G.PREMKUMAR**, solemnly declare that this dissertation titled **"A STUDY ON ASSOCIATION BETWEEN ULTRASONOGRAPHIC VISCERAL FAT THICKNESS AND CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS"** is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital , Madurai, under the guidance of **Prof.Dr.M.Natarajan M.D.**, Department Of General Medicine, Government Rajaji Hospital, Madurai Medical College, Madurai.

. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2015.**

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ABSTRACT

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin.

Currently the number of cases of diabetes worldwide is estimated to be around 150 million. India leads then world with the largest number of diabetic subjects earning the dubious distinction of being the “diabetic capital of the world”.

Obesity has induced many public health problems related to metabolic diseases, including glucose intolerance, hypertension, hyperinsulinemia, dyslipidemia and atherosclerosis. Moreover these complexes are known to increase the risk of cardiovascular diseases. In particular , the accumulation of adipose tissue predominantly in visceral cavity plays a major role in development of metabolic syndrome and cardiovascular disease.

Therefore estimating the visceral fat accumulation is important in terms of evaluating the patients with high risk of cardiovascular disease. Generally computerized tomography (CT) is recognized as the standard method of estimating the visceral fat. But, exposure to radiation, high cost of CT, low availability prevents the wide use of CT, in clinical and epidemiological studies.

Therefore alternative methods which are simple and non invasive have been used in assessing the visceral fat thickness. Some of the alternative methods are, Body mass Index, waist hip ratio, dual energy X-ray absorptiometry and ultrasonography.

Ultrasonography is a reliable and convenient method of quantifying the amount of visceral fat and the diverse USG values have been reported to be useful.

AIMS AND OBJECTIVES

1) To assess the independent relationship between visceral fat thickness and cardiovascular risk in type 2 diabetes patients.
2) To assess whether the above parameters helps to identify the high risk group for cardiovascular diseases.

MATERIALS AND METHODS

PLACE OF THE STUDY

The study was conducted at Government Rajaji Hospital, Madurai Medical college, Madurai.

STUDY DESIGN

Observational type of study

STUDY POPULATION

50 patients who are known case of type 2 diabetes mellitus were selected from Department of Diabetology , Government Rajaji Hospital , Madurai

METHODOLOGY

50 patients who are known case of type 2 diabetes mellitus were analysed for this study. A thorough clinical evaluation was made and detailed history, blood pressure, height, weight, waist and hip circumference were taken .

a) Fasting lipid profile was done by enzymatic methods like zaks method, and spot urine sample for microalbuminuria were taken.
b) Visceral fat thickness was measured in fasting and in full expiration. The distance between the internal surface of rectus abdominis muscle and the posterior wall of aorta is measured.

RESULTS

- Out of the 50 subjects, the visceral fat thickness was measured and patient were categorized into VFT < 5.5, 5.6 – 6.5 , 6.6 – 7.5 and > 7.5. The mean visceral fat was 6.08 among the 50 subjects.
- Among the 50 diabetic subjects (25 males and 25 females) attending the department of Diabetology in Government Rajaji Hospital, Madurai, with

BMI of > 25, increased visceral fat thickness was found in 12 males and 15 females.

- Among the 50 patients, all the patients who had increased visceral fat thickness had an increased triglyceride level and increased LDL level. Therefore there is a strong positive correlation between increased visceral fat thickness and LDL, TGL levels.
- Similarly , 13 patients had microalbuminuria, out of which more than 90% of patients had a Visceral fat thickness of more than 7.5 . They also had a increased triglyceride level and LDL levels.
- There was no significant correlation between visceral fat thickness and total cholesterol levels. Similarly even HDL didn't show show any strong correlation with visceral fat thickness levels.

CONCLUSION

Eventhough there are many parameters to assess the cardiovascular risk like BMI, WHR, etc, measuring the visceral fat thickness is a reliable indicator to assess the cardiovascular risk.

This study which was conducted in Government Rajaji Hospital among 50 type 2 diabetic subjects, showed a strong positive correlation between

visceral fat thickness with LDL and triglycerides levels. Similarly 13 patients had microalbuminuria whose visceral fat thickness was > 7.5.

Because of presence of microalbuminuia, there is evidence of subclinical endothelial injury in this patients who are more prone for cardiovascular risk in later part of their life. These patients also had a elevated LDL and TGL which supports the point on cardiovascular risk.

Eventhough CT was considered to be gold standard in measuring the visceral fat thickness, there are many studies which showed ultrasonographic measurement of visceral fat was equally efficient in assessing the cardiovascular risk. Moreover due to radiation exposure and cost of CT, this study was conducted with ultrsonographic measurement alone.

Therefore, it is concluded that , visceral adiposity has a strong positive correlation with lipid profile and microalbuminuria, by which it is easy to predict the diabetics who are more prone for cardiovascular risk .

KEY WORDS : diabetes mellitus, visceral fat thickness, microalbuminuria, BMI, triglycerides and LDL.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin.

Currently the number of cases of diabetes worldwide is estimated to be around 150 million. India leads then world with the largest number of diabetic subjects earning the dubious distinction of being the “diabetic capital of the world”. The international diabetes Federation estimates the total number of diabetic subjects to be around 40.9 million in India and this is further to be set to rise to 69.9 million by the year 2025.

Obesity has induced many public health problems related to metabolic diseases, including glucose intolerance, hypertension, hyperinsulinemia, dyslipidemia and atherosclerosis. Moreover these complexes are known to increase the risk of cardiovascular diseases. In particular , the accumulation of adipose tissue predominantly in visceral cavity plays a major role in development of metabolic syndrome and cardiovascular disease.

Therefore estimating the visceral fat accumulation is important in terms of evaluating the patients with high risk of cardiovascular disease.

Generally computerized tomography (CT) is recognized as the standard method of estimating the visceral fat. But, exposure to radiation, high cost of CT, low availability prevents the wide use of CT , in clinical and epidemiological studies.

Therefore alternative methods which are simple and non invasive have been used in assessing the visceral fat thickness. Some of the alternative methods are, Body mass Index , waist hip ratio, dual energy X-ray absorptiometry and ultrasonography.

Ultrasonography is a reliable and convenient method of quantifying the amount of visceral fat and the diverse USG values have been reported to be useful.

AIMS AND OBJECTIVES

1) TO ASSESS THE INDEPENDENT RELATIONSHIP BETWEEN VISCERAL FAT THICKNESS AND CARDIOVASCULAR RISK IN TYPE 2 DIABETES PATIENTS.
2) TO ASSESS WHETHER THE ABOVE PARAMETERS HELPS TO IDENTIFY THE HIGH RISK GROUP FOR CARDIOVASCULAR DISEASES.

REVIEW OF LITERATURE

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia . Several distinct types of Diabetes mellitus exist and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of DM, factors contributing to hyperglycemia include reduced insulin secretion , decreased glucose utilization and increased glucose production.

CLASSIFICATION OF DIABETES

1) Type I diabetes (beta cell destruction, leading to absolute insulin deficiency)
    a) Immune mediated
    b) Idiopathic
2) Type 2 diabetes (range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3) Other specific types types of diabetes
    a) Genetic defects of beta cell function characterized by mutations in
        - Hepatocyte nuclear transcription factor(HNF) 4 alpha (MODY 1)

- Glucokinase (MODY 2)
- HNF 1 alpha
- Insulin promoter factor 1(MODY 4)
- HNF 1 beta (MODY 5)
- Neuro D1 (MODY 6)
- Mitochondrial DNA
- Subunits of ATP sensitive potassium channels
- Proinsulin or insulin conversion

b) Genetic defects in insulin action
   - Type A insulin resistance
   - Leprachaunism
   - Rabson –Mendenhall syndrome
   - Lipodystrophy syndromes

c) Diseases of exocrine pancreas - pancreatitis , pancreatectomy , neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

d) Endocrinopathies- acromegaly, cushings dyndrome, glucaganoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

e) Drug or chemical induced – glucocorticoids, pentamidine, nicotinic acid, diazoxide, adrenergic agonists, thiazides, hydantoins.

f) Uncommon forms of immune medicated diabetes – “stiff person” syndrome, anti insulin receptor antibodies.

g) Other genetic syndromes sometimes associated with diabetes – Downs syndrome, Klinefelters syndrome, Turners syndrome, Wolframs syndrome, Friedreich’s ataxia, Huntington’s chorea, Laurence Moon- Biedl syndrome , myotonic dystrophy , porphyria, Prader Willi syndrome.

h) Infections – congenital rubella , CMV, coxsackie

i) Gestational diabetes mellitus.

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS

1. Symptoms of diabetes plus casual plasma glucose concentration - 200 mg/dl (11.1 mmol/L)

l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

2. FPG > 126 mg/dl (7.0 mmol/l).

Fasting is defined as no caloric intake for at least 8 h.

OR

A1C > 6.5%.

OR

3. 2-hr postload glucose > 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

1) Family history of diabetes (i.e., parent or sibling with type 2 diabettes)
2) Obesity (BMI > 25kg/m2)
3) Habitual physical inactivity
4) Race / ethnicity (eg : African American, Latino , Native American , Asian American, Pacific Islander)
5) Previously identified IFG or IGT or and A1c of 5.7 – 6.4 %
6) History of GDM or delivery of a baby of >4 kg
7) HDL cholesterol < 35 mg/dL(0.90mmol/L) and/or a triglyceride >250mg/Dl (2.82mmol/L)
8) Polycystic ovarian syndrome or acanthosis nigricans
9) History of vascular disease.

MODE OF PRESENTATION OF DIABETES MELLITUS

Diabetes can be detected in one of the following ways :

Some patients are found to have excess of glucose or sugar in urine incidentally on routine check up without any complaints or physical signs.

Some patients are found to have diabetes while investigating for an associated complaint like, ischemic heart disease, hypertension, eye diseases, kidney disease , non healing foot ulcers etc..

Diabetes can manifest as an acute illness - ketoacidosis with an acute infection or even without evidence of any cause. Pain abdomen and vomiting may be the presenting complaints in some patients. This most commonly occurs in juvenile onset diabetes mellitus (IDDM)

Some of the patients often present with classical symptoms of diabetes. E.g. , excessive thirst, frequent micturition , increased appetite , weight loss, severe weakness, repeated infections, intching in genitals, diminished vision, numbness in limbs and occasionally impotence

COMPLICATIONS OF DIABETES MELLITUS

ACUTE METABOLIC COMPLICATIONS

The two main metabolic complications of diabetes are diabetic ketoacidosis and hyperosmolar state. Initially DKA was considered as the hallmark of Type I DM, but it also in individuals who lack immunologic features of type 1 Diabetes, who can subsequently treated with oral glucose lowering agents. Hyperosmolar state is most frequently seen in type 2 diabetes. Both are anyway associated with relative insulin insulin deficiency, volume depletion and acid base abnormalities.

CHRONIC COMPLICATIONS OF DIABETES

1) Microvascular
    a) Eye disease - retinopathy (proliferative and non proliferative)

       Macular edema

    b) Neuropathy - sensory and motor (mono and polyneuropathy)

       Autonomic

    c) Nephropathy
2) Macrovascular
    a) Coronary artery disease
    b) Peripheral arterial disease
    c) Cerebrovascular disease
3) Others
    a) Gastrointestinal (gastroparesis, diarrhea)
    b) Genitor urinary (uropathy / sexual dysfunction)
    c) Infections
    d) Dermatological
    e) Glaucoma
    f) Cataracts
    g) Periodontal diseases

h) Hearing loss.

DIABETIC RETINOPATHY

Diabetic retinopathy is classified into proliferative diabetic retinopathy (PDR) and non proliferative diabetic retinopathy(NPDR). Hemorrhages or microaneurysms, cotton wool spots , hard exudates , intra retinal microvascular abnormalities , venous caliber abnormalities like venous loops, venous bleeding and venous tortuosity are some of the findings associated with early and progressive diabetic retinopathy. Micro aneurysms and saccular outpouchings of the capillary walls that can leak fluid and results in intra retinal edema and hemorrhages. These intra retinal hemorrhages are flame shaped or dot blot like appearance , reflecting the architecture of the layer of the retina in which they occur. Flame shaped hemorrhages occur in inner retina closer to the vitreous and dot blot hemorrhages occur deep in the retina. Intra retinal microvascular abnormalities are either new vessel growth within retinal tissue or shunt vessels through areas of poor vascular perfusion.

The micro infarcts in the nerve fibre layer of retina are called cotton wool spots. Retinal detachment can occur due to neovascularisation with fibrous tissue contraction that can distort retina and lead to traction.

However the most common cause of blindness in diabetes is macular edema. Especially macular edema involving the fovea or non perfusion of the capillaries in the central macula is responsible for loss of vision. Macular edema more likely to occur in patients withT2DM which represents 90% to 95% of diabetic population.

DIABETIC NEUROPATHY

Diabetic neuropathy has a number of clinical syndromes with subclinical or clinical manifestations depending upon the class of nerve fibres involved , it can manifest as polyneuropathy, mononeuropathy or autonomic neuropathy.

Distal symmetrical polyneuropathy is the most common form of diabetic neuropathy, where patients frequently present with distal sensory loss. Hyperesthesia, paresthesia and dysesthesia can also occur. Symptoms may include a sensation of numbness , tingling, sharpness, that begins in feet and spreads proximally. As diabetes progresses , the pain subsides and eventually disappears , but a sensory deficit in lower limbs persists.

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots, which can be accompanied by motor weakness. There can be severe pain in hip and thigh due to involvement of

lumbar plexus . Fortunately this condition is usually self limited and resolves in 6 – 12 months .

Mononeuropathy is less common than polyneuropathy in diabetes which presents with pain and motor weakness in distribution of single nerve. Third cranial nerve is more commonly involved and heralded by diplopia. Sometimes 4^{th} , 6^{th} and 7^{th} cranial nerves are also involved. Peripheral mononeuropathies can also occur.

Autonomic neuropathy in diabetes can involve multiple systems like cardiovascular, gastrointestinal, genito urinary etc. Patient can have resting tachycardia and orthostatic hypotension when cardiovascular system is involved. Gastropathy and bladder dysfunction are caused by autonomic neuropathy of gastrointestinal tract and genito urinary tract.

Hyperhidrosis of upper extremities and anhidrosis of lower extremities can occur due to sympathetic nervous system dysfunction. There is a increased chance of foot ulcers due to anhidrosis of lower extremities which causes dry skin and cracking.

Autonomic neuropathy may reduce the counter regulatory hormone release leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness) thereby subjecting the patient to the risk of severe hypoglycemia .

DIABETIC NEPHROPATHY

It is characterized clinically by hypertension, proteinuria and ultimately renal impairment. Diabetic neuropathy has 5 stages , out of which stage 1, 2 and 3 are considered as pre clinical or “silent” and stages 4 and 5 are called as clinical diabetic neuropathy .

Stage 1

Here GFR is elevated on an average by 20 – 40% above that of age matched normal controls in both adults and children with type 1 DM resulting in glomerular enlargement

Stage 2

It is an extension of stage 1. Histopathological changes like basal membrane thickness and messangial expression begins to be detected within 1st two years after onset of IDDM. This stage is usually silent clinically with normal albumin excretion rate despite structural changes. Most patients remain in stage 2 , however 30 % - 40% progress to subsequent stages.

Stage 3

Here patients will have microalbuminuria detected. Patients who have albumin excretion rates > 30µg /min are more likely to develop clinical diabetic nephropathy than those with less than 30 µg/min.

Stage 4

In this stage, patients develop overt nephropathy. By definition , patients have persistant clinical proteinuria with albumin exretion rate of > 250µg/min in 24 hours, hypertension and a decrease in GFR. Once proteinuria is persistently present, development of end stage renal disease or death occurs in 3 – 4.8 years.

Stage 5

This is a stage of advanced renal failure. In contrast to non diabetic patients, diabetics with end stage renal disease usually have other systemic manifestations in addition to their renal diseases.

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS.

The earliest abnormality seen in type 2 diabetes in impairment in tissue sensitivity to insulin. This results in an increase in demand on the β cell to maintain a sufficiently high rate of insulin secretion to the offset of insulin

resistance. After a certain time, when the insulin secretion fails to meet the insulin demand , overt diabetes occurs.

Defective first phase insulin secretion :

This phase of insulin secretion , helps in priming the insulin target tissues to maintain the normal glucose homeostasis. It is one of the early manifestation, which is found to occur when fasting glucose rise to 115 – 120 mg%

Defective pulsatile insulin secretion:

Insulin is normally secreted in pulses of rapid frequency. Abnormal oscillatory insulin secretion is a feature of early stage of type 2 diabetes.

Genetic factors affecting βcell function :

- Glucose transporter 2 defect
- Decreased glucokinase activity
- Defects in phosphoinositol
- Defects in intracellular calcium and potassium metabolism

Environmental factors affecting βcell function:

- Chemical toxins like alcohol
- Malnutrition
- Chronic pancreatitis

- Amylin accumulation
- Intrauterine environment
- Drugs like thiazides, beta blockers etc..,

Effects of chronic hyperglycemia :

Two different entities have been recognized.

a) Glucose desensitization :
   - Temporary reversible state of cellular refractoriness which occur as an impaired insulin exocytotic mechanism.

b) Glucose toxicity :
   - Irreversible alteration of cellular function occur as a result of impairment in the regulatory process responsible for normal insulin gene transcription.

ROLE OF LIVER IN GLUCOSE METABOLISM

1) Liver is the organ of glucose production and glucose consumption
2) It is exposed to insulin concentration in the portal circulation which is 3 – 10 times more the systemic circulation.
3) Sole site of glycol regulatory action of glucose.

4) Absorbed hexose's reach liver before reaching muscle and adipose tissues.

Liver has storage form of glucose and glycogen about 70 gm at a time. 75% of hepatic glucose output comes from glycogenolysis. Remaining 25% of hepatic glucose output comes from gluconeogenesis.

