"STUDY OF CAROTID INTIMA MEDIA THICKNESS AS A PREDICTOR OF MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS".

Submitted in partial fulfillment of the

Requirement for

M.D. DEGREE (BRANCH -I) GENERAL MEDICINE

OF

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI.

DEPARTMENTOFMEDICINE

KILPAUK MEDICAL COLLEGE, CHENNAI.

APRIL 2016

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **“”STUDY OF CAROTID INTIMA MEDIA THICKNESS AS A PREDICTOR OF MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS”.”** submitted by **Dr. K. JEEVITHA RAJALAKSHMI** to the Tamil Nadu Dr. M.G.R.Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch I (General Medicine) during the academic period from July 2013 to June 2016 is a bonafide research work carried out by her under my direct supervision & guidance.

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DECLARATION

I, DR.K.JEEVITHA RAJALAKSHMI**,** declare that, I carried out this work on, **"STUDY OF CAROTID INTIMA MEDIA THICKNESS AS A PREDICTOR OF MACROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS"** at the Department of Medicine, Kilpauk medical college & hospital during the period of February 2015 to July 2015. This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the requirement for the award of M.D degree (Branch –I) General Medicine.

Place : Chennai (**Dr.K.JEEVITHA RAJALAKSHMI)**

Date:

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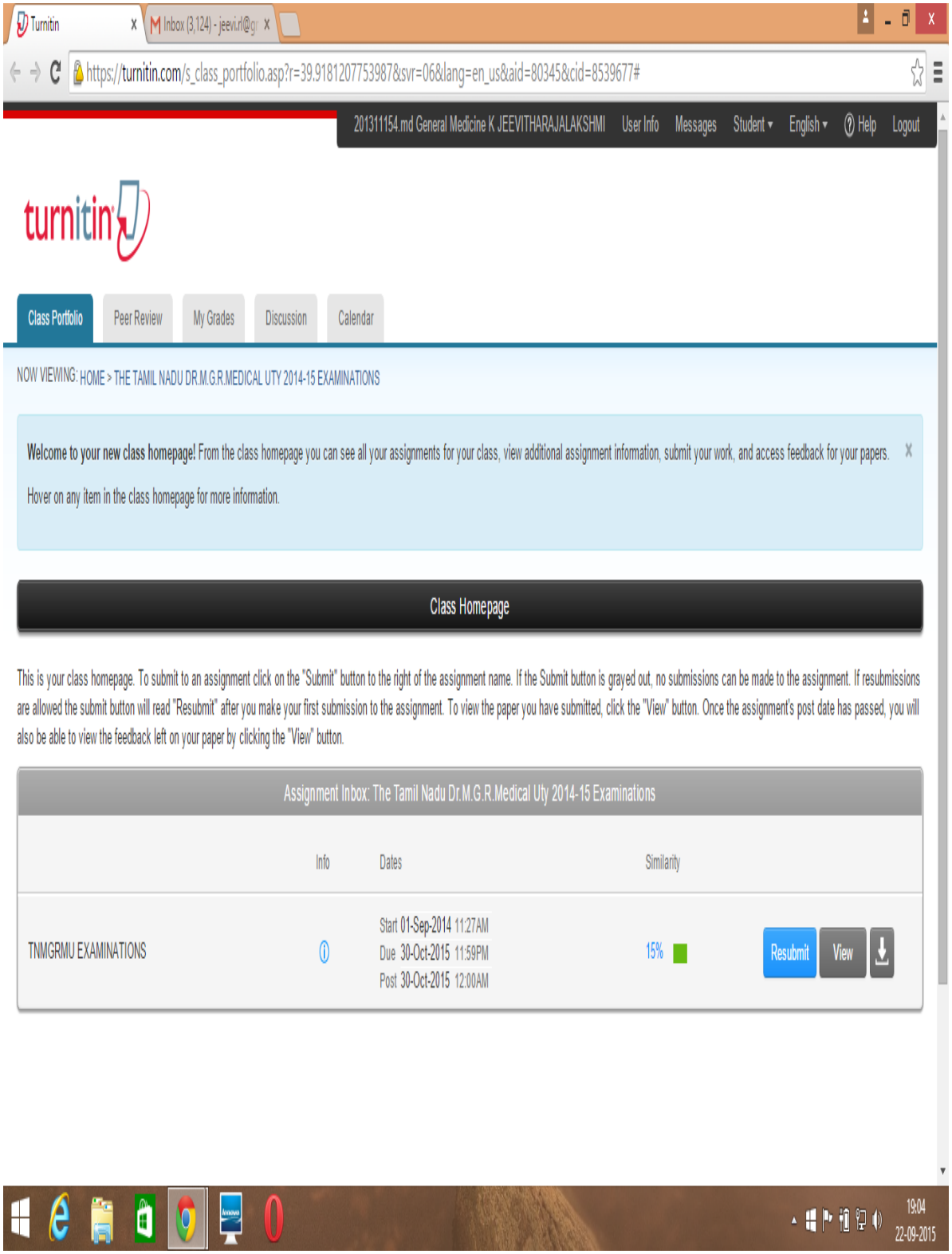
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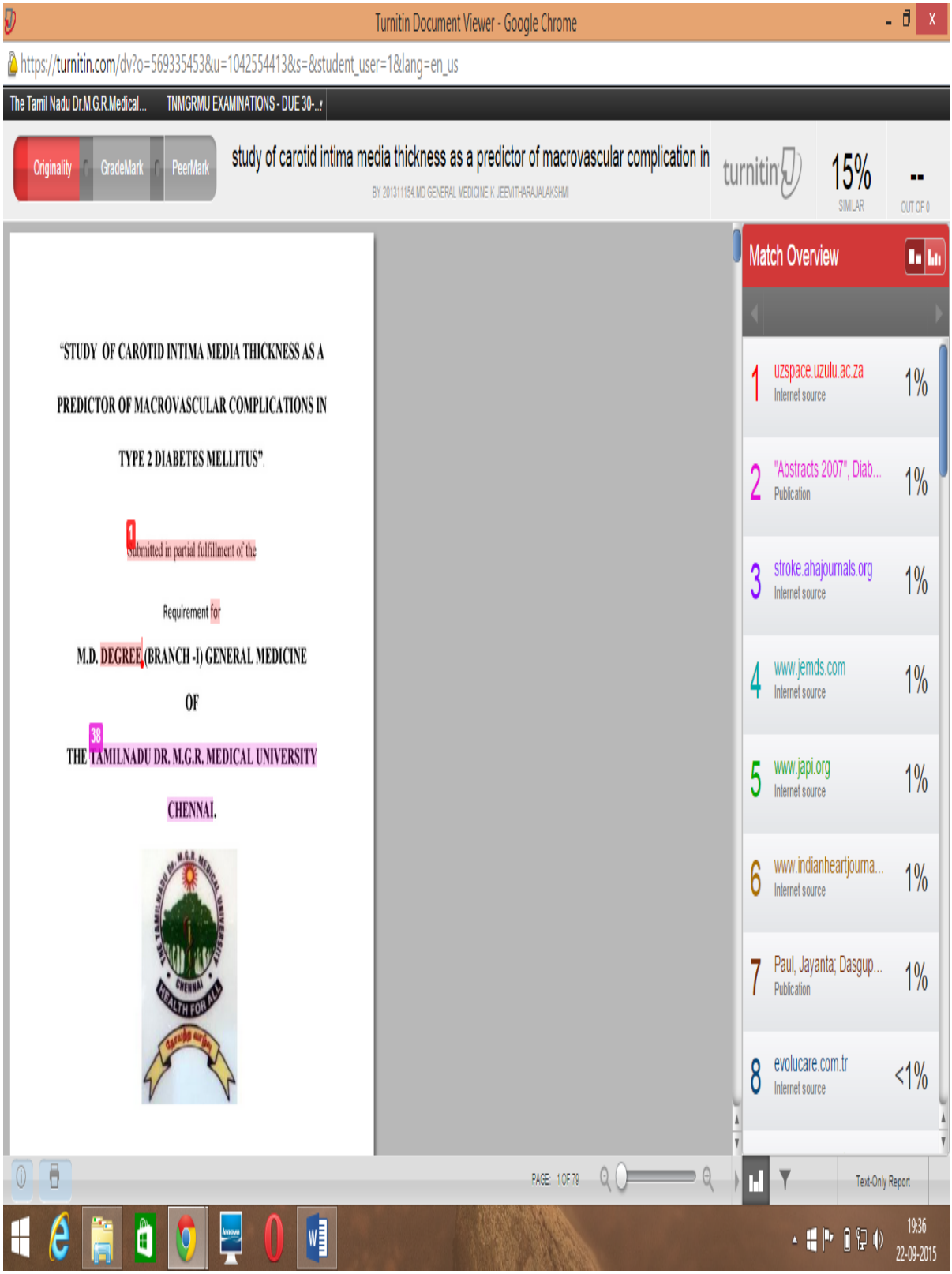
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INTRODUCTION

The most common cause of mortality in patients with type 2 diabetes mellitus (T2DM) are cardiovascular diseases.[1] The Multiple Risk Factor Intervention Trial (MRFIT) and the Framingham study showed a 2–3 fold increase in the risk of atherosclerotic disease in patients with T2DM.[2,3] Similarly, progression of atherosclerosis in persons with T2DM shown in Insulin Resistance Atherosclerotic Study.[4] The Cholesterol Lowering Atherosclerosis Study (CLAS) has shown the heightened risk of atherogenic profile associated with Diabetes Mellitus patients.[5]

World Health Organization has defined stroke as "the rapidly developing clinical signs of focal/global disturbances of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin".[6]

Two types of stroke are: (i) ischemic 80–85% and (ii) hemorrhagic 15–20%.[7] Ischemic strokes are further divided into (a) embolic (b) thrombotic and (c) secondary to systemic hypoperfusion. Apart from other risk factors like smoking, hypertension, hyperlipidemia, family history, etc., diabetes mellitus is a well-recognized risk factor of cerebro vascular ,coronary, peripheral vascular diseases.[7,8,9]

Carotid intima media thickness (CIMT) is widely used as a marker of atherosclerosis, considered to be an important pathogenic mechanism of Macrovascular diseases.[10]

Carotid artery intima-media thickness by B mode ultrasound is a simple, non-invasive and reproducible imaging parameter to evaluate atherosclerotic vascular diseases.

Recently, considerable attention has been directed at the carotid arteries intima media thickness as an early marker of atherosclerotic disease and as a means of showing the effectiveness of medical therapies in treating atherosclerosis. Non-invasive techniques such as B-mode ultrasound can directly assess the carotid intima-media thickness (IMT), which corresponds to the histologic intima and media thickness.

Ultrasound imaging of carotid vessels can provide information on Carotid Intima Medial Thickness (CIMT),wall diameter, plaque presence and type, and calcification, offers the ability to examine pre-symptomatic lesions, assess atherosclerotic burden and hence the risk of macrovascular events.

Such non-invasive screening procedures are valuable in identifying diabetic patients at risk for macro vascular complications. In clinical settings, this can potentially lead to early interventions and treatment.

The carotid arteries are among the vessels that are prone to developing overt atherosclerotic lesions in the presence of risk factors such as smoking, diabetes, hypertension, and dyslipedemia.[10,11]

Diabetes mellitus patients suffer unduly from premature and severe atherosclerosis. The Framingham study shown that " diabetic individuals have higher serum concentrations of lipids and hypertension, obesity, and thus they are more prone to metabolic syndrome and it's sequelae, namely coronary artery disease (CAD), cerebrovascular disease and vascular atherosclerosis" .[12]

In type 2 DM, carotid intimal thickness is significantly more than in corresponding healthy age and sex matched non diabetic subjects.

Hence measurement of carotid intimal thickness using high resolution B mode ultrasonography which is non- invasive well validated method is used to assess early manifestations of atherosclerosis .