Contribution of liver in glucose homeostasis depends on the following factors :

1) Sensitivity of hepatocytes to small increments in insulin levels
2) Ratio of insulin to glucagon
3) Responsiveness of glycogenolysis and gluconeogenesis to hormonal modulation.

HYPERINSULINEMIA AND INSULIN RESISTANCE

It is observed that population with type 2 diabetes have hyperinsulinemia and this reflects compensatory β cell response to the underlying insulin resistance. In Pima Indians , primary hypersecretion of insulin by β cells may represent the basic genetic defect.

Insulin secretion :

Much confusion is caused by discussion of inadequate secretion , yet there is a talk about hyperinsulinemia in type 2 diabetes. Hyperinsulinemia is a compensatory attempt to deal with chronic hyperglycemia. The β cells are

defective in that, they are unable to respond to any further increased by in plasma concentration caused by eating. This is essential point response of the β cells to ingested substrates is subnormal.

Histology of pancreas in type 2 diabetes has provided useful clues to the pathogenesis of poor insulin secretory response. Unlike in type 1 diabetes, is only moderately reduced in most cases. It is known that this results from chronic deposition of islet polypeptide which is co secreted with insulin. The amyloidal material is laid down in proximity to the β cell membrane and it interferes with the cell membrane based process of insulin resistance.

DIABETES – OBESITY AND INSULIN RESISTANCE

Insulin resistance and hyperinsulinemia is being increasingly implicated in the pathogenesis of various metabolic disturbances. Some of them has been clubbed under as a syndrome.

Diagnosis of metabolic syndrome is made in presence of atleast 3 of the following.

1) Waist circumference > 102 cm in male and > 88 cm in females
2) Triglycerides > 150 mg/dl (or) patients using nicotinic acid or fibrates.
3) HDL < 40 mg/dl in males and < 50 mg/dl in females

4) Systolic BP ≥ 130 mmHg (or) diastolic BP > 85 mmHg (or) patients using anti hypertensives
5) Fasting blood sugar > 100mg/dl (or) patients using OHA's.

Although much work is being carried out to learn the cellular mechanisms which are associated with resistance to insulin action especially in liver , muscles and fat cells, several conditions has been associated with insulin resistance. Obesity is one of them.

The combination of insulin resistance and hyperinsulinemia can lead to metabolic cascade which can lead to other disturbance like atherosclerosis , hypertension etc..

In patients who are prone to diabetes, the capacity of beta cells to increase the secretion of insulin is compromised and a stage is reached when beta cells are not able to augment insulin secretion , leading to glucose intolerance and diabetes. Many studies has analysed that BMI was associated with increased diabetes independently of fasting and postprandial levels. The American study showed that BMI>35kg/m2 has 40 old increase in type 2 DM as compared to BMI <23kg/m2.

Eventhough BMI was considered to be the tool for assessing cardiovascular risk in type 2 DM , there are certain limitations for using BMI for

diagnosing and assessing the cardiovascular risk in obese group, particularly in certain ethnic groups.

Two people with similar BMI and of same sex, height, age can have different phenotypes and presentations depending on body fat distribution (central or peripheral). Therefore, visceral adiposity measurement is now a days used to assess the cardiovascular risk in a patient with type 2 DM.

VISCERAL OBESITY

It has been now recognized that, insulin resistance is more likely related with the type of adiposity , which is greater with central obesity. Even some studies have proved that , there is a stronger correlation with intra abdominal visceral fat mass. Specific fat deposits like mesenteric fat and omental fat tissues are more important in this association. The visceral fat tissue is more closely associated with insulin resistance and cardiovascular risk when compared to the subcutaneous fat .

Why visceral fat ?

Visceral fat, especially mesenteric fat which is drained by portal circulation is metabolically more active than subcutaneous fat. Visceral adipocytes are more sensitive to the lipolytic effects of catecholamines and anti lipolytic effects of insulin leading to increased free fatty acids production.

This can lead to reduced fat oxidation and ectopic fat deposition which worsens the insulin resistance by reducing the peripheral glucose uptake. At the same time , visceral adipocytes are known to produce large number of cytokines like IL – 6, TNF α , angiotensin II, all of which can increase the cardiovascular risk in type 2 diabetes patients.

Free fatty acids in obese patients :

There is increase in the level and flux of free fatty acids in centrally obese patients. Insulin resistance can be associated with hyperinsulinemia in the presence of functioning beta cells. Insulin has a potent antilipolytic action. So, inspite of raised insulin, levels of FFAs should be increased. The increased levels of FFAs depend on the relative roles of lipolytic force against the antilipolytic force of insulin.

Adipose tissues at different sites has different metabolic properties. Similarly all the adipose cells do not respond to the stimuli in a same manner. Many authors have suggested that, people with visceral adiposity has a relative insulin resistance to the anti lipolytic effects of insulin. The reason behind this is, the adipose cells of the visceral mass have a relatively poor density of insulin receptors and therefore they are not susceptible to the antilipolytic effects of

insulin. At the same time, they have high density of glucocorticoid receptors and can respond to the lipolytic action of each steroid hormone.

How do fat cells affect insulin sensitivity?

The free fatty acids , interfere with the insulin action, glucose uptake and utilization in muscle through the glucose fatty acid hike. Even some studies have focused on the roll of free fatty acids on glucose receptors. Circulating free fatty acids has a role to play in translocation from their intracellular location to the cellular membrane.

Increased flux of free fatty acids will expose the liver to high levels of FFAs. In these circumstances, there is an increase in gluconeogenesis dependant on the levels of free fatty acid oxidation in liver. Similarly excess FFAs can also lead to hepatic insulin resistance and can decrease the hepatic clearance of insulin. Therefore visceral adiposity can explain the presence of both hepatic and peripheral insulin resistance which would be then refluxed by increased insulin secretion and hyperinsulinemia. At the same time , it would be naïve to suggest that elevated levels of FFAs would be the only cause of insulin resistance.

Role of fat cells and inflammation in obesity :

The human body has limited capacity to generate new fat cells.

A 70 kg man is thought to have 35 – 50 billions fat cells which are distributed in subcutaneous tissues and abdominal cavity . Once the person becomes overweight with type 2 diabetes, the ingested excess energy will be stored as fat in the existing fat cells by becoming hypertrophic.

Once the fat cells exceeds their capacityto intake circulating lipids, they will be enhanced to secrete variety of inflammatory cytokines and consequently fat begins to deposit in extracellular tissues such as muscle, liver , vascular walls and inflammatory viscious cycle begins. Hyperlipidemia and insulin resistance would further aggravate and development of atherosclerosis and other complications manifest.

Hypertrophied fat cells, particularly intra abdominal visceral fat produce increased amounts of cytokines that causes systemic inflammation. Moreover these cytokines that cause systemic inflammation, drain directly into the liver through portal circulation thus exposing the liver to high levels of inflammatory agents.

These potent inflammatory signals, increases the hepatic production of CRP, interleukins, TNF α , which are common findings in obese individuals. Excess

fatty acids further aggravates insulin resistance and abnormalities in other tissues, including development of fatty streaks and formation of atheromatous plaques in arterial walls.

Neuro endocrine aberrations :

The raised levels of free fatty acids would be dependant on increased degree of lipolytic drive. It has been proved that, this lipolytic drive which is associated with visceral adiposity is a complex hypothalamic driven endocrine aberration. The components of which are a) increase in sympathetic nervous system activity 2) complex steroid hormone disturbance.

a) **Sympathetic nervous system hyperactivity (SNS)** :

It has been postulated that , the main lipolytic stimuli in visceral obesity may be the sympathetic nervous system hyperactivity. The increased lipolysis associated with visceral obesity may be an additional activity of SNS hyperactivity. There are many works which have undergone in animals and humans, which showed that caloric intake increases and fasting decreases the activity of SNS. These changes are closely related to the levels of serum insulin. Some studies even showed that, higher the insulin levels, greater the activity of sympathetic nervous

system. Thus obesity associated with hyperinsulinemia and insulin resistance would again increase the activity of SNS.

In addition to the effects of catecholamines which has a prolipolytic action, it has been now recognized that, epinephrine is a very powerful insulin antagonist and it can inhibit insulin mediated glucose uptake by muscles and block the suppressive action of insulin in hepatic gluconeogenesis.

b) **Steroid hormone imbalance** :

In visceral obesity, there is a functional hyperactivity of the CRH – ACTH – cortical axis. Centrally, the hypothalamus plays a important role with increased sensitivity and preparedness of CRH – ACTH – axis to stimulate such a mental and physical stress. Peripherally there is an increased metabolic clearance of cortisol. The region where this take splace is the visceral fat depot as this is known to contain high density of glucocorticoid receptors and is well placed to respond to the raised cortisol levels as well as participate in increased clearance.

Raised androgen levels in women and hypogonadal levels in men with functional hypercortisolism which is seen in visceral obesity , amplify the degree of insulin resistance , either directly or through increase in free fatty

acid levels. Women with visceral obesity have hyperandogenesity , typical of women with polycystic ovarian disease. These women have hyperandrogen levels, central obesity , insulin resistance and hyperinsulinemia. The effect of androgens on lipid metabolism is that, they are known to increase the lipolytic sensitivity by expression of lipolytic beta-adrenergic receptors through an androgen receptor which in turn autoregulated by testosterone.

Thus it has been known that neuro endocrine disturbances can cause visceral obesity and insulin resistance and therefore hormonal imbalance has to be corrected as a primary aim . Inspite of this, the two aberrations namely visceral obesity and neuroendocrine disturbance are so interrelated in their effects, it is possible that, both play an important and symbiotic role leading to insulin resistance and hyperinsulinemia.

DIABETIC DYSLIPIDEMIA

Dyslipidemia is a common feature of both type 1 and type 2 diabetes.

The common patterns of dyslipidemia in type 2 diabetes are :

1) Elevated triglycerides levels
2) Low plasma HDL cholesterol (HDL – C)

3) Increased non HDL cholesterol (LDL + VLDL)

4) Increased small dense LDL particles

5) Normal or borderline increase in LDL cholesterol (LDL – c)

This type of dyslipidemia is most characteristic of type 2 diabetes .

LDL profile in type 2 diabetes :

Glycation of apoprotein b (APO – b) decrease the divinity for LDL receptors and they may delay in LDL clearance. These glycated LDL are more susceptible to oxidation, and this oxidized LDL plays a key role in atherogenesis. Especially small dense LDL is highly atherogenic because of its susceptibility to oxidation. A major determinant of LDL density distribution is the concentration of plasma TGL which accounts for approximately 75% of the variance of small dense LDL.

Hypertriglyceridemia in type 2 diabetes:

Hypertriglyceridemia is common in type 2 diabetes and it is usually accompanied by low HDL – c. Some triglycerides rich lipoprotein are atherogenesis especially IDL which accumulates in type 2 diabetes. Fasting hypertriglyceridemia is associate with abnormal post prandial lipidemia which is associated with increased cardiovascular risk .

Similarly hypertriglyceridemia leads to significant alteration in important lipoprotein species resulting in a shift in LDL subtraction distribution and also low levels of HDL – c.

Insulin resistance and lipid metabolism :

Insulin plays a major role in regulatory steps in lipid and lipoprotein metabolism. There is a reasonable hypothesis to explain the various components of diabetic dyslipidemia and their relationship to insulin resistance which include, increased hydrolysis of adipose tissue triglycerides results in enhance flux of non essential fatty acids(NEFA) to the liver. This is more important for VLDL production. Insulin resistance is associated with increased hepatic production of large VLDL independent of NEFA flux. The hepatic VLDL production is normally not suppressed post prandially resulting in competition for lipoprotein lipase with exogenous triglycerides carried on chylomicrons. This leads to accumulation of triglycerides which stimulates increased transfer of cholesterol ester transfer proteins(CETP) . As a result HDL and LDL are enriched in triglycerides. These particles are substrates for hepatic lipase activity which is increased in insulin resistance producing small dense LDL and small dense HDL.

Prothrombotic tendency of dyslipidemic patients :

It has been well proved that there is a close relationship between dyslipidemia and prothrombotic tendancy. What we have to know is whether lipid lowering therapy can reverse the coagulatory abnormalities in dyslipidemic patients . A small but significant reduction in factor VII antigens was seen with simvastatin. VWF was reduced following treatment with various lipid lowering drugs.

There is 20% and 37% reduction in total and LDL cholesterol following 12 weeks treatment of fluvastatin , according to some studies. Significant correlations was found between reduction in factor VII with total and LDL cholesterol levels. These suggests that prothrombotic tendancy in type 2 DM can be ameliorated by effective lipid lowering therapy.

MANAGEMENT

DIET MANAGEMENT

The diet management in diabetes is very controversial due to lack of consensus among the specialization in this field. Even today there are inconsistencies in the recommendations. The suggested diet to the patient should have the main objective of achieving normal weight. British physician produced

the black line diets , followed by the ‘exchange system of point system’ from USA descriptive of caloric contents of the carbohydrate food items.

DIET IN TYPE 2 DIABETES

As we know, the majority of diabetes is type 2, with an increased risk of morbidity and mortality related to atherosclerotic cardiovascular disease. As a result, diet that affect the serum lipids have become an important consideration in the management of diabetes. It is therefore appropriate to briefly analyse and summarise the present information on dietary fats.

Reason for diet is to achieve the following goals:

1) Weight control
2) Blood sugar control
3) Blood pressure control
4) Lipid control
5) To prevent short term and long term complications of diabetes.

Achieving above goals is by the following balanced food choices

1) Eat starch foods regularly (proper quantity)
2) Eat more fruits and vegetables
3) Eat high dietary fiber foods

4) Reduce animal or saturated fats
5) Cut down on sugar
6) Reduce salt

MEDICAL NUTRITION THERAPY

It is defined as the nutritional diagnostic therapy and counseling services for the purpose of disease management which are furnished by registered dietitian or nutritional professionals. This type of therapy has its own goals in the diet modification of diabetes mellitus.

Goals of medical nutrition therapy are:

1) To achieve and maintain blood sugar level in a normal range or as close to normal
2) To achieve a lipid and lipoprotein profile that reduce the risk of vascular diseases.
3) To prevent the rate of development of chronic complications of diabetes by modifying nutrient uptake and lifetstyle.

GLYCEMIC INDEX

It is the effect of carbohydrate on the blood sugar levels. The carbohydrates which breakdown very quickly during digestion and release glucose rapidly in

the blood stream have a high glycemic index. Similarly the carbohydrates that break down slowly and release glucose gradually have a low glycemic index. The current methods use glucose as the reference food, giving it a glycemic index of 100.

Low GI – 55 or less

Medium GI – 56 to 69

High GI – 70 and above

Dietary fiber:

Consuming high fiber diet (>50 gm fiber/day) reduces glycemia in type 1 diabetes and glycemia, hyperinsulinemia, lipemia in type 2 diabetes. Legumes, fiber rich cereals, fruits, vegetables and whole grain products are some of the fiber containing foods.

Dietary fat and cholesterol:

Usually dietary fat and cholesterol provide 20 – 35 % of energy intake. In diabetes, the limit of dietary cholesterol is upto < 200mg/day. Limitation of saturated fat to < 7% is necessary. Two or more servings of fish per week provide polyunsaturated fatty acids.

Proteins :

In case of diabetic patients with normal renal function , there is insufficient evidence to suggest the normal protein intake. In diabetics, these proteins can increase the insulin response without any increase in plasma glucose concentration. Therefore protein should not be used to treat acute or to prevent night time hypoglycemia.

Alcohol :

Alcohol consumption in men should be ≤3 standard drinks /day (or) <15 drinks per week. In women, it is ≤ 2 standard drinks /day (or) < 10 drinks per week. Alcohol should be consumed with food in order to reduce the risk of nocturnal hypoglycemia in the individuals using insulin.

NUTRITIONAL RECOMMENDATIONS FOR ADULTS WITH DIABETES

Weight loss diet (in prediabetes and type 2 DM)
- Hypocaloric diet that is low – fat or low – carbohydrate
Fat in diet
- Minimal trans fat consumption
Carbohydrate in diet

- Monitor carbohydrates intake in regards to calories
- Sucrose containing foods may be consumed with adjustments in insulin dose.
- Amount of carbohydrate diet determined by estimating grams of carbohydrates in diet
Proteins in diet
- As a part of optimal diet
Other components
- Non nutrient sweeteners
- Routine supplements of vitamins, antioxidants

INDIAN DIET IN RELATION TO FAT CONSTITUENTS

25 – 30 gms/day of fat in Indian diet is from invisible fat sources like cereals, pulses, nuts, oil seeds, fresh coconuts and milk products. There has been a great shift from high carbohydrate diet to a high fat diet due to urbanization, as cooking makes easier and more palatable. At present , the carbohydrate to fat ratio in rural areas is 4 : 1 and this shifts approximately 1.5:1 in urban areas.

It is more important to indicate the polyunsaturated fatty acid content of various cooking oils. From the table based on ICMR figures, it is clear that soyabean oil or mustard oil have sufficient omega 3 content .

POLYUNSATURATED FAT CONTENT

Fat or oil	Linoleic acid (omega 6) in g/100gms	Linolenic acid (omega 3) in g/100gms	Total PUFA in g/100gms
Sunflower oil	74	0.5	74.5
Soyabean oil	52	5	57
Cottonseed oil	50.3	0.4	50.7
Corn oil	50	2	52
Sesame oil	40	0.5	40.5
Rice bran	33	1.6	34.6
Groundnut oil	28	0.3	28.3
Mustard oil	13	9	22
Vanaspathi	3.4	-	3.4
Ghee	1.6	0.5	2.1
Coconut oil	2.2	-	2.2

ORAL HYPOGLYCEMIC AGENTS (OHA's)

The major defects that accounts for disturbance in type 2 diabetes are, impaired insulin action and decreased insulin secretion. The relative contribution of insulin deficiency vary considerably in causing hyperglycemia in diabetes. The goal of therapy in type 2 diabetes should not only improve the beta cell function, but also enhance the glucose utilization in the peripheral tissues. These oral drugs also have the potential to correct the hormonal and metabolic abnormalities in diabetes.

SULFONYLUREA

This oral hypoglycemic agent is being used for almost 50 years. The earliest sulfonylurea was tolbutamide which was introduced in 1957. Subsequently second generation sulfonylurea have been introduced which are 20 – 100 times more potent than the first generation.

Sulfonylureas act by binding to the so called sulfonylurea receptors (SUR – 1) on the pancreatic beta call membranes causing depolarization, calcium influx and degranulation of secretory granules with insulin release. Therefore, these drugs primarily augment second phase of insulin secretion and has very less action on first phase.

The delay in the first phase of insulin release in type 2 diabetes contributes to the excessive post prandial rise in blood sugar levels. The more rapid onset of action of sulfonylureas, the lesser is the delay in post prandial insulin release. Glipizide results in rapid post prandial insulin release and lowers post prandial glucose. In contrast glibenclamide exerts a better effect on fasting glucose. This is attributed to the longer duration of action of glibenclamide and suppression of hepatic glucose production. Hence , where fasting glucose levels are high, glibenclamide may be preferred to glipizide and vice versa.

Drug	**Peak level in hours**	**Half life in hours**	**Metabolites**	**Excretion**
TOLBUTAMIDE	3 – 4	4.5 – 6.5	Inactive	Kidney
CHLORPROPAMIDE	2 – 4	36	Active or unchanged	Kidney
GLIMEPRIDE	2 – 4	36	Active or unchanged	Kidney
GLIPIZIDE	1 – 3	2 – 4	Inactive	Kidney 20% bile

				80%
GLIBENCLAMIDE	4	10	Inactive and weakly active	Kidney 50% bile 50%
GLICLAZIDE	4	6 – 15	Inactive	Kidney

Sulfonylurea are mainly indicated in type 2 diabetes , especially in patients who still have adequate beta cell function and who fail to achieve glycemic control.

Even among them, there are still reasons which are not clear for about 15 – 20 % of patients who have no effect or little effect in glycemic control to sulfonylurea therapy. Moreover, the remaining patients who initially responded well to this therapy loose responsiveness after several months or years after therapy . Secondary failure, decreasing the beta cell function and increasing the insulin resistance are important disease related factors for sulfonylurea failure besides the duration of the disease. In a small percentage of patients, sulfonylurea therapy reduces remission in early stages.

Sulfonylurea and hyperinsulinemia :

Insulin resistance and hyperinsulinemia causes increases sympathetic activity and sodium retention thereby causing hypertension . It also causes

hypertriglyceridemia and lowers the HDL cholesterol. It also promotes the proliferation of arterial smooth muscle cells and collagen synthesis in the vascular walls. Administration of sulfonylureas improves the insulin action on peripheral tissues, correct insulin resistance and hyperinsulinemia.

BIGUANIDES

Metformin, phenformin and buformin belongs to this group. The later two drugs are withdrawn long back. Metformin is an old, but still the best agent of choice to start with in treatment of type 2 diabetes. Its efficacy, safety profile and its capacity to be associated with other anti diabetic agents makes metformin the first glucose lowering drug of choice in diabetes management.

The principle site of action is in the liver and muscles. The effect of metformin on liver is mediated by activation of liver kinase B1. This drug is equally effective in normal weight patients, contrary to its widespread perception in our country that it is preferred in obese patients.

Metformin in different situations:

1) Childhood and adolescence - the beneficial effect has been documented in this age group. There are studies which suggest improvement in metabolic control in poorly controlled children and adults with type 1 diabetes , when metformin is added along with insulin therapy.

2) Pregnancy – metformin crosses the placenta and thus concerns regarding its safety in mother and fetus have limited its use in pregnancy. There are studies which showed , infants of mother exposed to metformin in utero had reduction in insulin resistance examined 2 years after birth.
3) Poly cystic ovarian disease – metformin in PCOS leads to ovulation leading to achievement of pregnancy. This drug can be continued after conceiving where studies didn't show any fetal loss if the drug is being continued.
4) Metformin in cardiovascular protection – this drug is often associated with decreased LDL cholesterol, fasting as well as post prandial decrease in TGL and free fatty acids thereby having an cardioprotective action.
5) Metformin and cancer – recent studies have shown that, metformin reduces tumorigenesis and cancer cell growth probably through reduction of hyperinsulinemia and IGF – 1 levels.

THIAZOLIDINEDIONES

Thiazolidinediones are potent insulin sensitisers, that act through the nuclear receptor, peroxisome proliferator activated receptor gamma. This PPAR gamma mediated transcriptional effects have been shown to improve whole body insulin sensitivity.

Drug used are, troglitazone, rosiglitazone and pioglitazone. Among these drugs, troglitazone have been banned in the year 2000, due to its fatal hepatotoxicity after which rosiglitazone was introduced. Pioglitazone is the third drug used that has been shown to improve insulin sensitivity.

Eventhough pioglitazone has cardiovascular benefits when compared to rosiglitazone , it has its own side effects. Some of the common side effects are weight gain, edema, congestive cardiac failure because of fluid retention and plasma volume expansion. Some other factors which contribute to edema are, vasodilatation, increased vascular permeability and increase in renin and aldosterone activity. There are studies which showed association between use of glitazones and occurrence of macular edema. Therefore it has to be withdrawn if macular edema is suspected.

GLP – 1 ANALOGUES

This incretin hormone GLP – 1 is secreted from intestinal L cells , in distal ileum and colon in response to food intake. The effect of subcutaneous injection of GLP – 1 analogue is very short acting due to N terminal degradation by the enzyme dipeptidyl peptidase IV (DPP – IV), restricting its cardiac use.

Based on its duration of action this group of drugs are divided into

a) Short acting - duration of action is < 24 hours

e.g., exenatide and lexisinatide

b) long acting - duration of action > 24 hours.

e.g., liraglutide (once daily)

exenatide LAR (once weekly)

This drug has been proved to be non inferior to metformin, glitazones, sulfonylureas and insulin and therefore they are currently approved in treatment of type 2 diabetes as a monotherapy and add on therapy to the existing medication. This drug has beneficial effect on cardiovascular system, lipid profile, obesity and also in central nervous system.

List of GLP - 1 ANALOGUES

Drug	**Approval status**	**Dose**	**Frequency**	**HbA1c reduction**	**Effect on weight**
Exenatide	Approved	5 – 10mcg	Twice daily	1- 1.9 %	Yes
Liraglutide	Approved	0.6 – 1.8mg	Once daily	0.9 – 1.6 %	yes
Exenatide LAR	Approved	2mg	Once weekly	1.5%	Yes
Lixisenatide	Awaited	20mg	Once daily	0.74%	Yes

Albiglutide	Awaited	30mg	Once weekly	0.57%	Yes
Dulaglutide	Awaited	>1mg	Once weekly	1.28 – 1.52%	Yes
Taspoglutide	Halted	-	-	1.1%	Yes
Semaglutide	Awaited	1mg	Once weekly	Awaited	Yes

DIPEPTIDYL PEPTIDASE - IV INHIBITORS (GLIPTINS)

DPP – IV inhibitors are novel antidiabetic drugs based on the incretin therapy. These drugs help in decreasing the degradation of endogenous incretin hormone .

Gliptins as a monotherapy generally carries a mow risk of interprandial hypoglycemia . Similarly gliptins are generally regarded as weight neutral agents and may assist a small amount of weight loss. Four drugs have been introduced till now.

a) Sitagliptin

b) Vildagliptin

c) Saxagliptin

d) Linagliptin

All the drugs have been approved except vildagliptin. Gliptins have demonstrated similar reduction in fasting , post prandial glucose levels and Hb A1c as compared to sulfonylurea, alpha glucosidase inhibitors, except for metformin , because of which metformin is said to be the first line drug to be started as a monotherapy. Therefore gliptins are preferred 2nd line drugs for monotherapy.

LIST OF DPP – IV INHIBITORS

Drug	**Absorption**	**Dose**	**Elimination route in percentage**
Sitagliptin	87%	100mg OD	Renal (80% unchanged)
Vildagliptin	85%	50 mg BD	Renal (22% as parent, 55% as primary metabolite)

Saxagliptin	67%	5mg OD	Renal(>70% as unchanged)
Linagliptin	30%	5 mg OD	Biliary (>70% unchanged as parent, <6% via kidney)

ALPHA – GLUCOSIDASE INHIBITORS

1) Acarbose
2) Voglibose

Mechanism of action of alpha glucosidase inhibitors involves block of the enzyme alpha glucosidase in the intestine which normally clears carbohydrates into absorbable monosaccharides.

INSULIN SECRETAGOGUES – PRANDIAL GLUCOSE REGULATORS

Repaglinide – it is a benzoic acid derivative which stimulate beta cell function. Prandial glucose regulators act on a unique binding site at beta cell. The compound is very potent, very rapid, and short acting . repaglinide is capable of causing a substantial reduction in post prandial blood glucose level. The

treatment is tailored to the meals, meaning that the dose is preprandial and omitted if a meal is omitted.

Repaglinide is metabolized in liver . insulin sensitisers could be used for obese patients suffering from insulin resistance and prandial glucose regulators such as repaglinide could be used for type 2 diabetic patients who cannot produce sufficient insulin and still have some beta cell function.

ROLE OF INSULIN IN TYPE 2 DIABETES

Type 2 diabetes constitutes nearly 95-97% of all diabetes. The successful management of type 2 diabetes involves around an individual tailored nutritional plan, exercise regimen, use of oral agents and or insulin.

Tissues insensitivity to insulin and impaired insulin secretion are the pathogenetic factors underlying type 2 diabetes. The primary defect is tissue insensitivity to insulin. It becomes clear that it soon leads to higher blood glucose level.

Macrovascular complications due to atherosclerosis are the major problem in type 2 diabetes. Long term hyperglycemia is a significant predictor for excess cardiovascular mortality in type 2 diabetes.

Why should hyperglycemia be treated in type 2 diabetes is to relieve symptoms and improve subjects well bring. Glucose toxicity as adverse effects on insulin resistance and beta cell function.

DCCT provides strong evidence that tight glycemic control prevents microvascular complications. Hyperglycemia is a predictor of excessive cardiovascular mortality.

INITIATING INSULIN THERAPY IN TYPE 2 DIABETES

Apart from temporary indications of insulin therapy, long term insulin therapy is always challenging. In case if the patient is on oral hypoglycemic agent with failure, adding a basal insulin a shot while continuing oral agents is simply effective way of initiating insulin therapy.

Some of the indications for insulin use in type 2 diabetes are :

a) Primary oral agent failure
b) Secondary oral agent failure
c) Peri operative
d) Pregnancy
e) Acute or chronic sepsis
f) Acute medical or surgical event
g) Major organ failure
h) Glucotoxicity

Hypoglycemia and weight gain - these are the 2 main complications of insulin therapy. Eventhough basal bolus insulin therapy is a step forward to physiological insulin secretion, majority of studies have reported incidence of hypoglycemia. The following steps to be followed to reduce incidence of hypoglycemia.

a) Dietary discipline
b) Patient education
c) Self monitoring of blood glucose
d) Sick day rule management
e) Usage of insulin analogues
f) Lowering the HbA1c target in high risk groups
g) Usage of insulin sensitisers over insulin secretogogues

The current targets for metabolic control in type 2 diabetes should be achieved by OHA, otherwise insulin should be started.

Blood glucose in mmol/l	**Good**	**Acceptable**	**Poor**
Fasting	4 – 6	≤8	≥8
Post prandial	4 – 8	≤10	≥10
HbA1c in %	4 – 6	6 – 8	≥8
BMI	<25	<27	≥27

INSULIN INITIATION, INTENSIFICATION AND CONTINUATION IN T2DM

All patients with type 2 diabetes have both inadequate insulin secretion and also insulin resistance. Most of the diabetic patients, especially type2 diabetics, require treatment to achieve and maintain a target HbA1c between 6.5-7.

Eventhough the pharmacological management of type 2 diabetes start with oral medications, majority of the patients require exogenous insulin therapy at one point of time. Although insulin therapy is prescribed on an individualized basis, treatment usually begins with basal insulin added to background of oral agents. Currently available insulin analogues may represent an important therapeutic alternative for many patients.

Glucose dependant insulin secretion occurs in 2 phases.

a) In first phase, insulin response occurs more quickly within 3 – 5 mins period immediately after eating and ends rapidly. This phase of response is normal in genetically predetermined and usually abnormal in subjects with a first degree relative with diabetes.

b) Fifteen minutes after carbohydrates are consumed and the process of digestion begins, 2nd phase of insulin response in initiated. During this phase , beta cells produce and secrete insulin until all carbohydrates has been absorbed from gastro intestinal tract and the plasma glucose levels have been normalized. This phase plateaus in 2 – 3 hours , yet the post absorptive state can last upto 6 hours.

Prolonged exposure to even moderately elevated glucose is associated with beta cell desensitization , increased apoptosis, delay in first phase response and attenuated second phase of response.

WHEN TO START INSULIN ? (INDIAN GUIDELINES)

a) At diagnosis, fasting glucose > 200mg/dl , post prandial glucose > 300mg/dl with HbA1c > 9%
b) After oral drug failure, despite receiving optimal dose of 2 or 3 OAD's, fasting glucose > 150 mg/dl , post prandial glucose > 200mg/dl with HbA1c levels of > 8.5%

INITIATION OF INSULIN WITH BASAL VERSUS PREMIX INSULIN

At present the most common approach to initiate insulin are with a basal insulin analogue usually at bed time or with a premix insulin usually with

breakfast and dinner. There are 3 important exceptions to initiate insulin with basal insulin. they are,

a) Patients with high HbA1c (>8.5%), who may not be able to reach the HbA1c goal solely with basal insulin since they also need insulin 'cover' for their post prandial glucose.
b) Patients with lower compliance who are often hesitant to titer their insulin doses.
c) Patients with relatively low fasting or post prandial glucose and relatively high HbA1c suggests high post prandial hyperglycemia.

PREMIX VERSUS BASAL BOLUS REGIMEN

Premix insulin analogues	**Basal plus/ basal bolus**
Patient preference	Type 1 diabetes (any age)
Older age	Younger age
Need assistance with injections	Highly motivated and compliant
Organized lifestyle	Active lifestyle
2 meals a day or evening main meal	High variability in eating habits.

INSULIN ANALOGUES - Why do we need insulin analogues?

a) Initially, the earliest insulin used was a soluble (regular) insulin, which is a animal derivative, impure, because of which it was often associated with insulin allergy, lipodystrophy and antibody mediated insulin resistance.
b) Combination of insulin with zinc or basic proteins(protamine) also lead to delayed absorption of insulin from the subcutaneous sites leading to development of longer acting lente and ultra lente insulin.
c) Similarly , the conventional longer acting insulin (NPH insulin) use is limited by lack of 24 hour effect, thereby need of 2 injections in majority of the patients and a delayed peak effect , have associated with increased risk of nocturnal hypoglycemia.

All of these above limitations, have lead to the development of insulin analogues which are designed to improve on the subcutaneously administered pharmacokinetic and pharmacodynamic inadequacies of conventional human insulin. The pharmacodynamic effect of the insulin analogues of native insulin better approximate endogenous insulin secretion and have expected to result in superior clinical end points.

RAPIDLY ACTING INSULIN ANALOGUES

Insulin Lispro ,Aspart and Glulisine are the 3 rapidly acting insulin analogues which are approved for clinical use as bolus or meal time insulin.

Because of the structural changes in the amino acid sequence of these insulin, they have a faster onset of action (10 – 15 mins) , peak of action (0.5 – 2 hours) , shorter duration of action (3 – 4 hours) and less variability between injection site in comparison with regular insulin.

These short acting insulin analogues also have the benefits of improved normalization of post prandial glucose, decreased hypoglycemic events and enhancement in quality of life. Potential clinical disadvantages are, risk of early post prandial hypoglycemia and preprandial hyperglycemia.

LONG ACTING INSULIN ANALOGUES

This group includes Insulin Glargine and Insulin Detemir. These insulin analogues have undergone structural alterations allowing for prolonged absorption following a subcutaneous injection and relatively peakless 24 hours action profile, which is much more analogous to basal insulin release when compared to NPH.

Both Glargine and Detemir have a onset of action with in 1- 3 hours of administration and a relatively peakless , dose dependant, mean duration of action of approximately 24 hours. One more advantage of these long acting analogues is that, both have lesser inter individual variability in absorption rates

from injection sites along with reduced incidence of hypoglycemia, especially nocturnal hypoglycemia when compared to NPH insulin.

LATEST INSULIN ANALOGUE – DEGLUDEC

- It is the latest approved longer acting insulin analogue.

Various trials have been conducted comparing degludec with other longer acting insulin analogues, which showed that degludec is associated with lower rates of hypoglycemia in type 1 diabetes mellitus and superior post prandial glucose control compared with glargine in those with type 2 diabetes mellitus.

Development of insulin analogues has significantly contributed to improving glycemic control in patients with diabetes. The future of insulin analogues is bright with several new drugs in the pipeline. However, the use of insulin analogues in our country may be limited because of high cost .