REVIEW OF LITERATURE

EPIDEMIOLOGY OF TYPE 2 DIABETES:

The global burden due to diabetes is mostly contributed by type 2 diabetes which constitutes 80% to 95% of the total diabetic population. Diabetes mellitus is the most common metabolic disease which is prevalent in every part of the world and is a major public health challenge of the twenty-first century. The explosive increase in the prevalence of diabetes seen in the last three decades poses huge clinical and economic burden in many countries. The estimates by the International Diabetes Federation (IDF) show that 285 million adults (20 to 79 years) are affected by the disorder in 2010. Epidemiological trends indicate that without proper control and prevention, its prevalence will increase further to 438 million in 2030. This accounts for a global increase by 54%, i.e. a rise from a prevalence of 6.6% to 7.8% in 20 years. Nearly 70% of the people with diabetes live in developing countries; the largest numbers are in the Indian subcontinent and China. Nauru has the highest prevalence of diabetes (30.9%) and will continue to be so in 2030 (33.4%). Many Arab countries, Tonga, and Malaysia are among the top ten countries having high percentages of people with diabetes. There is little gender difference in the distribution in the number affected with

diabetes. The largest numbers with diabetes are in the 40 to 59 age groups (132 million, in 2010) which is expected to rise further. By 2030, there will be more diabetic people in the 60 to 79 age groups (196 millions).(25,26)

DIABETES PREVALENCE IN INDIA

Diabetes prevalence in India in 1970's was 2.3% in urban and 1.5% in rural areas, as shown by the multi-centric study by the Indian Council of Medical Research (ICMR). In 2000s, the prevalence has risen to 12% to 19% in urban areas and to 4% to 9% in rural areas. Though, the studies are not strictly comparable due to methodological differences, the rising trend in prevalence of diabetes in urban and rural areas in India, is evident. National studies or population based studies on diabetic complications are sparse in India.(26,27) A few population based studies indicate the prevalence of retinopathy to be 18% to 27.0% and overt nephropathy to be about 2.2% with a large percentage (27%) having microalbuminuria. Peripheral vascular disease is prevalent in 6.3%, peripheral neuropathy in 26%, and coronary artery disease (CAD) is detected in 21%. The major contributory factors for the high prevalence of the complications are; delayed diagnosis of diabetes, inadequate control of glycaemia, hypertension, and lack of awareness about the disease among majority of the public.

ECONOMIC BURDEN DUE TO DIABETES

Diabetes care cost high and is escalating world wide. It is estimated by the WHO that the global expenditure for diabetes care would increase from 234 Billions in 2007 to 411 Billions in the next 20 years. The WHO estimate is based on " lost productivity due to diabetes, heart diseases, and stroke together show that over the next 10 years, lost national income in billions of USD will amount to 555.7 in China, 303.2 in Russian Federation, 336.6 in India, 49.2 in Brazil, and 2.5 in Tanzania".(26,27)

A study in India showed that the median expenditure had risen from INR 4,200 to INR 9,000 between 1998 to 2005. The indirect cost is much higher than the direct cost and is more difficult to assess. The proportion of annual income spent on health care is about 25% to 30% by the people. The cost increases many fold when diabetic complications are present.

PREVENTION OF DIABETES

Several systematic long-term prospective studies from different parts of the world have shown that type 2 diabetes is largely preventable. Although the genetic factors cannot be modified, its interaction with the diabetogenic environmental factors can be prevented by modifying obesity, diet, and physical

activity. Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2) have shown that by improving physical activity and by using healthy diet, incidence of diabetes can be significantly reduced with a relative risk reduction of ~ 30%, in persons with IGT. Metformin in small doses was also found to be effective in primary prevention of diabetes. Lifestyle changes due to urbanisation and modernisation have caused unhealthy diet habits, lack of physical activity, and increased stress leading to overweight or obesity with higher levels of insulin resistance. India and many other developing countries are going through this scenario and as a result, we notice more of chronic metabolic disorders than communicable diseases posing increasing challenge to the national health.(29)

Type 2 diabetes mellitus patients are at 2- to 6-fold higher risk for macrovascular disease than persons without diabetes. Moreover, atherosclerosis is thought to begin in the early prediabetic stage and to progress silently for years before clinical events such as acute coronary syndromes, cerebrovascular accidents or peripheral vascular disease occur. So, The above facts compels strongly for detecting early changes of atherosclerosis and starting intervention earlier in type 2 diabetic patients.(15).

GENETIC FACTORS IN DIABETES:

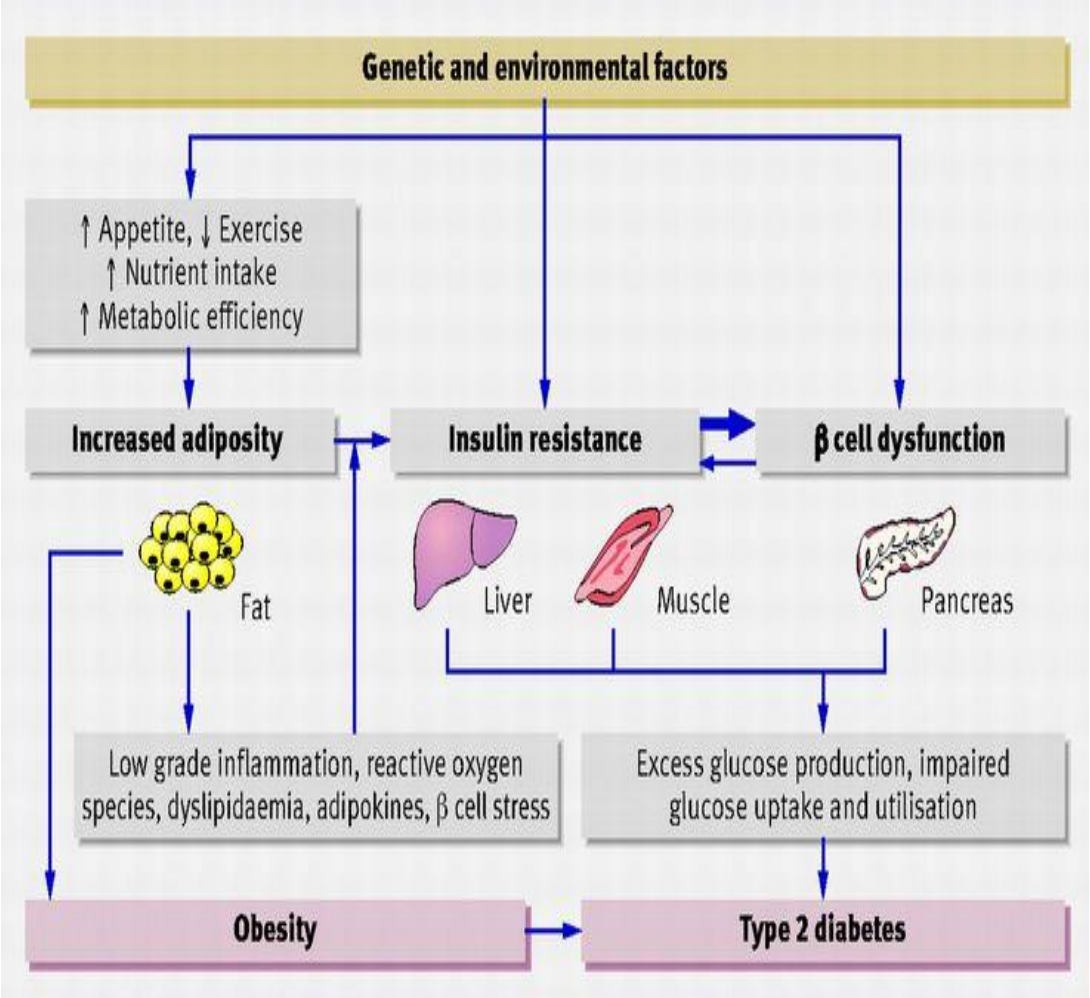
Type 2 diabetes is a polygenic disorder, caused by a cluster of susceptibility genes. The classic method of candidate gene identification has been unsuccessful in unravelling these genes. The problem has also been approached by studying the functional candidate genes, tracing back the functional or biochemical abnormality to the genetic abnormality. Further, linkage analysis and micro satellite genotyping technique followed by positional cloning has been tried with limited success. (38)