PROPERTIES OF INSULIN SECRETOGOGUES

CLASS/GENERIC NAME	**Daily dose in mg**	**Duration of action(h)**
SULFONYLUREAS		
Glimepride	1 – 8	24
Glipizide	5 – 40	12 – 18

Glyburide	1.25 – 20	12 – 24
MEGLITINIDES		
Repaglinide	0.5 – 16	2 – 6
Nateglinide	180 – 360	2 – 4
GLP – 1 ANALOGUES		
Exenatide	0.01 – 0.02	4 – 6
Liraglutide	0.6 – 1.8	12 – 24
DPP – IV inhibitors		
Saxagliptin	2.5 – 5	12 – 16
sitagliptins	100	12 – 16
Vildagliptin	50 – 100	12 – 24

PROPERTIES OF INSULIN PREPARATIONS

PREPARATION	**ONSET in hours**	**PEAK in hours**	**DURATION in hours**
Aspart	< 0.25	0.5-1.5	3 – 4

Glulisine	<0.25	0.5-1.5	3 – 4
Lispro	<0.25	0.5-1.5	3 – 4
Regular	0.5 – 1.0	2 – 3	4 – 6
Detemir	1 – 4		Upto 24 hrs
Glargine	1 – 4		Upto 24 hrs
NPH	1 – 4	6 – 10	10 – 16
75/25-75%protamine lispro, 25%lispro	<0.25	1.5	10 – 16
70/30-70%protamine aspart, 30%aspart	<0.25	1.5	10 – 16
50/50-50%protamine lispro,50%lispro	<0.25	1.5	10 – 16
70/30-70%NPH,30%regular	0.5 – 1	Dual	10 – 16

DIABETIC DYSLIPIDEMIA

Individuals with diabetes mellitus have various forms of dyslipidemia. Generally in type 1 diabetes mellitus, dyslipidemia is uncommon if the patient is under good glycemic control. Conversely in case of type 2 diabetes mellitus eventhough if the patient is in good glycemic control, dyslipidemia is more

common. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities in case of diabetes should be aggressively treated.

The most common dyslipidemic pattern seen in diabetes is increased triglycerides and reduced HDL cholesterol. Diabetes itself doesn't elevate the levels of LDL, but the small dense LDL particles found in diabetes are more atherogenic because they are more easily glycated and susceptible to oxidation. Eventhough increased LDL is not a common feature of type 2 diabetes, its presence indicates a underlying lipoprotein abnormality or development of diabetic nephropathy. Almost all treatment studies of diabetic dyslipidemia have been performed in individuals with type 2 diabetes because of greater frequency of lipid abnormalities in this form of diabetes.

Large prospective studies of primary and secondary intervention for CHD have included some individuals with type 2 diabetes subset analysis have consistently found that reduction in LDL reduce the cardiovascular events in individuals with diabetes. No prospective studies have addressed similar questions in individuals with type 1 diabetes. Since the frequency of cardicovascular disease is low in children and young adults with diabetes, assessment of CV risk should be incorporated into guidelines discussed below.

Based on the guidelines by the American diabetes association and American heart association, the following should be the priorities in the treatment of dyslipidemia in a patient with diabetes.

a) Lower the LDL cholesterol
b) Raise the HDL cholesterol
c) Decrease the triglycerides

Initial therapy in all forms of dyslipidemia should focus on the dietary modifications as well as life style changes which are being practiced for non diabetic individuals like smoking cessation, blood pressure control, weight loss and increased physical activity.

The dietary recommendations for individuals with diabetes mellitus are similar to those advocated by the national cholesterol education program and it includes increased monosaturated fats and carbohydrates and reduced saturated fats and cholesterol. Though viewed as important, the response to dietary alterations if often modest. Improvement in glycemic control will lower the triglycerides and have a modest beneficial effect on HDL.

According to American heart association, the target lipid values in a diabetic individual (age > 40) should be as follows :

a) LDL < 2.6mmol/l (100mg/dl)

b) HDL > 1 mmol/l (40mg/dl) in men and > 1.3 mmol/l (50mg/dl) in women

c) Triglycerides < 1.7 mmol/l (150 mg/dl)

If the patient is more than 40 years, American diabetes association recommends addition of statin irrespective of the LDL levels in patients with coronary heart disease and those without CHD, but has the risk factors for developing coronary artery disease. If the patient is known to have coronary artery disease, American diabetes Association recommends the LDL goal to be < 1.8 mmol/l (70mg/dl) as an option.

HYPOLIPIDEMIC AGENTS

	BILE ACID BINDING RESINS	**NICOTINIC ACID**
Dose	Cholestyramine 8 – 12gm in BD or TDS	Niacin 50 – 100 mg tid initially, then increase to 1 – 2.5 gm tid, later 0.5 – 1 gm tid
Mode of action	Interrupts inter hepatic circulation of bile acid. Increase the synthesis of new bile acids	Decrease the synthesis of VLDL and LDL

Lipoprotein class affected	Decrease LDL cholesterol Increase HDL and TGL	Decrease VLDL by 35% Decrease LDL 15-20%
Side effects	Constipation, nausea, bleeding	Flushing, tachycardia, arryhtmias, pruritis, dry skin, nausea, diarrhea, hyperuricemia, peptic ulcer, glucose intolerance, hepatic dysfunction etc.
Contra indications	Biliart tract obstruction, gastric outlet obstruction, hypertriglyceridemia	Peptic ulcer disease, cardiac arryyhtmias, gout, diabetes, liver disorders.

	HMG Co A REDUCTASE INHIBITORS	**FIBRIC ACID DERIVATIVES**
Dose	Lovastatin 10-8-mg/d Pravastatin 10-40mg/d	Gemfibrozil 600mg BD

	Simvastatin 5-40mg/d Fluvastatin 10-80mg/d	
Mode of action	Decrease the cholesterol synthesis, increase LDL receptors	Increase LPL Increase TGL hydrolysis Decrease VLDL synthesis Increase LDL catabolism
Lipoprotein class affected	Decrease LDL 30 – 40% Decrease VLDL	Decrease TGL Increase or decrease LDL Increase HDL
Side effects	Abnormalities in liver function	Increased lithogenicity of bile, nausea , liver function abnormalities
Contraindications	Increased myositis in patients with renal failure and in patients with gemfibrozil, nicotinic acid or cyclosporine.	Hepatic or biliary disease, renal insufficiency.

ROLE OF EXERCISE IN DIABETES MANAGEMENT

Due to favourable metabolic adaptations from regular exercise , physical activity gives a promising strategy in improving the complex disturbances which are characteristically seen in development andprogression of type 2 diabetes. Most of the beneficial effects of exercise is mainly due to improved insulin resistance.

PATHOPHYSIOLOGY OF EXERCISE IN TYPE 2 DIABETES

A single bout of exercise can lead to an acute increase in the glucose uptake by the working muscles , where most of the glucose is oxidized to supply energy. Regular physical training performed over long period lead to chronic muscular adaptations. Various comparative studies of trained and untrained subjects indicate that , regular exercise induces several cytoplasmic and mitochondrial enzymes and increase the expression of glucose transporter system, particularly GLUT – 4 in skeletal muscles.

The number and binding affinity of insulin receptors as well as capillary density of skeletal muscles are increased . this shows that, regular exercise can increase insulin sensitivity not only in the periphery in muscles but also centrally in liver. Most of the effects are primarily induced by aerobic

exercise, which may increase the insulin sensitivity mostly by increasing the skeletal muscle mass.

It is a well established fact that, macrovascular complications contribute to the poor prognosis of type 2 DM, not only the glycemic control but also the other factors like dyslipidemia and hypertension must be controlled.

Many of these factors can easily by controlled by regular moderate physical activity such as walking. The stimulus were these improvements appears to increase physical activity enery expenditure by 1000kcal/week. Even the new physical activity recommendations by the centre of disease control (CDC) and American college of sports medicine state that, every adult should do, 30 minutes or more of moderate intensity physical activity preferably all days of the week.

DIABETES AND PATIENT EDUCATION

There is often a true fact that diabetes affects several aspects of life and ideally requires the patients to make several changes. Simply it affects diet, lifestyle, physical well being, mental state, economic conditions, sexual and marital life. Therefore the outcome variables that need attention are ,

a) Quality of life
b) Life span
c) Mortality rates

d) Biochemical outcomes

e) Knowledge, attitude and practice

f) Skill.

CONTENTS OF PATIENT EDUCATION PROGRAMMES

PRIMARY	SECONDARY	TERTIARY
Overview	Self insulin	Travel
Meal plans	Adjustments and supplements	Pregnancy
Insulin injection technique	Sick day guidelines in detail	Chronic complications
Monitoring blood glucose and ketones	Foot care	
Hypoglycemia	Meal exchanges	
Sick day guidelines – basic		

As the first step of patients education, the educator should assess the patients perception about the disease. At the same time, the patient should know why they should know about the disease, what are the target of the education and what are the long term goals .

There are few principles of education. Neither unnecessary details nor dull superficial information could benefit the patients. Message should be given in a non threatening manner. At the same time, the patient should feel free and express doubts.

METHODOLOGY OF TEACHING

1. Verbal
    a) Diabetic lecturing
    b) Discussion/ seminar / group discussion
    c) Demonstration
2. Print material
    a) Magazines for the lay public

        Eg., balance, challenge, diabetic news etc.,
    b) Lay books
    c) Lay articles
    d) Cartoon books
3. Audio visual aids
    a) Films / videos
    b) Flip charts
    c) Slide talks
4. Other methods

a) Games

b) Plays

c) Dramas

d) Role playing

e) Computer programs

f) Quizzes

g) Contracting

5. Residential camps and diabetic melas like

    a) Camps organized by juvenile diabetic foundation.

Atlast it is very important to educate the family members in the management of diabetes care.

a) The family members should attend diabetes education classes along with the affected family member.
b) Provide the family with reading materials.
c) Practice skills at home with your family. Perform finger sticks for blood glucose, inject saline into a orange doll, and review the treatment for hypoglycemia so that the family members can understand what you go through and also carry out in case of emergencies.

d) Make sure family members know your meal and medication schedule . they have to be explained how we are planning to handle any achedule changes so that they are prepared in the event of complications.

e) Encourage any family members who is having trouble coping with your having diabetes to seek counseling to discuss his or her feelings and anxieties.

f) Active participation of the family members involves more than just explaining what was taught, and they have the opportunity to ask questions to the diabetes educator. Family members should discuss , ask diabetes nurse educator to clarify any discrepancies .

g) Persons with diabetes having complications like nephropathy, retinopathy and cardiovascular diseases have to be educated more, as they are more affected both physically and mentally because, with each complication, financial burden of the family increases.

GUIDELINES FOR ONGOING MEDICAL CARE FOR DIABETIC PATIENTS

Self monitoring of the blood glucose (individualized frequency)

HbA1c testing 2 – 4 times / year
Patient education in diabetes management (annual)
Medical nutrition therapy (annual)
Eye examination (annual)
Foot examination (1-2 times/year by physician and daily by patients)
Screening for diabetic nephropathy (annual)
Blood pressure measurement (quarterly)
Lipid profile and creatinine (annual)
Influenza / pneumococcal vaccinations
Consider antiplatelet therapy.

MATERIALS AND METHODS

PLACE OF THE STUDY

The study was conducted at Government Rajaji Hospital, Madurai Medical college, Madurai.

PERIOD OF STUDY

April 2014 to September 2014

STUDY DESIGN

Observational type of study

CONSENT

Informed written consent was obtained from all patients.

STUDY POPULATION

50 patients who are known case of type 2 diabetes mellitus were selected from Department of Diabetology , Government Rajaji Hospital , Madurai

INCLUSION CRITERIA

a) Known type 2 diabetes patients

b) Age > 35 years, both sexes

c) BMI > 25

EXCLUSION CRITERIA

a) Self reported diabetes mellitus

b) Dyslipidemia

c) Pregnancy

d) Hypothyroidism

e) Hypertension

f) Renal failure

g) Smokers and alcoholics

h) Patients on thiazolidinediones

METHODOLOGY

50 patients who are known case of type 2 diabetes mellitus were analysed for this study.

A thorough clinical evaluation was made and detailed history, blood pressure, height, weight, waist and hip circumference were taken .

a) Fasting lipid profile was done by enzymatic methods like zaks method, and spot urine sample for microalbuminuria were taken.

b) Waist circumference was measured at the midpoint between lower costal margin and anterior superior iliac spine in mid axillary line.

c) Hip circumference was measured at the level of greater trochanter of femur.

Waist hip ratio (WHR) $\geq$ 0.90 in males and $\geq$ 0.80 in female are taken to be significant .

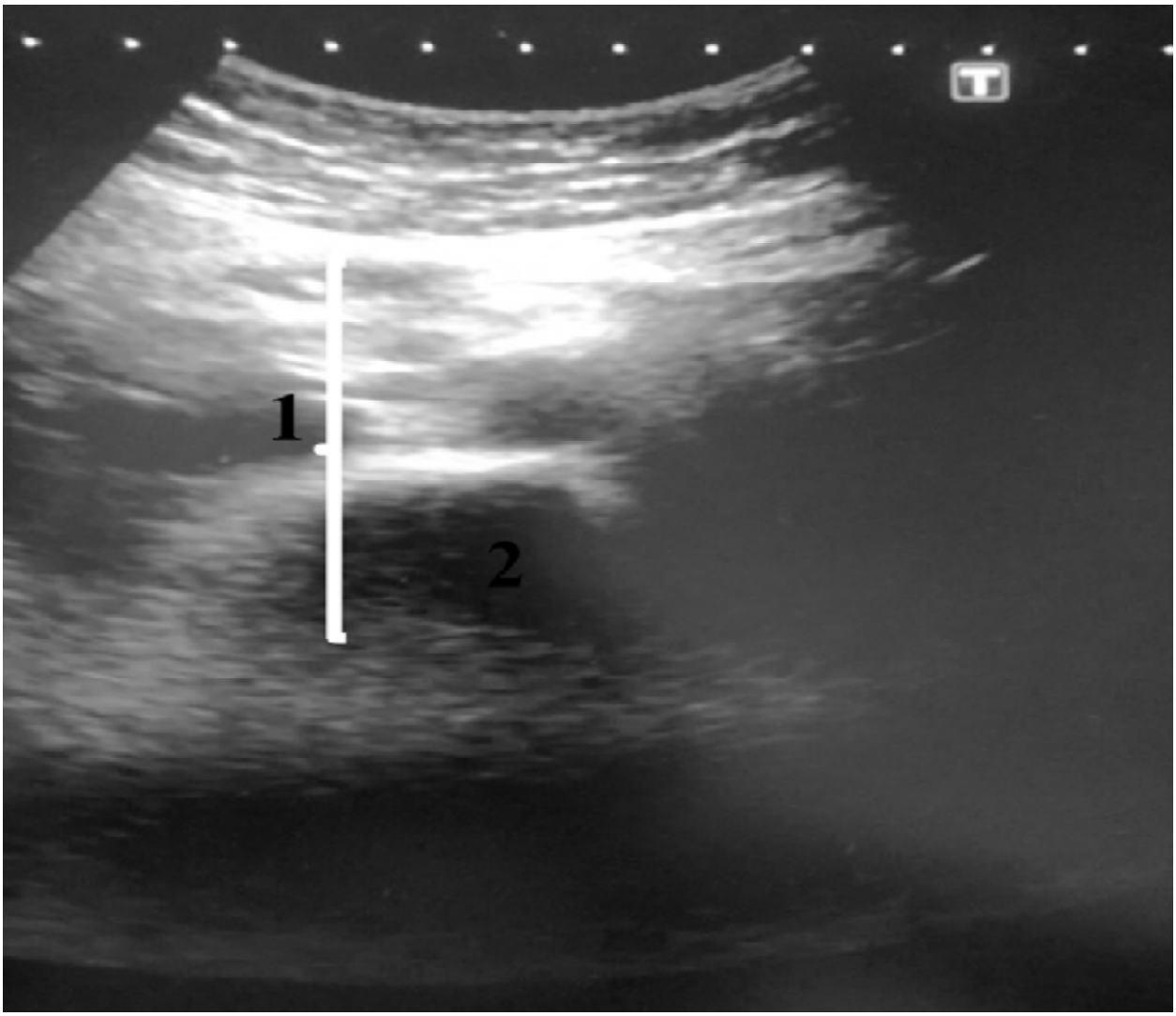
d) Anthropometric measurements are done to calculate BMI and WHR .

BMI > 25 for males and females are taken to be significant to indicate obesity.

e) Visceral fat thickness (VFT) was measured by ultrasound. The following procedures are made out in measuring the visceral fat thickness.

- Patient should be in fasting
- Bowel preparation done by enema
- Patient in supine posture with full expiration
- USG probe is kept 5 cm above the umbilicus in the midline joining xiphisternum and umbilicus
- Distance between the internal surface of rectus abdominis muscle and posterior wall of aorta are measured.
- Frozen images are taken. Atleast 3 measurements are taken and its mean in calculated to avoid measurement errors.

VISCERAL FAT THICKNESS MEASUREMENT



1 - distance between the internal surface of rectus abdominis and aorta

2 - aorta

OBSERVATIONS AND RESULTS

In the present study, 50 patients of type 2 diabetes were selected and studied. They were subjected to detailed clinical examination. The age distribution is as follows.

TABLE I

AGE DISTRIBUTION:

AGE IN YEARS	NO.OF CASES
< 40	3
41 – 50	20
51 – 60	18
> 60	9
Total	50

This is the bar diagram showing the age distribution of the study . 50 males and 50 females were taken equally. Most of the patients fall in between the age group of 41 – 50. The second highest group was between 51 – 60.