Although the prevalence of these varieties of diabetes would vary in various ethnic groups, it is estimated that they do not make more than about 5% to 10% of young-age diabetes. Some rare genetic abnormalities described are insulin gene abnormality which produces an abnormal insulin or a convertase deficiency which impairs the conversion of proinsulin to insulin. Abnormalities of insulin receptor are rare. They produce syndromes of extreme insulin resistance (type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome; Table 1). If all these anomalies are put together, they may not make more than 1% of all type 2 diabetes. The search for genetic abnormalities in the common form of type 2 diabetes has been very intense but not very fruitful. Most susceptibility genes described increased the hazard ratio in diabetics versus the normal population only marginally.(39,40)

Of a variety of candidate genes, calpain-10, Kir 6.2, peroxisome proliferator activated receptor-γ, hepatocyte nuclear factor-4α gene and transcription factor 7-like 2 gene are important. Many of these genes predispose to obesity, thus leading to diabetes. However, an interesting gene, ENPP-1 K121Q causes insulin resistance in the non-obese Asian Indians and is one of the susceptibility genes in this population.

ENVIRONMENTAL FACTORS

Physical inactivity and excessive caloric intake are well recognised environmental factors producing type 2 diabetes. These factors can produce the disease independently in a genetically susceptible person, but usually work via production of obesity. Obesity and type 2 diabetes are inextricably interrelated. They further coexist in the form of metabolic syndrome, together with other anomalies like hypertension, high triglycerides, and low HDL-cholesterol. It is estimated that 25% to 30% of the population in India and elsewhere suffers from the metabolic syndrome. In the shadow of a global spurt of obesity, type 2 diabetes is emerging as an epidemic. Obesity results from the interaction of multiple susceptibility genes with environmental factors. By various estimates, aetiologically hereditary factors account for 50% to 70% of the obesity. Obesity is characterised by insulin resistance, an important feature of type 2diabetes.


Genetic and environmental factors
↑ Appetite, ↓ Exercise
↑ Nutrient intake
↑ Metabolic efficiency
Increased adiposity
Insulin resistance
β cell dysfunction
Fat
Liver
Muscle
Pancreas
Low grade inflammation, reactive oxygen species, dyslipidaemia, adipokines, β cell stress
Excess glucose production, impaired glucose uptake and utilisation
Obesity
Type 2 diabetes

GENE-ENVIRONMENT INTERACTIONS

The mechanism of interaction of gene and environment is a very complex issue. The environmental factors interact by altering the expression of genes. There is also a gene-gene interaction. Intrauterine environment also may influence the subsequent development of many non-communicable diseases like diabetes, obesity, and hypertension. Low birth weight, presumably due to poor maternal nutrition leads to development of insulin resistance in childhood and adult life. This is further exacerbated by over-nutrition in the post-natal period.(39,40) Epigenetic phenomenon, where unchanged DNA sequence can lead to altered phenotype, probably due to enhanced or suppressed expression of certain genes that may be responsible for obesity and diabetes Environmental factors may operate through epigenesis.

BIOCHEMICAL PERTURBATIONS

The biochemical perturbations in type 2 diabetes were described earlier than the genetic factors. Of these, the most well known abnormalities are of peripheral and hepatic insulin resistance, and impaired β-cell function. Peripheral and Hepatic Insulin Resistance With the advent of radioimmunoassay, massive data on serum insulin levels in obesity and diabetes became available.

Hyperinsulinaemia was described first in obesity and later in type 2 diabetes, including type 2 normal weight diabetic. Thus, the concept of insulin resistance emerged. In spite of high insulin levels, there is poor glucose utilisation and insulin inaction in the muscle, adipose tissue, and liver.

In type 2 diabetes, adipose tissue in general and visceral fat in particular, exhibits a decreased inhibition of lipolysis and increased lipoprotein lipase activity, both resulting in a heightened flux of fatty acids in the liver and other tissues. High fatty acids levels are known to inhibit glucose utilisation, as demonstrated by Randle (glucose-fatty acid cycle).(40,41) In type 2 diabetes and obesity, the adipose tissue also expresses increased amounts of 11β-hydroxysteroid dehydrogenase type 1 (11 β HSD-1), leading to increased cortisol levels and increased lipolysis locally. Adipose tissue is known to cause insulin resistance by secreting TNF-α and interleukins. Of the multiple adipose tissue hormones, resistin is responsible for insulin resistance, while adiponectin and leptin ameliorate insulin resistance. Although leptin levels are high in type 2 diabetes, there is also a state of leptin resistance. These biochemical abnormalities are accentuated in the abdominal adipose tissue, which is known to be abundant in type 2 diabetes.

Interestingly, Asian Indians have increased adiposity even at a

relatively low BMI, which may be one of the reasons for the increased type 2 diabetes. For this reason, the BMI above 23 kg/m2 is also considered overweight in the Asian Indians, unlike the cut-off point of 25 kg/m2 in the Caucasians. The skeletal muscle glucose utilisation is impaired to a greater degree than adipose tissue in type 2 diabetes (Figure 1). In the post-prandial state, the glucose is primarily deposited as glycogen in the muscle. Hyperinsulinaemic-euglycaemic clamp studies have shown that the non-oxidative glucose disposal, like that in hexose monophosphate (HMP) shunt is severely impaired in type 2 diabetes and other insulin resistant states. The cause of this resistance is a high free fatty acid (FFA) concentration in the myocytes, as demonstrated in several studies by using a nuclear-magnetic resonance imaging. This would limit the glycogen synthesis through the HMP shunt. Recently, a defect in glucose transport has been described in the milieu of high fatty acids.(41,42) In insulin resistant state, fatty acid oxidation or re-esterification leading to triglyceride synthesis is also impaired, thus leading to high levels of intra-myocellular FFA. On exercise, many of the abnormalities, including the diminished amount of glycogen synthase gets corrected, thus improving insulin sensitivity. Exercise increases glucose transporter activity, improves capillary density, increases mitochondrial mass, and increases type 2 A muscle fibres which are involved in the glycolytic process.

The hepatic insulin resistance leads to enhanced gluconeogenesis and glycogenolysis. Thus, increased hepatic glucose production is a hallmark of uncontrolled diabetes. Type 2 diabetes is often associated with a fatty liver, with or without elevated liver enzymes and evidence of hepatic necrosis.

It is also a manifestation of hepatic insulin resistance and is often reversed by weight loss and the use of insulin sensitisers. The molecular mechanism of insulin resistance has been a subject of intensive studies (Figure 2).

The resistance is very rarely due to an abnormal insulin or insulin receptor. Sustained hyperglycaemia produces glucotoxicity, probably by a failure to enhance hexosamine pathway, leading to increased glucosamine levels. Increased glucosamine levels can produce insulin resistance in adipose tissue and skeletal muscle. Sustained hyperinsulinaemia also down-regulates the insulin receptor and further aggravates insulin resistance.(39,40) The main locus of the resistance appears to reside at the post-receptor level. Insulin signalling is initiated by the binding of insulin to alpha subunits of the receptors. This initiates a cascade of auto-phosphorylation and dephosphorylation through the intra-cellular tyrosine kinase, insulin receptor substrates (IRS-1, 2, 3, 4) and other signal regulatory protein family (Gab-1,Cb-1, CAP, APS).

The β subunit of insulin receptor has been shown to undergo besides tyrosine auto-phosphorylation, a serine-threonine phosphorylation. The latter type of phosphorylation increases insulin resistance and impairs insulin signal transduction. The insulin signal is terminated by dephosphorylation of the β subunit of receptor by tyrosine phosphatases, the activities of which is increased in insulin resistant states.(43)

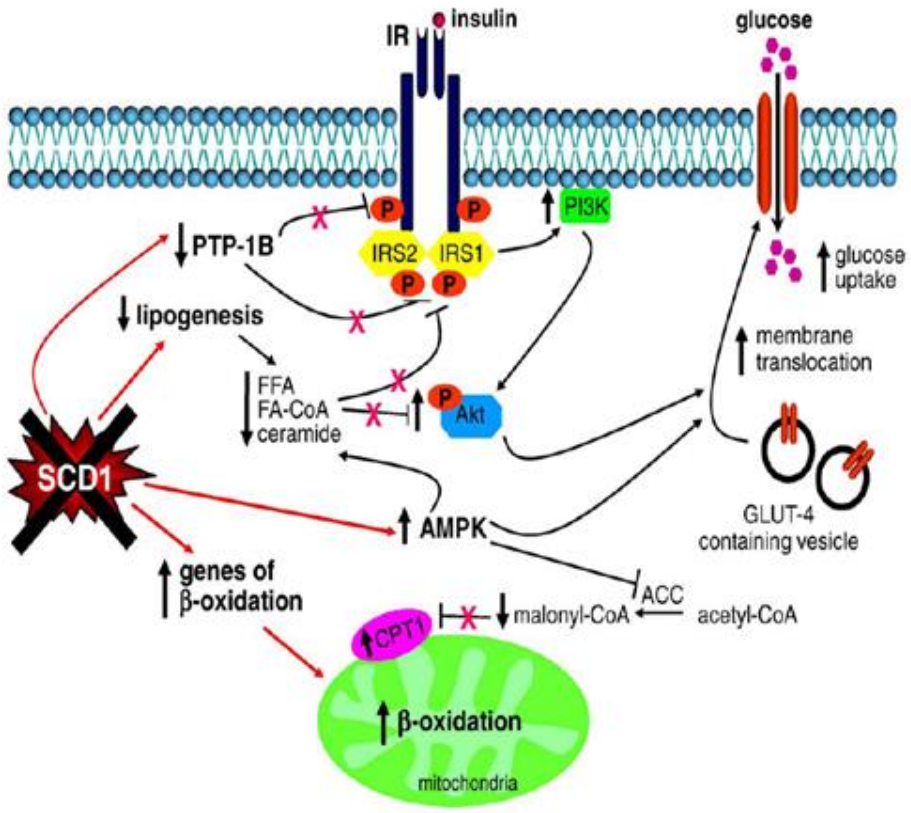


Fig: Molecular mechanisms of insulin resistance.

Following the insulin receptor phosphorylation a number of down stream events, including an increase in phosphatidyl inositol-3 kinase (Pl-3 kinase) leads to the translocation of GLUT4. In insulin resistant state, the

GLUT-4 is not depleted, but its translocation is hampered. The glucocorticoid-induced insulin resistance is also associated with a reduced insulin stimulated IRS-1 associated Pl-3 kinase.