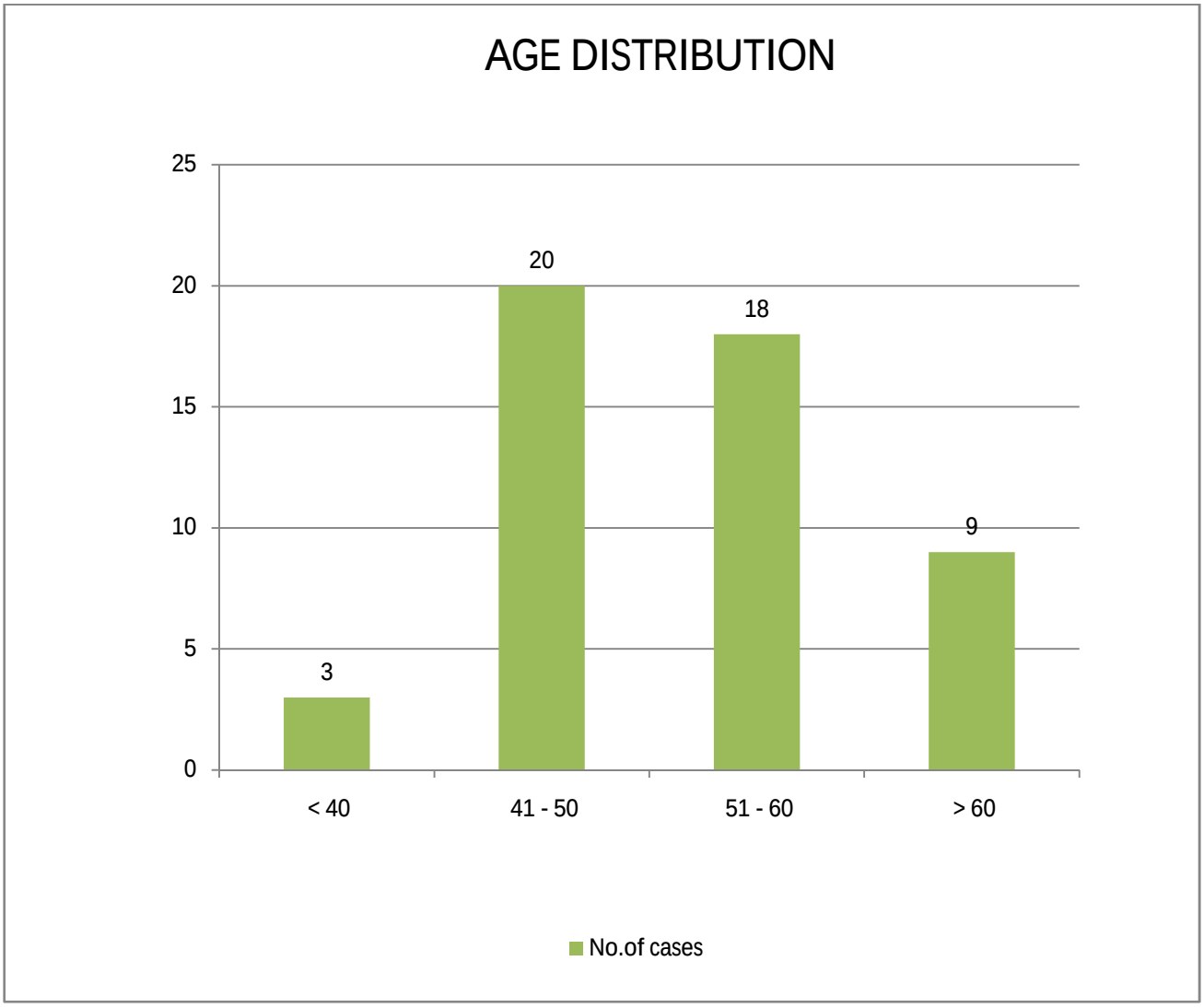


TABLE II

SEX DISTRIBUTION OF THE STUDY

SEX	NO.OF CASES
Male	25
Female	25
Total	50

As previously mentioned , 25 males and 25 females were taken equally for the study. They were selected according to the inclusion and exclusion criteria of the study. This picture shows the sex distribution of the study.

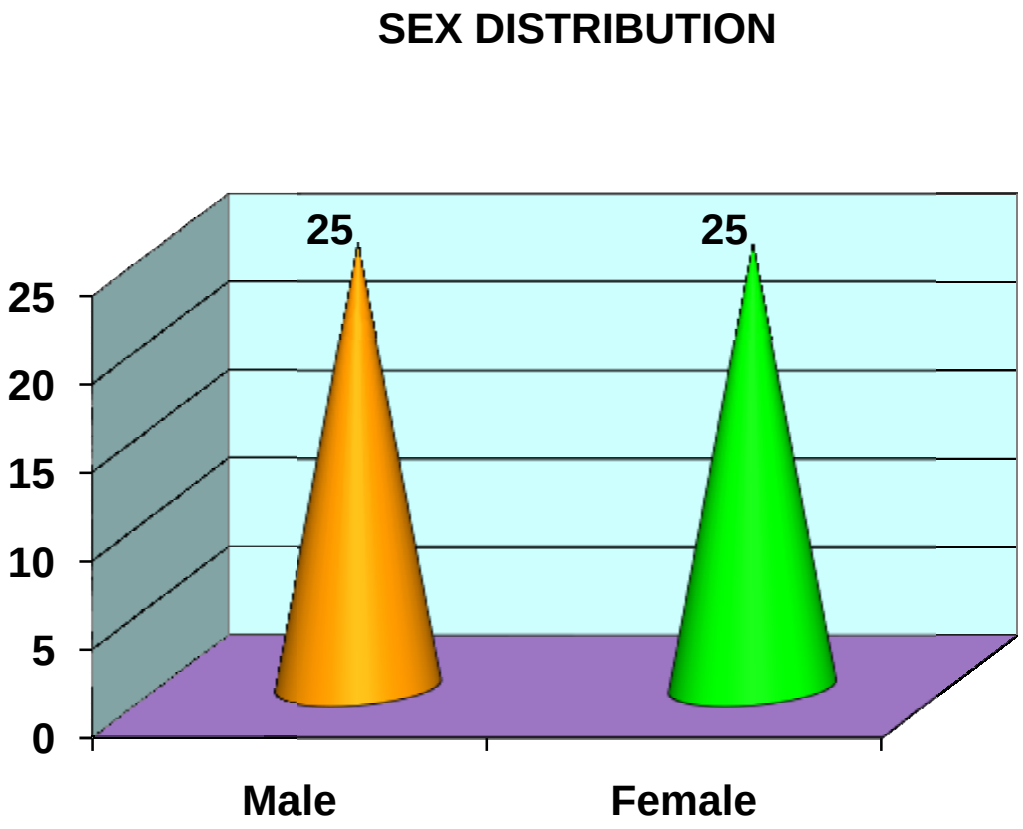


TABLE III

BMI DISTRIBUTION IN TYPE 2 DIABETIC SUBJECTS

BMI	No.of cases
< 26	7
26.1 to 28.0	27
28.1 to 30.0	8
> 30	8
Total	50

As per inclusion criteria, subjects were selected with BMI > 25. This diagram shows the BMI distribution of the study. Among 50 patients selected , around 27 patients fall in BMI between 26 – 28 .

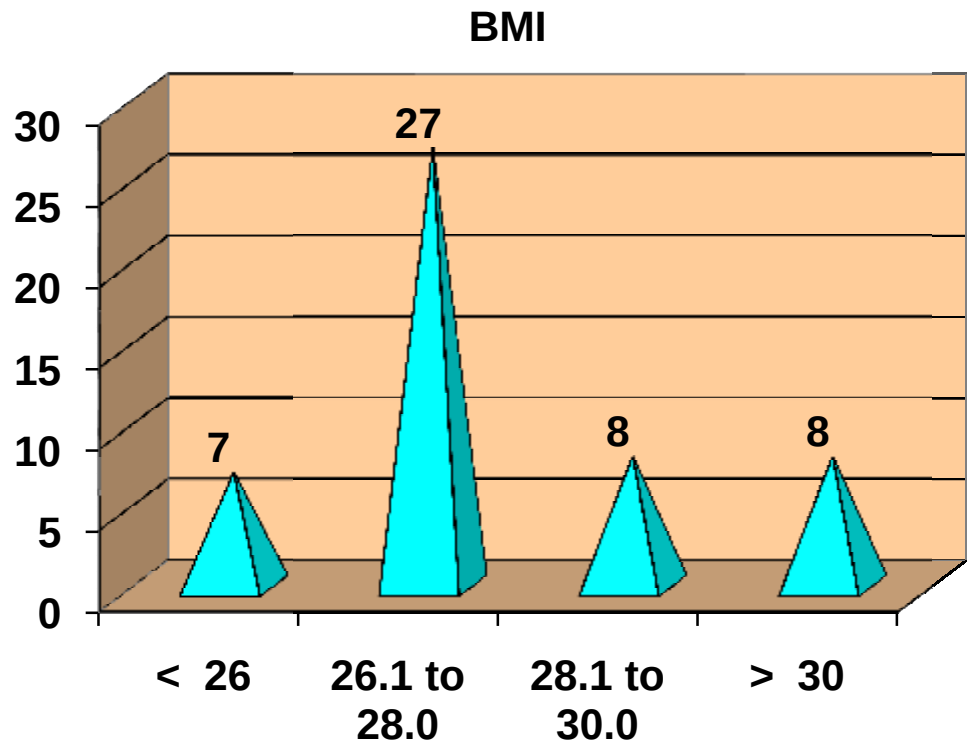


TABLE IV

CORRELATION BETWEEN VISCERAL FAT THICKNESS AND TOTAL CHOLESTEROL IN TYPE 2 DIABETIC SUBJECTS.

	Mean	SD	p value
Visceral Fat	6.08	0.97	
Cholesterol	220.72	34.43	< 0.001

This diagram shows the correlation between the mean visceral fat thickness and total cholesterol levels. The mean visceral fat thickness in overall subjects was 6.08. The total cholesterol mean was 220.72, which was almost in the high normal range.

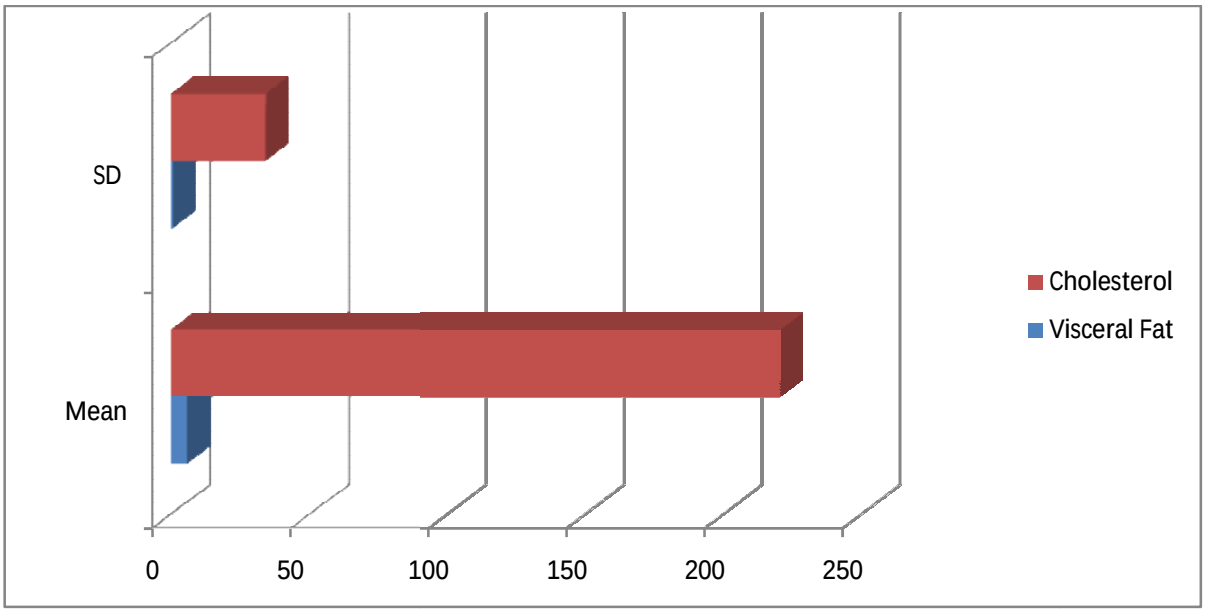


TABLE V

CORRELATION BETWEEN VISCERAL FAT THICKNESS AND TRIGLYCERIDES IN TYPE 2 DIABETIC SUBJECTS.

	Mean	**SD**	**p value**
Visceral Fat	6.08	0.97	
TGL	178.3	41.87	< 0.001

This diagram shows the correlation between mean visceral fat thickness and triglycerides level in type 2 diabetes subjects. The mean visceral fat thickness among 50 patients was 6.08. The mean triglycerides level was 178.3, which was high. Among the 50 subjects, 16 patients who had their VFT between 5.6 – 6.5 had a mean TGL level of 176.6, and patients who had VFT of more than 6.5 had a mean TGL levels of around 210.4.

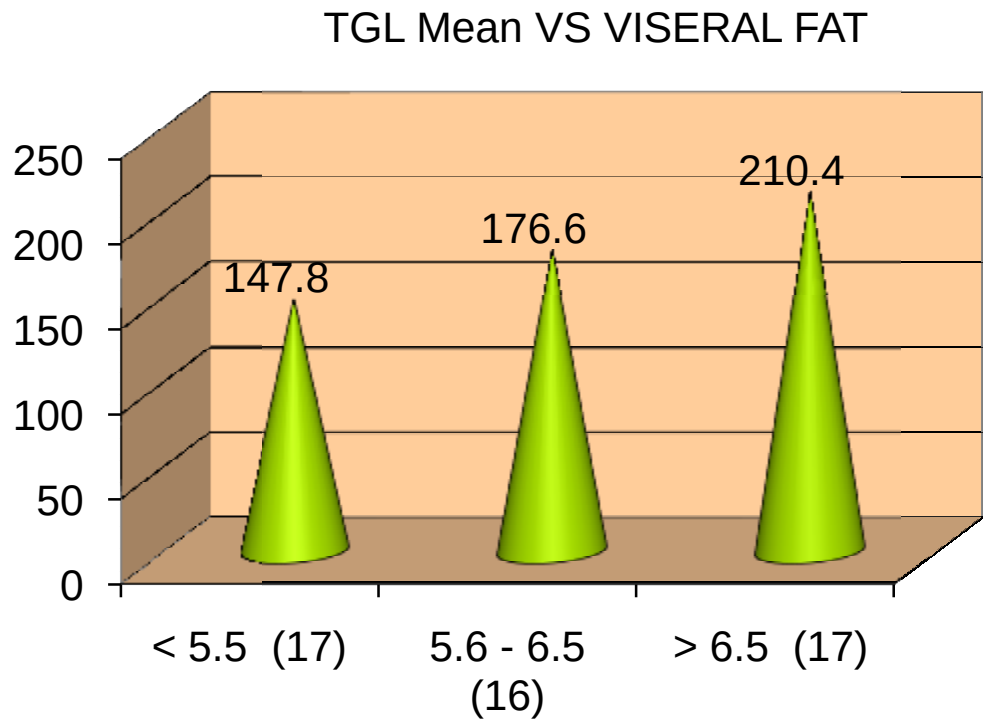


TABLE VI

COMPARISON BETWEEN MEAN VISCERAL FAT THICKNESS AND MEAN OF LIPID PROFILE

Visceral fat and lipid profile	Mean
Visceral Fat	6.08
Cholesterol	220.72
TGL	178.3
HDL	39
VLDL	35.67
LDL	145.32

This diagram shows the overall mean of lipid profile. The mean visceral fat thickness was 6.08 in 50 subjects. The mean total cholesterol was 220.72, mean triglycerides level was 178.3 which was very high, mean HDL was 39, mean LDL was 145.32. Therefore there is a positive correlation between visceral fat thickness with triglycerides and LDL.

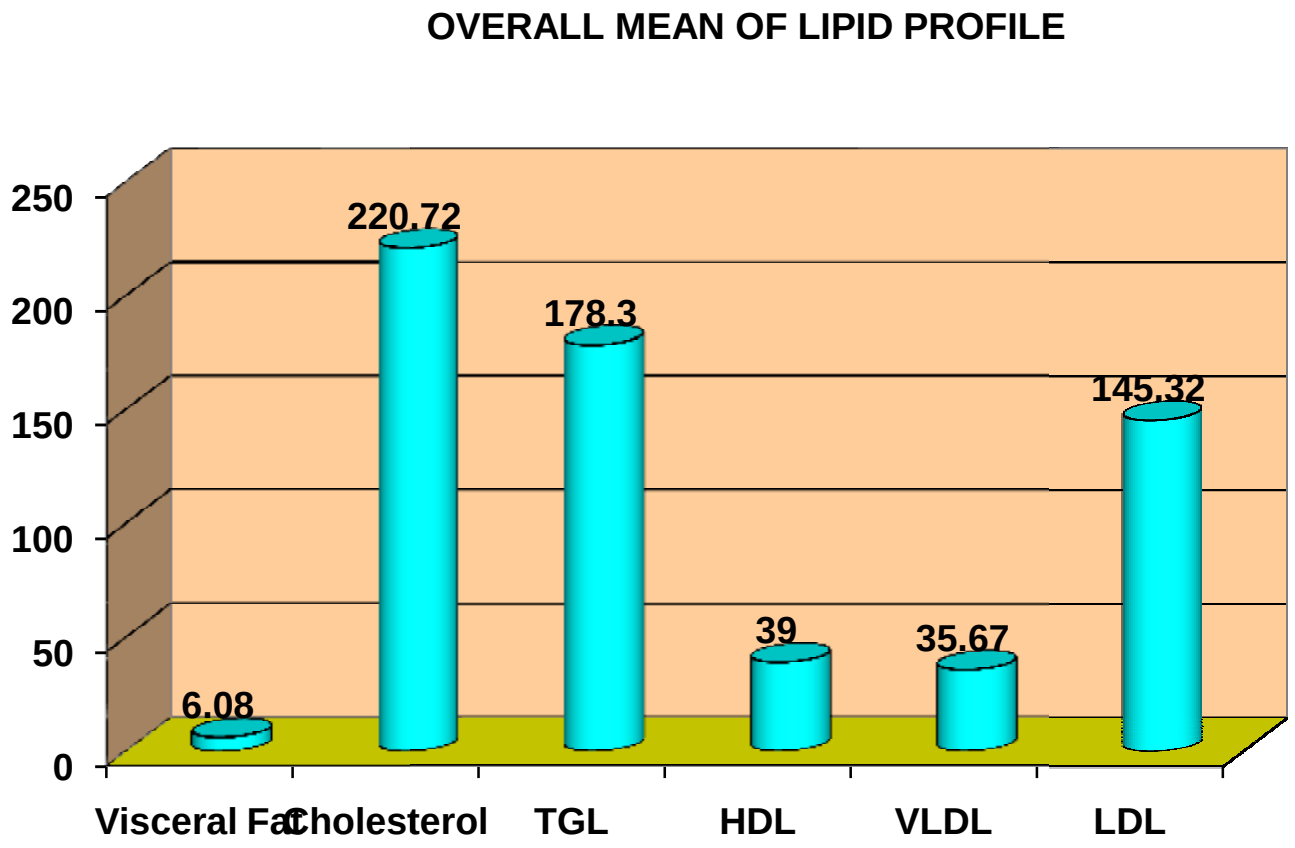


TABLE VII

CORRELATION BETWEEN VISCERAL FAT THICKNESS AND HIGH DENSITY LIPOPROTEINS IN TYPE 2 DIABETIC SUBJECTS

	Mean	SD	p value
Visceral Fat	6.08	0.97	
HDL	39	2.67	< 0.001

This picture shows the correlation between mean visceral fat thickness and mean high density lipoproteins level. The mean visceral fat thickness was 6.08 , whereas the mean JDL level was 39, which was almost in a normal range. Unlike triglycerides level, HDL didn't show an positive correlation with visceral fat thickness.