Insulin Secretory Defects in Type 2 Diabetes

In a non-diabetic individual, besides the meal-related insulin secretion, there are rapid oscillations in insulin secretion every 8 to 15 min, without any glycaemic stimulus. There is also a circadian rhythm occurring every 80 to 150 min. Overall, about 18 to 32 units of insulin are secreted daily and about 50% is extracted by the liver for local action during its first passage. In type 2 diabetes, the rapid meal-related insulin secretion, which primarily occurs in about 30 min post-meal and mostly represents the preformed insulin, is attenuated. The post-meal response for the 2-hour period post-meal appears to be exaggerated but in relation to the high glycaemic levels is indeed also impaired. In obesity and impaired glucose tolerance group, absolute amounts of insulin secreted may be excessive.(38,39)

The molecular mechanism of this phenomenon is probably an overexpression of hexokinase gene as compared to the glucokinase gene. As the former has a low Michaelis constant (Km) for glucose, hypersecretion is produced. The circadian rhythm of both types of non-

meal related insulin responses is also altered or attenuated. The β-cell mass appears to be slightly reduced at the time of diagnosis of diabetes; however, the functional capacity is impaired out of proportion to its mass and hence in many studies, a 50 % reduced insulin response has been described at the onset of type 2 diabetes. Subsequently, the β cell mass declines further in a relentless fashion with increasing insulinopaenia. This is at time correlated to fibrillary amylin deposition in the β-cells.(43)

The genetic factors that determine β cell differentiation, growth and apoptosis are being intensively studied at present. The growth factors and their biology is yet to be elucidated. It obviously holds the key to a fruitful avenue for intervention. However, it is characterised by an early apoptosis of β cells. The insulin resistance and β cell failure exist and progress pari passu. In early phases there is predominately a resistant state. Subsequently, β cell failure dominates the scene. The β-cell is able to compensate by increased insulin secretion in the face of rising blood glucose, but at about 140 mg/dL of blood glucose the insulin secretion levels off and a further rise in blood glucose results in diminishing insulin secretion (Figure 3). In about 10% of type 1 diabetics, the β cell failure may be due to auto immunity. This is called latent autoimmune diabetes of adults (LADA) and aetiologically represents a forme fruste of type 1 diabetes.(14)

OTHER PATHOGENETIC MECHANISMS

Besides the role of β cell, skeletal muscle, adipose tissue, and liver in the genesis of type 2 diabetes, a few other important pathogenetic mechanisms have been described. The gastrointestinal tract secretes a group of important hormones, collectively labelled as incretins. This includes two extremely wellknown members: glucagon like peptide (GLP-1) and glucosedependent insulinotropic peptide (GIP). The former is secreted from the L-cells of the ileum and the latter from the K-cells located in the proximal small intestine. These hormones account for the enhanced insulin secretory response upon ingestion of glucose orally, as compared to that obtained by intravenous glucose administration. This has been termed the incretin effect. In type 2 diabetes, the incretin effect is blunted, which can be corrected by injecting GLP-1 or its longer acting analogue, like exenatide or liraglutide. GLP-1 is normally destroyed by a group of enzymes called dipeptyl peptidases, of which dipeptyl peptidase-IV (DPPIV) is the predominant one. Compounds inhibiting DPP-IV inhibitors prolong the effect of endogenous GLP-1 and are being used therapeutically at present.(14)

Although non-suppressibility of glucagon following a meal was described in type 2 diabetes almost 4 to 5 decades ago, it gained further relevance recently, with the availability of therapeutic tools to correct this

anomaly. GLP-1 analogues and DPP-IV inhibitors described above correct this defect by suppressing glucagon levels post-prandially. Tachy-alimentation has also been described to aggravate diabetes by exposing the body to sudden surge of nutrients. GLP-1 analogues and DPP-IV inhibitors are known to retard gastric emptying, thus offering an additional mechanism of action.

The hypothalamic neurons and neurotransmitters have been considered in the pathogenesis of type 2 diabetes. There are numerous changes described in the neurotransmitter secretion in obesity and type 2 diabetes. The rapid first phase insulin response is mediated through these pathways. It has been demonstrated that the hypothalamic nuclei regulating appetite are also insulin resistant. After the ingestion of glucose, the elevated plasma insulin levels are unable to exert the inhibitory response in these nuclei in obese, insulin resistant individuals. Hence, pharmacological manipulation of these neurons by promoting satiety can be utilised in type 2 diabetes. More recently, dopamine agonists, like bromocriptine have been shown to improve hyperglycaemia in type 2 diabetes.

Another new pathogenetic mechanism described shows involvement of kidney in the pathogenesis of type 2 diabetes. Normally about 160 g of glucose is filtered in the glomerular filtrate; 90% of it is

absorbed in the proximal convoluted tubule by a high capacity glucose transporter called SGLT2. Remaining 10% of the filtered glucose is absorbed in the straight descending part of the proximal tubule by another glucose transporter SGLT-1. It has been demonstrated that in type 1 diabetes the tubular maximum for the glucose absorption is increased. Although it is not clear whether the same holds true of type 2 diabetes, the levels of SGLT-2 mRNA is four-fold increased in the proximal tubular renal cells. This may account for increased glucose resorption and hence, hyperglycaemia. Inhibition of SGLT has provided another avenue to treat type 2 diabetes.

In summary, type 2 diabetes originates from a complex interaction of genetic and environmental factors, which express themselves in the form of myriad biochemical abnormalities.

ATHEROSCLEROSIS IN DIABETES:

The increased prevalence of macrovascular disease among diabetic subjects prompted research workers to probe into the causes for the acclerated atherogenic process of diabetic subjects. Dyslipidemias contribute to considerable increased risk of atherosclerosis and consequent mortality in diabetes. Dyslipidemias often precedes onset of type 2 DM and may persist inspite of adequate control of blood sugar.2.

HISTORY OF ATHEROSCLEROSIS:

1449-1519- Leonardo Da Vinci described thickening of tunica of blood vessels in aged People. Rokinstansky proposed the Incrustation theory for pathogenesis of Atherosclerosis.

1858- Virchow proposed Inhibition Hypothesis for pathogenesis of atherosclerosis.

1904- Marchand introduced the term atherosclerosis.

1957 - Robertson modified the Incrustation theory and proposed that intimal thickening results from fibrin deposition with subsequent organization of fibroblasts and secondary accumulation of lipids.

1960s and 1970s - concepts such as endothelial cell damage and injury were described.

1979- Garret et al proposed that monocyte accumulation in sub-endothelial space was responsible for formation of fatty streak.

1985- Davies et al proposed that plaque fissuring with thrombosis as the cause of acute coronary syndrome.

1994-George Howard and co-workers concluded that increased CIMT at one site is positively associated with thickened walls at other carotid sites.