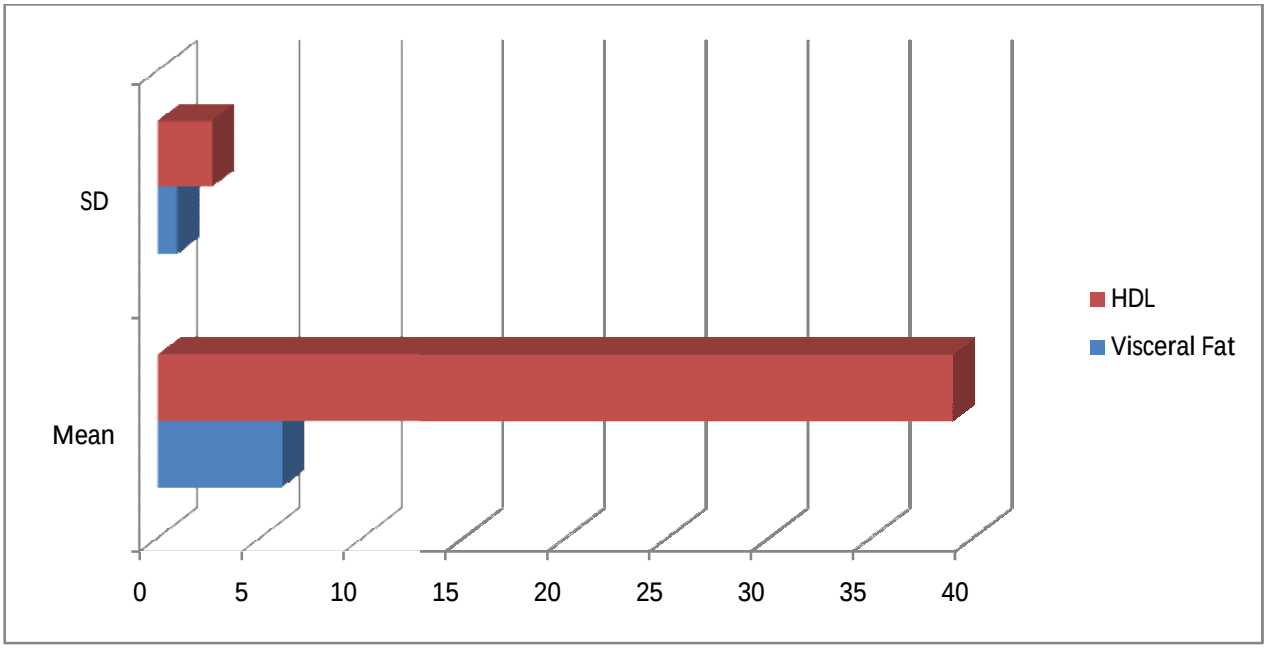


TABLE VIII

CORRELATION BETWEEN VISCERAL FAT THICKNESS AND VERY LOW DENSITY LIPOPROTEINS LEVEL IN TYPE 2 DIABETIC SUBJECTS

	Mean	SD	p value
Visceral Fat	6.08	0.97	
VLDL	35.67	8.47	< 0.001

This diagram shows the correlation between the mean visceral fat thickness and mean very low density lipoprotein levels. The mean visceral fat thickness was 6.08, whereas the mean VLDL levels was 35.67.

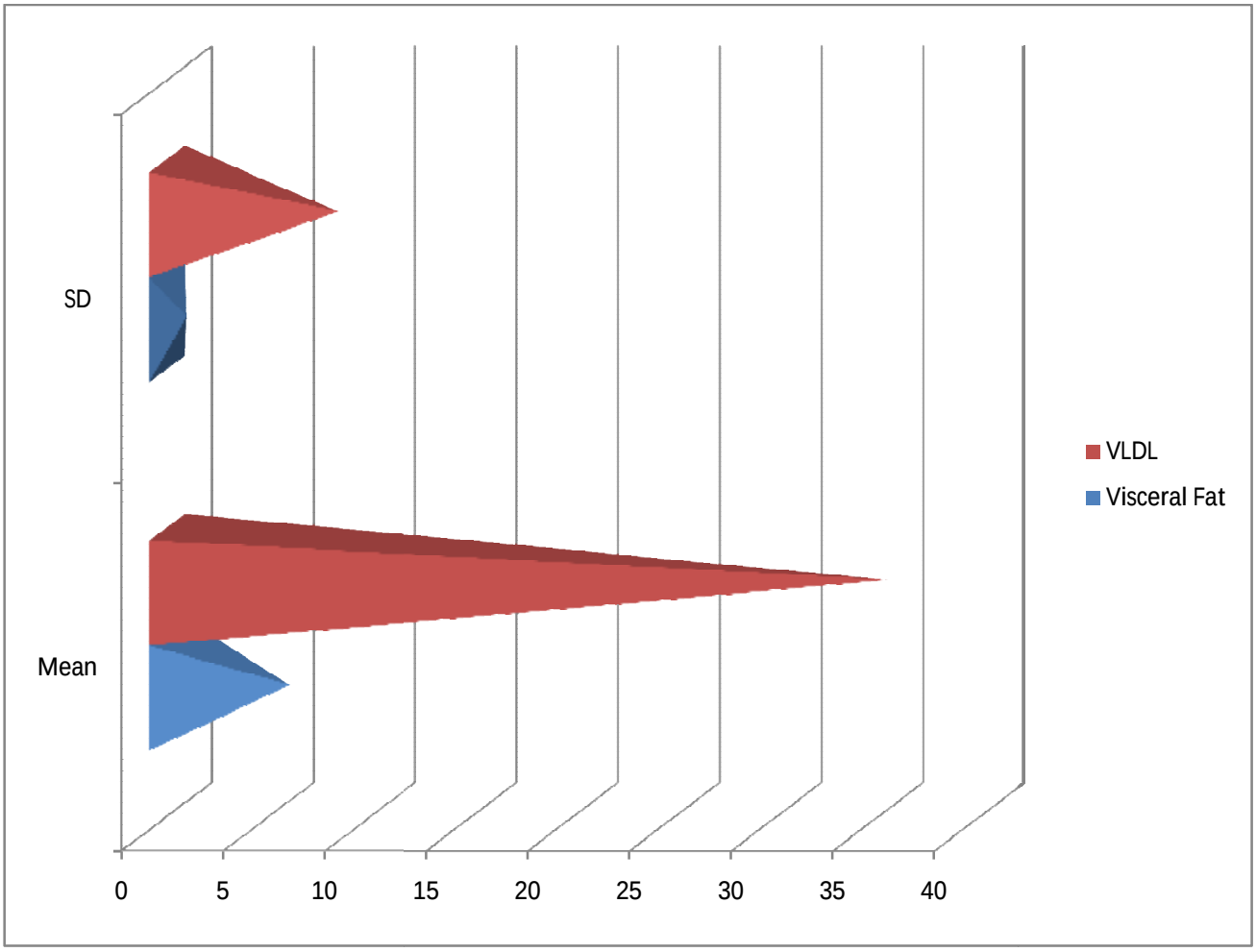


TABLE IX

CORRELATION BETWEEN VISCERAL FAT THICKNESS AND LOW DENSITY LIPOPROTEINS IN TYPE 2 DIABETIC SUBJECTS.

	Mean	**SD**	**p value**
Visceral Fat	6.08	0.97	
LDL	145.32	31.41	< 0.001

This picture shows the comparison in the mean of visceral fat thickness and low density lipoproteins level. As already mentioned the mean visceral fat thickness in 50 subjects was 6.08. The mean LDL levels was 145.32, which was almost in the high normal range. Moreover , subjects with VF between 5.6 – 6.5 had a greater LDL levels of around 170. Therefore there is a strong positive correlation between increased visceral fat thickness and LDL levels.

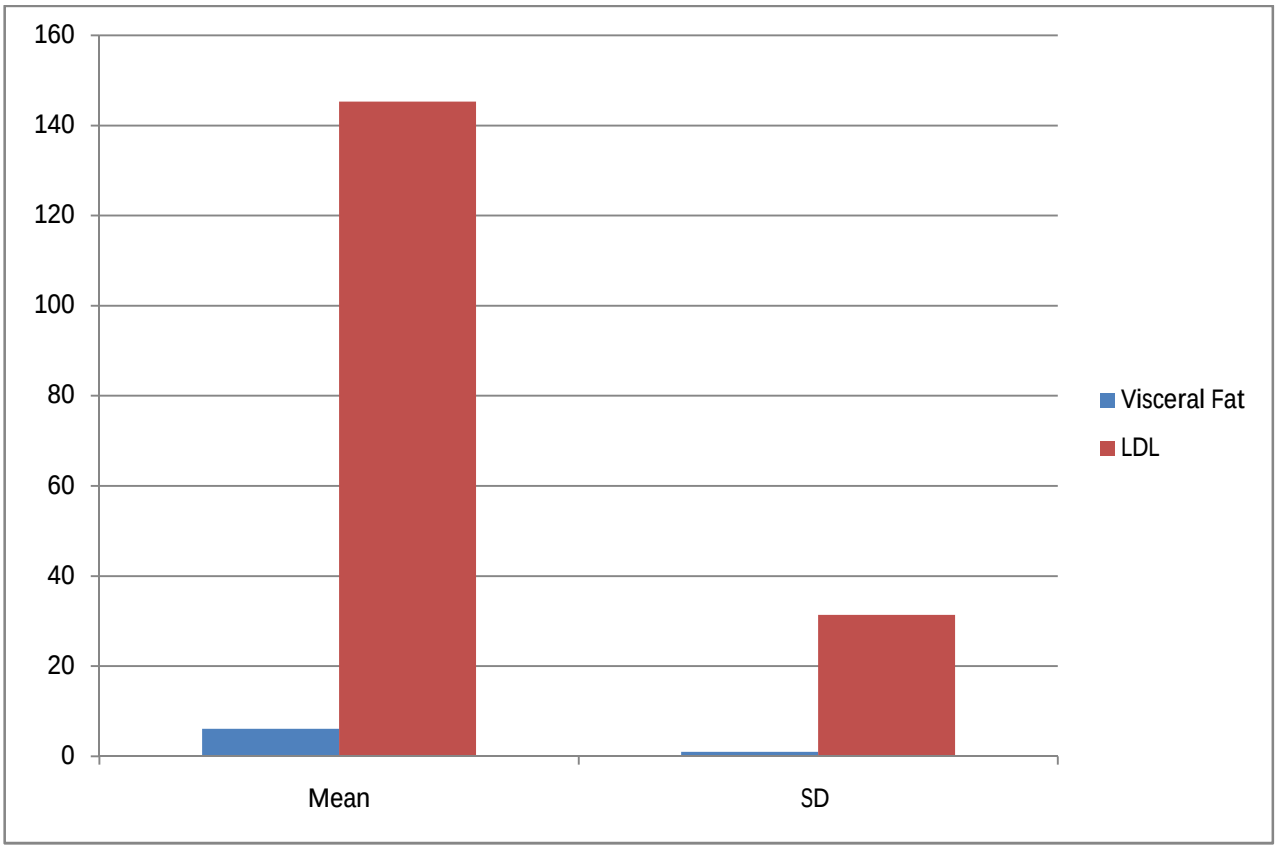


TABLE X

COMPARISON OF VISCERAL FAT THICKNESS AND BMI IN TYPE 2 DIABETES SUBJECTS

	Mean	SD	p value
Visceral Fat	6.08	0.97	
BMI	27.61	1.81	< 0.001

This picture shows the correlation between mean visceral fat thickness and the mean BMI of the 50 subjects taken in this study. Eventhough the subjects with BMI > 25 was taken as the inclusion criteria, the mean BMI was 27.61 among the 50 subjects. Around 27 patients fall in BMI between 26 – 28 . the mean visceral fat thickness was 6.08.

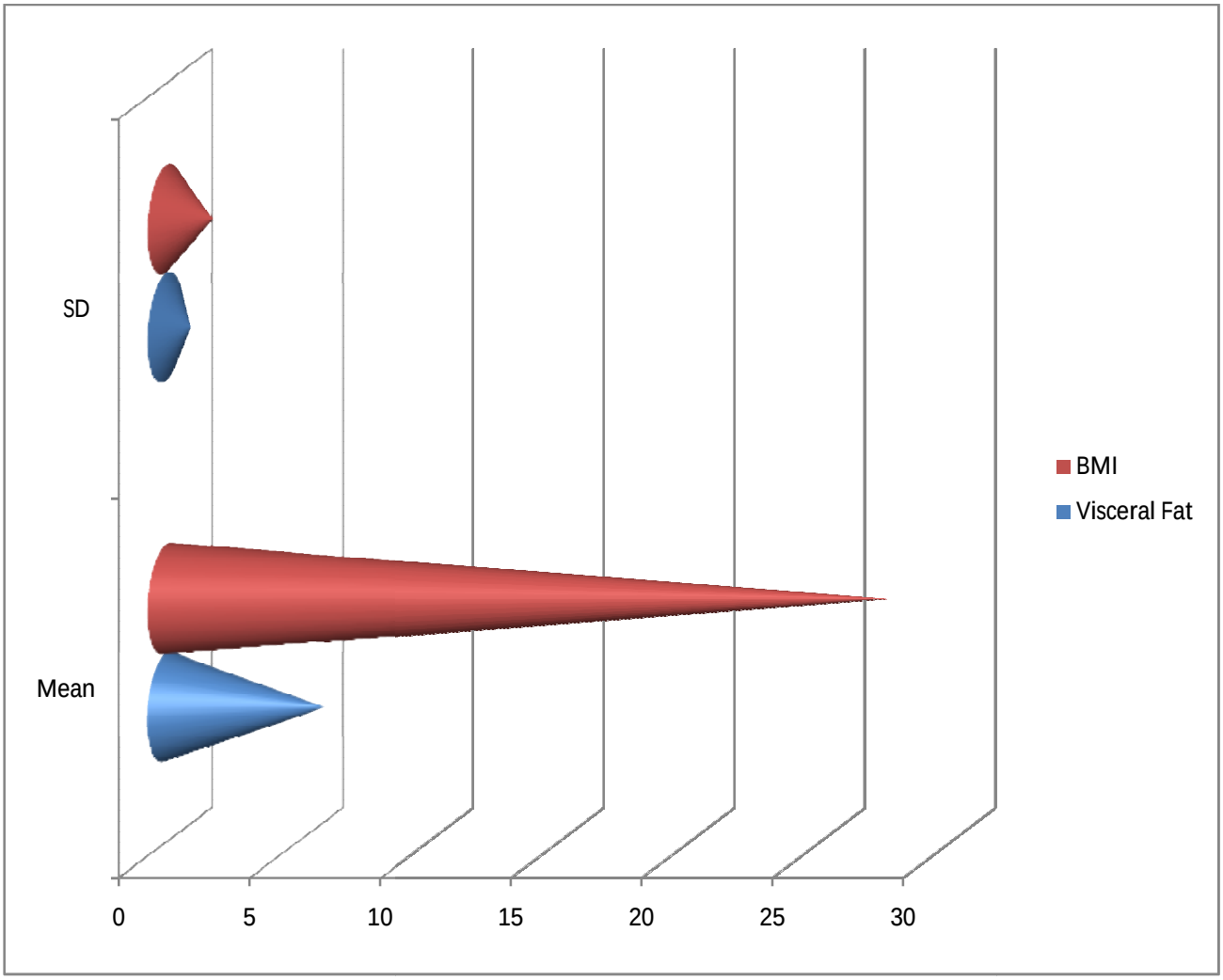


TABLE XI

COMPARISON BETWEEN VISCERAL FAT THICKNESS AND MICROALBUMINURIA IN TYPE 2 DIABETIC SUBJECTS

Microalbuminuria vs Viseral Fat	Mean	SD	p value
Present (13)	7.22	0.59	< 0.001
Nil (37)	5.68	0.74	

This picture shows the correlation between visceral fat thickness and presence of microalbuminuria in 50 type 2 diabetic individuals. Among the 50 patients it was found that 13 patients had microalbuminuria out of which more than 90% of the patients had a visceral fat thickness of more than 7. This clearly shows that there is a strong positive correlation between increased visceral fat and microalbuminuria.

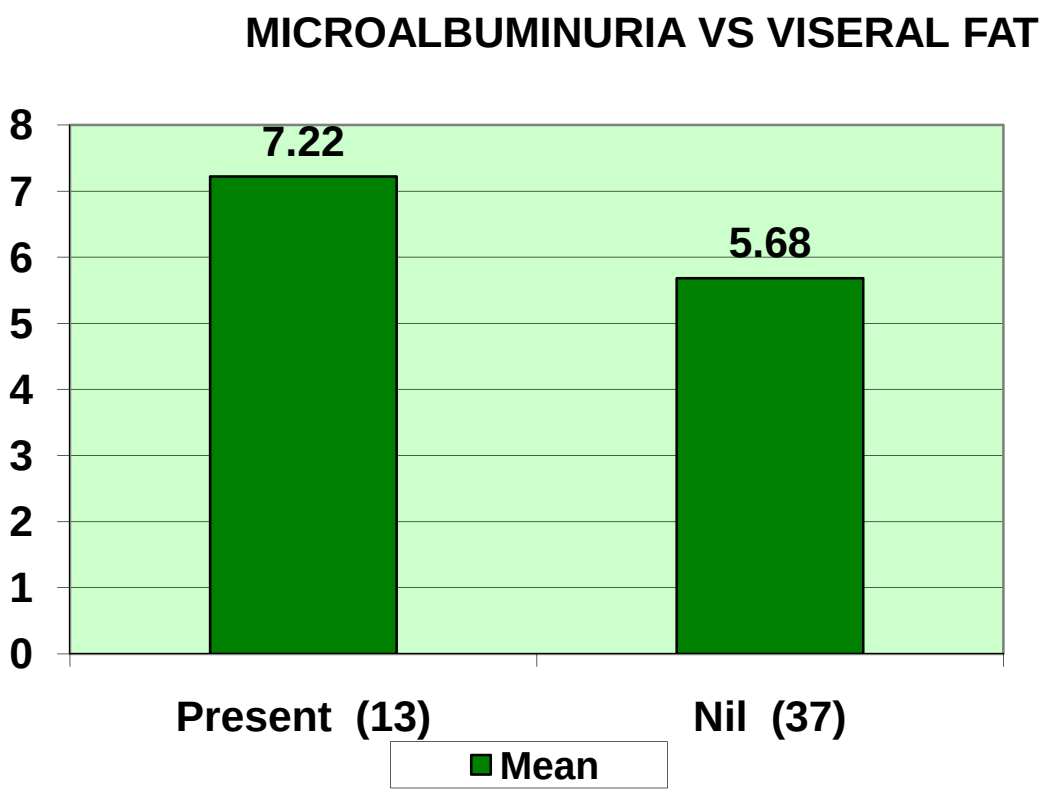


TABLE XII

COMPARISON BETWEEN BODY MASS INDEX AND MICROALBUMINURIA IN TYPE 2 DIABETIC SUBJECTS.

Microalbuminuria vs BMI	Mean	SD	p value
Present (13)	29.59	1.82	< 0.001
Nil (37)	26.92	1.19	

As visceral fat and microalbuminuria was compared, this picture shows the comparison between BMI and microalbuminuria. 13 patients among 50 were found to have microalbuminuria, out of which most of the patients belong to the group of BMI > 28. The mean BMI among the patients who had microalbuminuria was 29.59 .

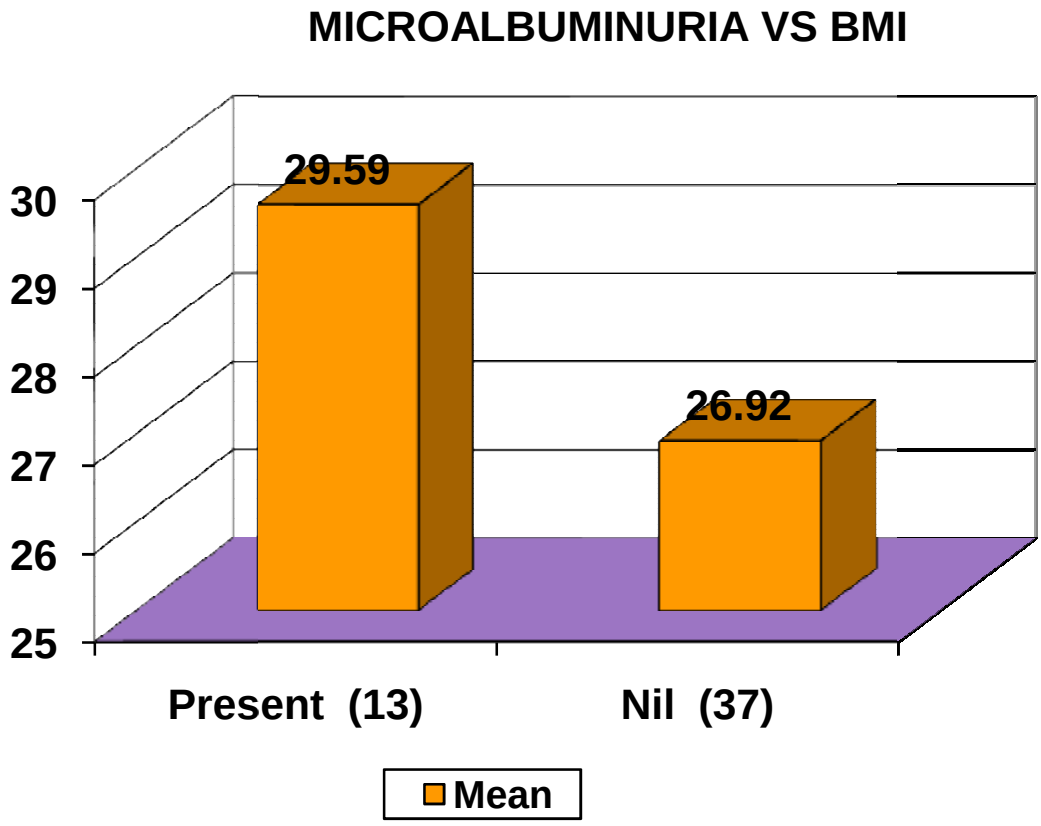


TABLE XIII

NUMBER OF PATIENTS IN DIFFERENT MEASUREMENTS OF VISCERAL FAT THICKNES

Viseral Fat	No.of cases
< 5.5	17
5.6 - 6.5	16
6.6 - 7.5	13
> 7.5	4
total	50

This picture shows the number of cases with different visceral fat thickness measurements. Around 34% of patients had a visceral fat of < 5.5. Around 32% of patients had a visceral fat thickness between 5.6 – 6.5. Around 26% of patients had visceral fat thickness of 6.6 – 7.5.And 8% of subjects had a visceral fat thickness of more than 7.5, who had high levels of TGL , LDL and positivity for microalbuminuria too.

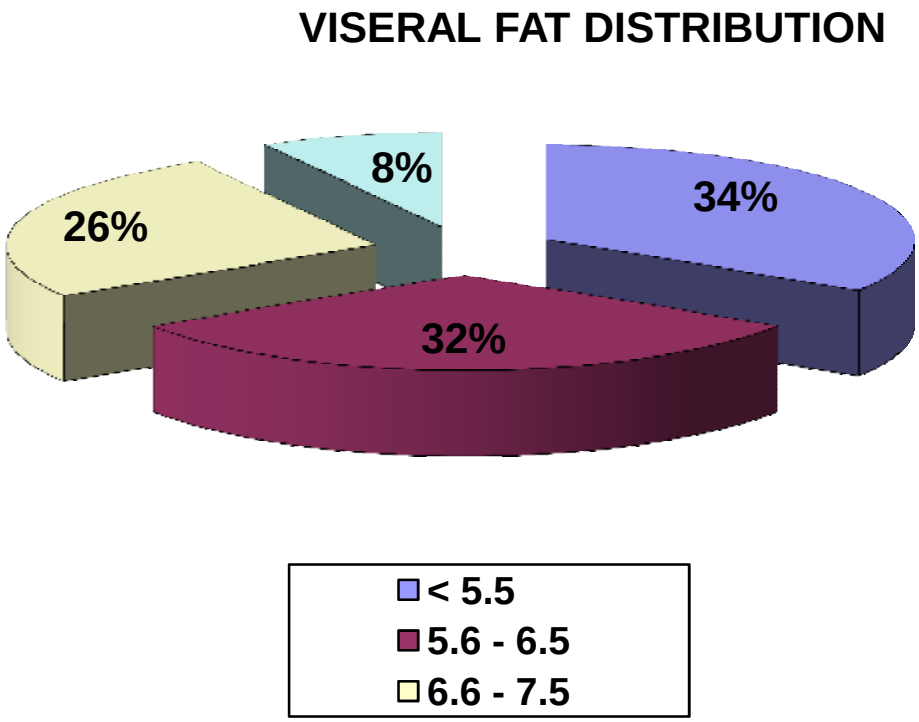


TABLE XIV

COMPARISON OF OCCURRENCE OF INCREASED TGL IN DIFFERENT LEVELS OF VISCERAL FAT THICKNESS IN TYPE 2 DIABETIC SUBJECTS

Viseral Fat	TGL Mean	SD	p' value
< 5.5 (17)	147.8	34.9	
5.6 - 6.5 (16)	176.6	18.2	
> 6.5 (17)	210.4	41.8	< 0.001

This picture shows the triglyceride mean levels in different measurements of visceral fat thickness. Of the 50 subjects, 17 patients had a VFT of < 5.5 who had a TGL levels of around 147.8. But patients who had high visceral fat thickness of more than 6.5 significantly had high levels of triglycerides and their mean level was around 176.6. Therefore there is a strong positive correlation between increased visceral fat thickness and triglycerides levels.

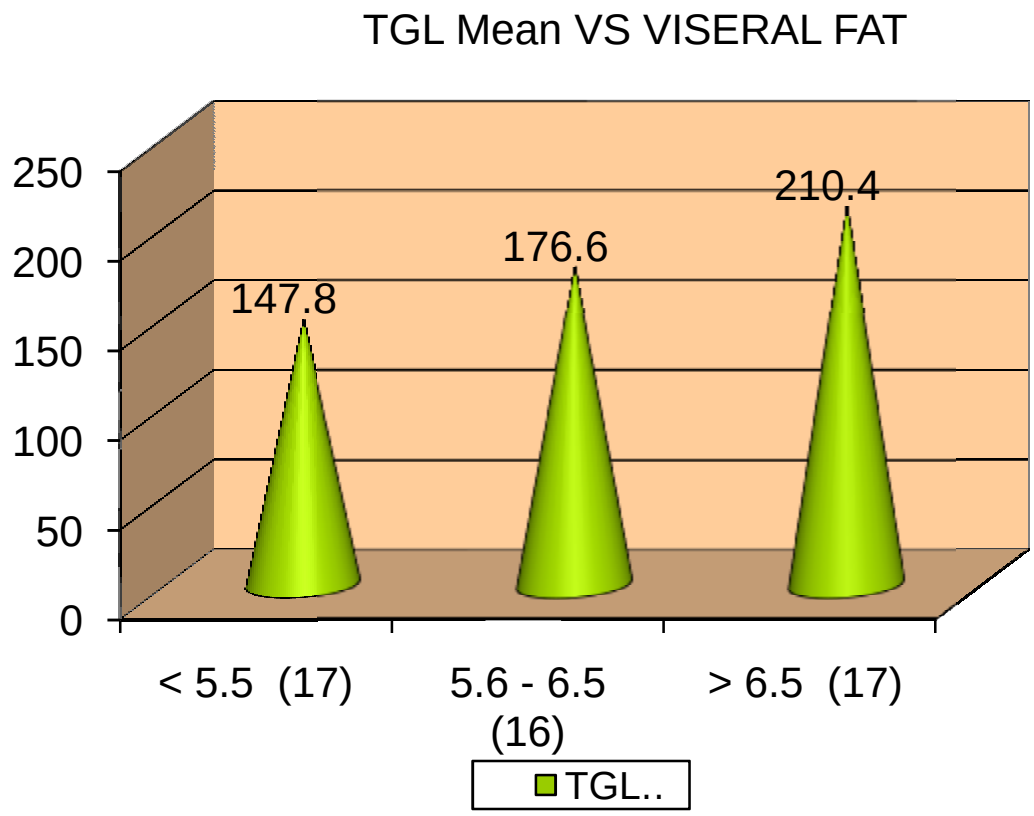


TABLE XV

COMPARISON BETWEEN MICROALBUMINURIA AND TRIGLYCERIDES LEVEL IN TYPE 2 DIABETIC SUBJECTS

Microalbuminuria vs TGL	TGL Mean	SD	p value
Present (13)	212.15	42.4	< 0.001
Nil (37)	166.41	35.02	

This picture shows the comparison between presence of microalbuminuria and triglyceride levels in 50 subjects of type 2 diabetes mellitus. As already mentioned 13 patients had microalbuminuria. More than 90 % of these patients had a visceral fat thickness of more than 7.5. Similarly when their triglyceride levels were compared, the mean TGL level was around 212. Therefore there a strong positive correlation between increased visceral fat thickness with microalbuminuria and triglycerides levels.

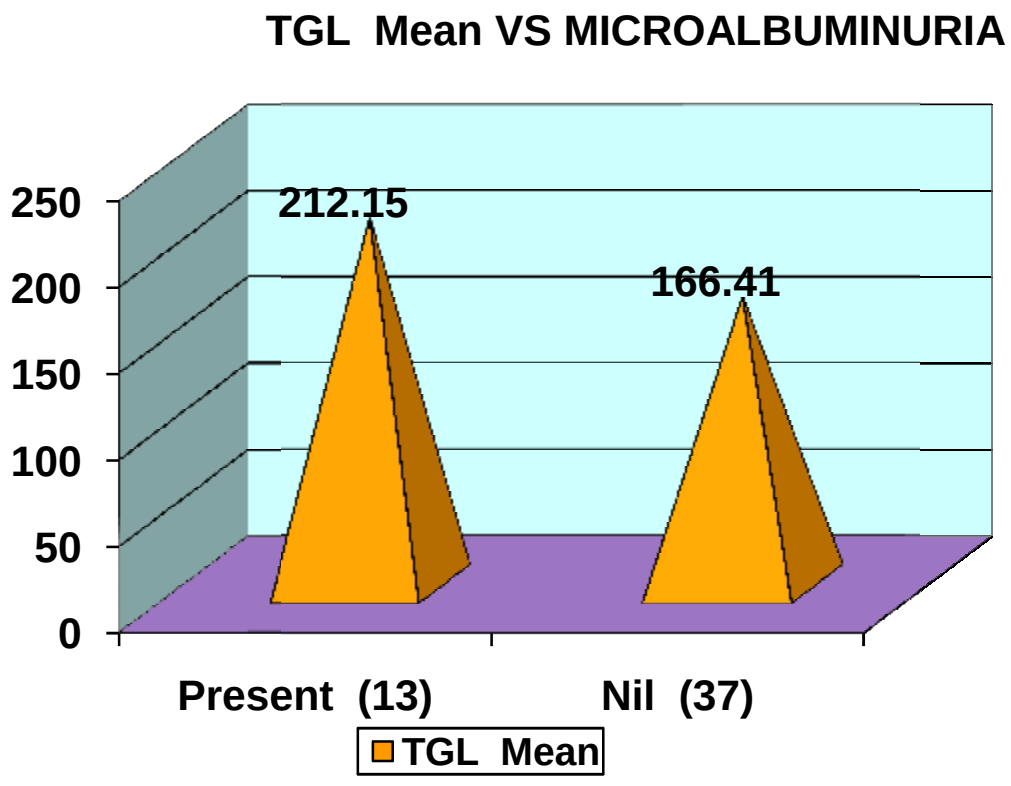
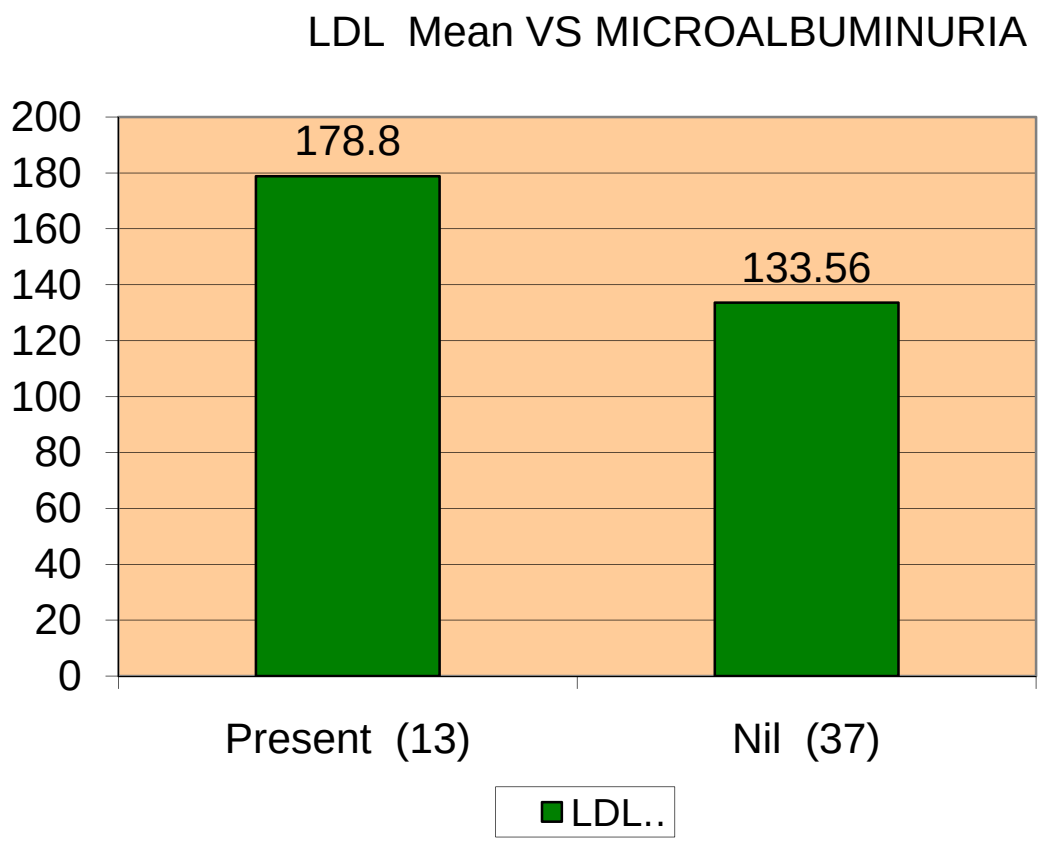


TABLE XVI

COMPARISON BETWEEN MICROALBUMINURIA AND LDL LEVELS IN TYPE 2 DIABETIC SUBJECTS

Microalbuminuria vs LDL	LDL Mean	SD	p value
Present (13)	178.8	22.74	< 0.001
Nil (37)	133.56	24.96	

This picture shows the correlation between the presence of microalbuminuria and LDL levels. Out of the 13 patients who had microalbuminuria, the mean LDL levels was around 178.8. Therefore there is a positive correlation between increased visceral fat thickness with microalbuminuria and LDL levels.



DISCUSSION

Diabetes mellitus refers to a group of metabolic disorders and india is referred to the diabetic capital of the world. At the same time obesity is the emerging problem in most of the developing countries and also in developed countries.

Previously many parameters were used to assess the cardiovascular risk of any individual. BMI, waist hip ratio etc were used previously. But now measuring the visceral adiposity is considered as the method of choice in assessing the risk for cardiovascular diseases. This visceral adiposity or visceral fat thickness can be measured by computerized tomography , dual energy X ray absorptiometry etc..

Eventhough measuring the VFT by CT was considered the gold standard method, there are various study which has been conducted with measurement of visceral adiposity with ultrasonography , and it has been proved that , ultrasound measurement of visceral adiposity is equally efficacious when compared with CT. So, in our study also, ultrasound was used to measure the visceral adiposity .

Moreover, due to high cost and radiation exposure, CT is not preferred. And since ultrasound is a non invasive , easily measurable and less costly, USG is preferred over CT. Another emerging method in measuring the visceral adiposity is measuring the sagittal abdominal diameter (SAG).

Many studies have been done on sagittal abdominal diameter, and this will also show the cardiovascular risk of the patients. SAG is measured by a separate caliper known as Sagittometer.

But in our study, USG guided visceral adiposity measurement in type 2 diabetic subjects with BMI > 25 showed a strong positive correlation with TGL, LDL and microalbuminuria. The cut off for visceral fat thickness was kept in a range as less than 5.5, 5.6 to 6.5 , 6.6 to 7.5 and more than 7.5. patients were classified according to these categories and their lipid profile was compared.

There was a clear positive correlation between increased visceral fat thickness and elevated LDL, TGL and microalbuminuria .

SUMMARY

- Among the 50 diabetic subjects (25 males and 25 females) attending the department of Diabetology in Government Rajaji Hospital, Madurai, with BMI of > 25, increased visceral fat thickness was found in 12 males and 15 females.
- Among the 50 patients, all the patients who had increased visceral fat thickness had an increased triglyceride level and increased LDL level. Therefore there is a strong positive correlation between increased visceral fat thickness and LDL, TGL levels.
- Similarly , 13 patients had microalbuminuria, out of which more than 90% of patients had a Visceral fat thickness of more than 7.5 . They also had a increased triglyceride level and LDL levels.
- There was no significant correlation between visceral fat thickness and total cholesterol levels. Similarly even HDL didn't show show any strong correlation with visceral fat thickness levels.

CONCLUSION

Eventhough there are many parameters to assess the cardiovascular risk like BMI, WHR, etc, measuring the visceral fat thickness is a reliable indicator to assess the cardiovascular risk.

This study which was conducted in Government Rajaji Hospital among 50 type 2 diabetic subjects, showed a strong positive correlation between visceral fat thickness with LDL and triglycerides levels. Similarly 13 patients had microalbuminuria whose visceral fat thickness was > 7.5.

Because of presence of microalbuminuia, there is evidence of subclinical endothelial injury in this patients who are more prone for cardiovascular risk in later part of their life. These patients also had a elevated LDL and TGL which supports the point on cardiovascular risk.

Eventhough CT was considered to be gold standard in measuring the visceral fat thickness, there are many studies which showed ultrasonographic measurement of visceral fat was equally efficient in assessing the cardiovascular risk. Moreover due to radiation exposure and cost of CT, this study was conducted with ultrsonographic measurement alone.

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PROFORMA

NAME : AGE: SEX:

I)GENERAL ASSESSMENT

1) **ANTHROPOMETRIC MEASUREMENTS**

   Height (mts): Weight (kgs) :

   BMI (kg/m^2) :

   Waist (cms) : Hip (cms) :

   WHR :

2) **BLOOD PRESSURE** : mmHg (supine position)

3) **SMOKIING :**

4) **ALCOHOL:**

5) **FAMILY HISTORY :**

   Diabetes -

   Hypertension –

   CAD –

   Renal failure –

6) **TREATMENT HISTORY**

   Diet :

   Oral hypoglycemic drugs / insulin :

II)BLOOD INVESTIGATIONS

1) Fasting blood sugar:
2) Post prandial blood sugar:
3) Blood urea:
4) Serum creatinine:
5) Fasting lipid profile :

III) URINE EXAMINATION

1) Spot urine sample for microalbuminuria :

IV) ULTRASOUND MEASUREMENT OF VFT

1) Subcutaneous fat thickness :
2) Visceral fat thickness :

ABBREVIATIONS

DM – DIABETES MELLITUS

BMI – BODY MASS INDEX

WHR – WAIST HIP RATIO

VFT – VISCERAL FAT THICKNESS

SFT – SUBCUTANEOUS FAT THICKNESS

VFA – VISCERAL FAT ADIPOSITY

HbA1c – GLYCATED HEMOGLOBIN

LDL – LOW DENSITY LIPOPROTEIN

HDL – HIGH DENSITY LIPOPROTEIN

VLDL – VERY LOW DENSITY LIPOPROTEIN

TGL – TRIGLYCERIDES

CT – COMPUTERISED TOMOGRAPHY

USG – ULTRASONOGRAPHY.

MASTER CHART

S.No	Name	Age	Sex	Weight in kg	Height in mt	BMI	Visceral fat thickness(VFT)	Lipid profile					Microalbuminuria
								T.Chol	TGL	HDL	VLDL	LDL	
1	Murugan	65	M	65	1.47	30.08	7.6	248	286	38	57.2	152.8	P
2	Chandran	46	M	63	1.52	27.268	6.8	256	236	39	47.2	169.8	N
3	Bose	50	M	58	1.49	26.124	6.4	210	198	40	39.6	130.4	N
4	Palpandi	49	M	72	1.57	29.21	7.9	290	278	36	55.6	198.4	P
5	Maruthu	48	M	68	1.59	26.897	6	224	160	36	32	156	N
6	Neelamegam	37	M	70	1.51	30.7	8.2	294	204	42	40.8	211.2	P
7	Duraipandi	55	M	59	1.48	26.124	6.6	248	252	39	50.4	158.6	N
8	Karigalan	41	M	61	1.48	27.841	7.1	276	168	38	33.6	204.4	P
9	Manoharan	65	M	75	1.69	27.548	6.2	208	184	39	36.8	132.2	N
10	Durai	56	M	77	1.68	27.281	6	234	204	38	40.8	155.2	N
11	Chellapan	58	M	85	1.72	28.731	7.4	240	262	40	52.4	147.6	P
12	Ravi	45	M	80	1.75	26.122	6.9	224	160	36	32	156	N
13	Balamurugan	57	M	65	1.61	25.076	5.2	204	182	38	36.2	129.6	N
14	Rajkumar	42	M	79	1.59	31.248	6.8	286	238	34	47.6	204.4	P
15	Kannan	40	M	76	1.7	26.297	5.8	208	164	36	32.8	139.2	N
16	Sethupathy	66	M	61	1.54	25.721	5.6	200	176	36	35.2	128.8	N
17	Jeevaraj	43	M	82	1.76	26.472	5.2	200	168	40	33.6	126.4	N
18	Kanthan	66	M	79	1.62	30.102	7.9	262	178	40	35.6	186.4	P
19	Sundaram	63	M	85	1.72	28.731	7.1	228	174	36	34.8	157.2	N
20	Balu	43	M	68	1.6	26.562	6.8	224	196	38	39.2	146.8	N
21	Abraham	60	M	75	1.72	25.351	5	208	185	36	37	137	N
22	Mariappan	44	M	79	1.74	26	5.2	210	198	40	39.6	130.4	N
23	Natarajan	47	M	73	1.65	26.813	5.1	210	195	38	39	133	N
24	Murali	53	M	56	1.45	26.634	5.4	164	92	42	18.4	103.6	N
25	Pothumponnu	65	F	61	1.5	27.111	5.4	184	136	40	27.2	116.8	N
26	Geetha	53	F	64	1.45	30.439	7.5	232	198	36	39.6	156.4	P
27	Mahalakshmi	44	F	68	1.58	27.239	6	224	195	36	39	149	N
28	Agila	62	F	76	1.67	27.25	6.8	252	160	38	32	182	P
29	Swarnam	55	F	65	1.56	26.709	6	212	157	40	31.4	140.6	N
30	Nargeez	60	F	60	1.5	26.66	5.1	156	116	44	23.2	88.8	N

S.No	Name	Age	Sex	Weight in kg	Height in mt	BMI	Visceral fat thickness(VFT)	Lipid profile T.Chol	TGL	HDL	VLDL	LDL	Microalbuminuria
31	Jeeva	52	F	68	1.59	26.897	5.8	212	190	38	35	133	N
32	Malar	50	F	70	1.63	26.346	6.9	206	175	38	35	133	N
33	Jothi	47	F	53	1.45	25.208	4.9	172	120	42	19.6	78.4	N
34	Ponnuthai	52	F	62	1.47	28.691	5	196	152	40	30.4	125.6	N
35	Ramya	45	F	67	1.53	28.621	5.2	160	140	46	30	84	N
36	Meera	60	F	55	1.42	32.235	6.5	232	198	36	39.6	156.4	P
37	Maruthi	65	F	72	1.57	29.21	6.4	224	156	40	31.2	152.8	N
38	Meena	40	F	69	1.59	27.292	6.2	262	176	36	35.2	190.8	P
39	Karpagam	50	F	68	1.49	30.629	5.9	216	160	40	32	144	N
40	Vijaya	48	F	59	1.45	28.061	5.9	210	195	38	39	133	N
41	Lakshmi	65	F	61	1.54	25.721	4.2	172	142	46	28.4	97.6	N
42	Divyalakshmi	55	F	67	1.6	27.171	5.2	166	102	43	20.4	102.6	N
43	Gayathri	45	F	56	1.46	26.271	6	254	156	42	31.2	180.6	N
44	Jothiammal	60	F	59	1.52	25.536	4.2	150	92	40	18.4	91.6	N
45	Eswari	52	F	76	1.67	27.25	6.9	258	184	42	36.8	179.2	P
46	Valliammal	54	F	68	1.59	26.897	6	254	156	42	31.2	180.8	N
47	Maheswari	49	F	70	1.62	26.7	5	220	158	38	37.6	144.4	N
48	Manimegalai	56	F	65	1.42	32.325	7	240	228	40	45.6	154.4	P
49	Swarnam	58	F	56	1.45	26.634	4.8	208	185	36	37	135	N
50	Mohan	42	M	76	1.63	28.604	5.2	208	150	38	30	140	N

ETHICAL COMMITTEE APPROVAL LETTER

Ref.No.8102/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 24.09.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for September 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on September 12th 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the Ethical Committee

Name of P.G.	Course	Name of the Project	Remarks
Dr.G.Premkumar Premkumar.guna @yahoo.com	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai.	**"A study on Association between ultrasonographic visceral fat thickness and cardiovascular risk in type 2 diabetes mellitus"**	**Approved**

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

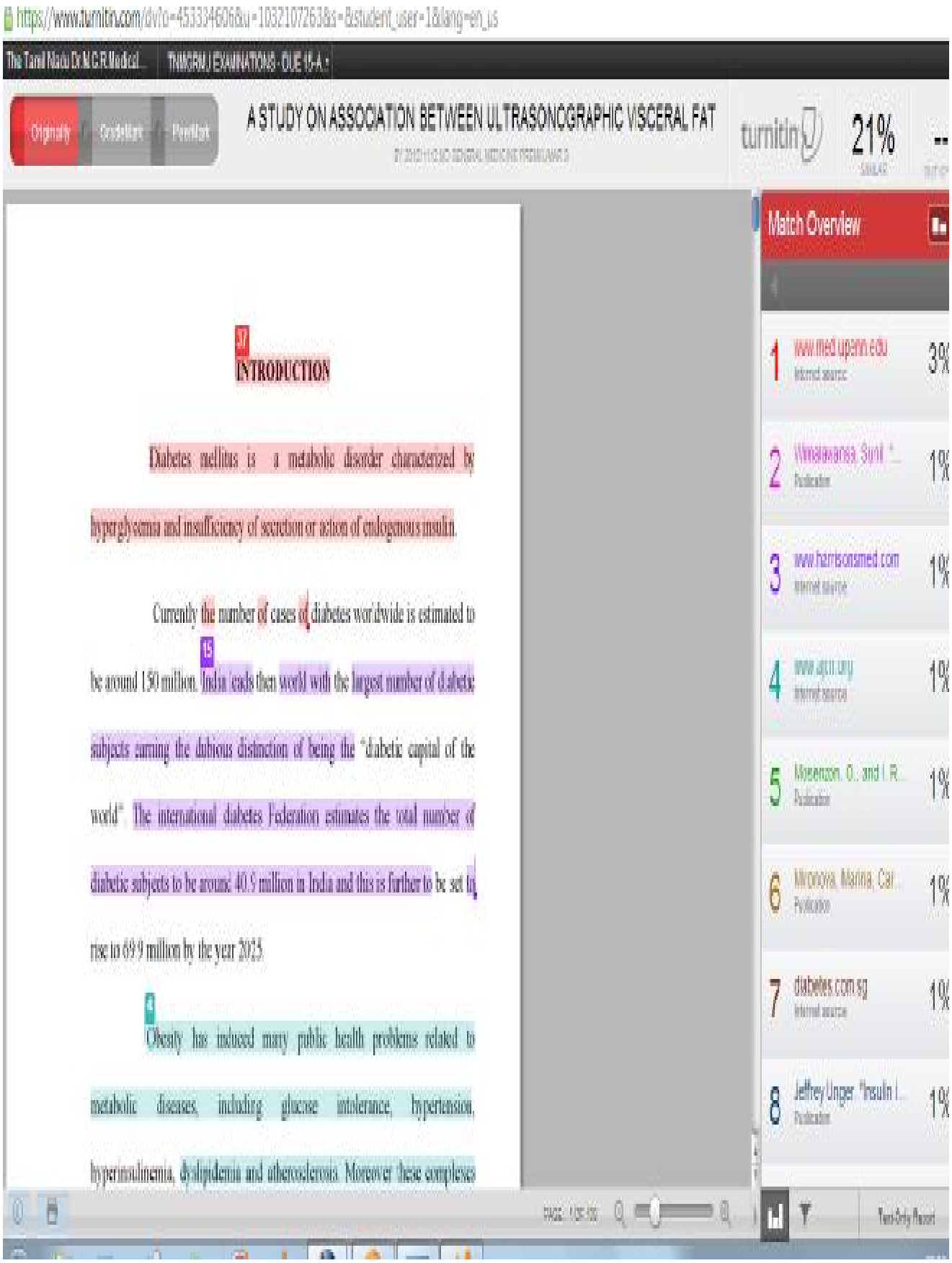
Chairman
Ethical Committee

24.9.14

DEAN/Convenor
Madurai Medical College &
Govt. Rajaji Hospital, Madurai.

24/9/14

To
The above Applicant
-thro. Head of the Department concerned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INTRODUCTION
Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin.
Currently the number of cases of diabetes worldwide is estimated to be around 150 million. 15 India ranks then world with the largest number of diabetic subjects earning the dubious distinction of being the "diabetic capital of the world" The international diabetes Federation estimates the total number of diabetic subjects to be around 40.9 million in India and this is further to be set to rise to 69.9 million by the year 2025.
4
Obesity has induced many public health problems related to metabolic diseases, including glucose intolerance, hypertension, hyperinsulinemia, dyslipidemia and atherosclerosis. Moreover these complexes
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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin.

Currently the number of cases of diabetes worldwide is estimated to be around 150 million. India leads then world with the largest number of diabetic subjects earning the dubious distinction of being the "Diabetic capital of the world". The International diabetes Federation estimates the total number of diabetic subjects to be around 40.9 million in India and this is further to be set to rise to 69.9 million by the year 2025.

Obesity has isolated many public health problems related to metabolic diseases, including glucose intolerance, hypertension, hypertriglyceridemia, dyslipidemia and atherosclerosis. Moreover these complexes are known to enhance the risk of cardiovascular diseases. In particular, the accumulation of adipose tissue predominantly in visceral cavity plays a major role in development of metabolic syndrome and cardiovascular disease.

1