1997-M.L. Bots and co-workers concluded that common carotid intima media thickness and carotid plaques are markers for increased risk of stroke, coronary heardisease and death within 12 years(7)

LIPIDS

Lipids are organic substances occurring in biologic systems. They are esters of fatty acids and are insoluble in water but soluble in organic solvents. Lipids are broadly grouped into

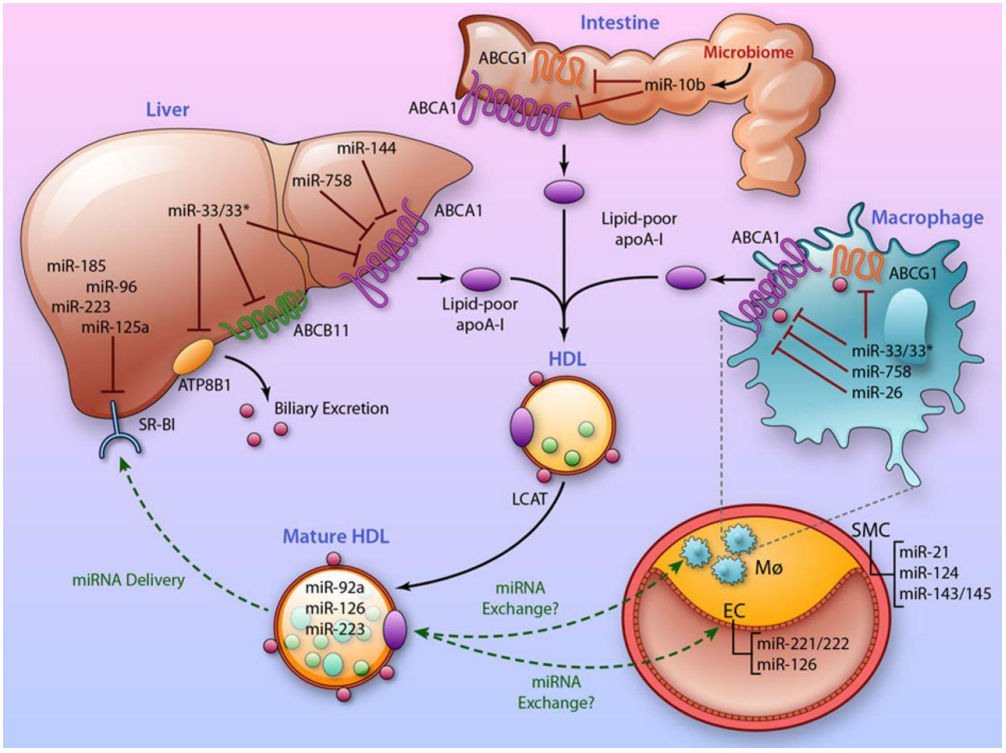
A) Simple lipids -Naturals fats, waxes

B) Compound lipids-Phospholipids, glycolipids, lipoproteins

C) Derivatives-Fattys acid, glycerol, sterols.

Among naturals fats, triglycerides form the major part of the dietary fat intake. Compound lipids are structural lipids. Glycolipids in cell membrane , sphingomyelins in nervous system and lipoproteins in blood serve as important physiologic functions. sterols are solid alcohol .The principle sterol in man is cholesterol.

Fatty acids are esters of a naturally occuring alcohol like glycerol. Fatty acids from animal tissues are usually unbranced and contain an even number of carbon atoms. They are classified based on the presence or absence of double bond between the carbon atoms. when two or more than two double bonds exist they are called poly unsaturated fatty acid.(16)



Functions of lipids:

1) Cholesterols are structural components of cell membrane. They are precusors of bile acids and steroid hormones

2) Triglycerides form the major energy stores of the body.

3) Phospholipids are structural constituents of cell membrane.

LIPID METABOLISM IN DIABETES:

Insulin is an anabolic hormone which promotes a) esterification of fatty acids b) stimulates glucose uptake in peripheral tissues and c) conversion of glucose to glycogen. Insulin inhibits the hormone sensitive lipase activity in adipose tissue. hence in insulin deficiency there is enhanced mobilisation of fatty acids from adipose tissue. This lipolysis results both from insulin lack of and in the setting of associated counter hormone excess. Fatty acids and ketone bodies thus formed secondarily enhance insulin resistance. adequate level of insulin are necessary for triglyceride synthesis and VLDL secretion. HMG Co A is the rate limiting enzyme in cholestrol synthesis. Insulin increases its activity and thus regulates hepatic cholesterol synthesis. In addition insulin, affect LDL transport kinetics. The fractional catabolic rate of LDL is reduced without changes in synthesis in type 2 DM.(16)

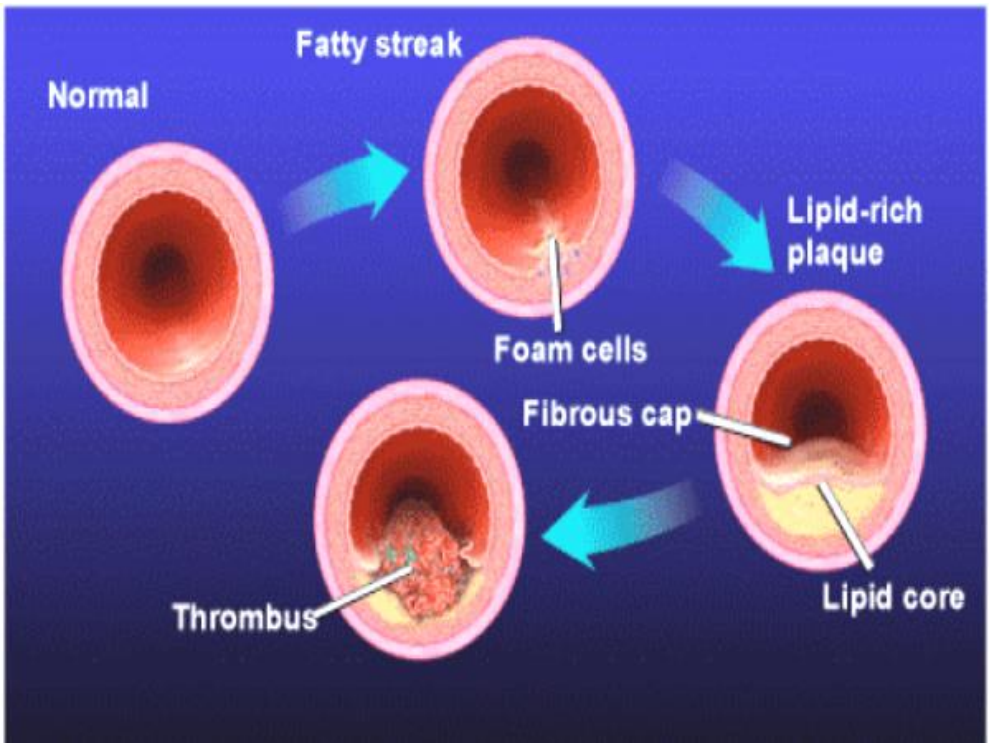


FIG: DEVELOPMENT OF ATHEROSCLEROTIC PLAQUES

Pathologic changes in atherosclerosis process:

1. Intimal thickening

2. Fatty streaks

3. Gelatinous lesions

4. Atheromatous plaque

5. Complicated plaques

1. **Intimal thickening:**

   The Initial lesion consists of smooth muscle cells, fibrous tissue and collagens, but no lipid.

2. **Fatty streaks:**

   These composed of very closely packed foam cells, lipid containing elongated smooth muscle cells and some lymphoid cells. Small amount of extra cellular lipid, collagen and proteoglycans are also seen. They are considered as the precursors of plaques.

3. **Gelatinous lesions:**

   These are foci of the increased ground substance in intima with thinned overlying endothelium. They are also considered as the precursors of plaques.

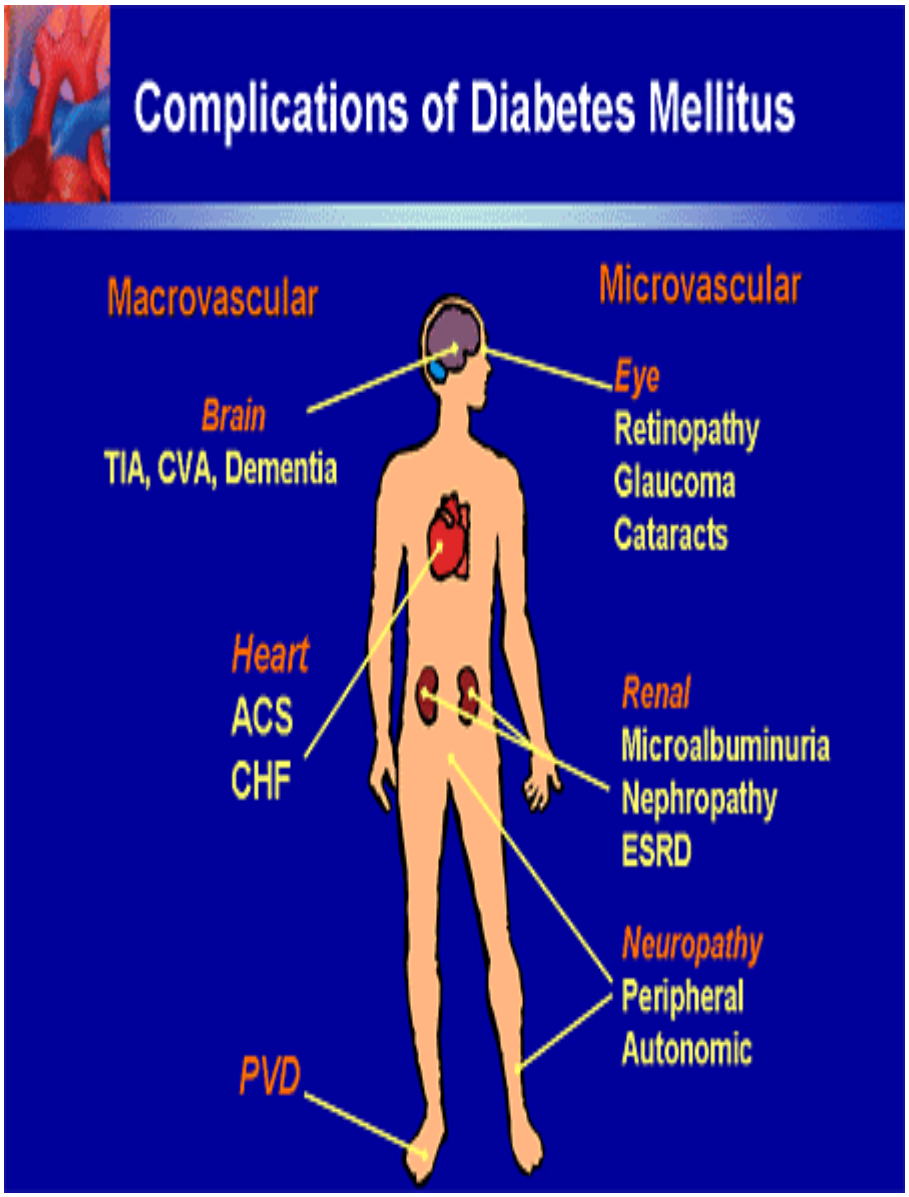
4. **Atheromatous plaques:**

Atheromatous plaque is a fully developed atheromatous lesion.

4. **Complicated plaques:**

   Various complications may occur in fully developed lesions. These include thrombosis, hemmorhage, calcification, ulceration, and aneurysm formation.(12)

CHRONIC COMPLICATIONS OF DIABETES MELLITUS:



Macrovascular complications

- Coronary artery disease
- Cerebrovascular disease
- Peripheral vascular disease

Microvascular disease

- Neuropathy
- Nephropathy
- Retinopathy

Mechanisms of Complications:

1. Endothelial Dysfunction: “ Endothelium which is the innermost layer of the blood vessels and in fact the largest organ of the body is the initial and common target of all cardiovascular risk factors. The functional impairment of the vascular endothelium in response to injury occurs long before the development of visible atherosclerosis.

The endothelial cell behaves as a receptor-effective structure which senses different physical or chemical stimuli that occur inside the vessel and, therefore, modifies the vessel shape or releases the necessary products to counteract the effect of the stimulus and maintain homeostasis. The endothelium is capable of producing a large variety of different

molecules including the vasodilators (nitric oxide [NO] and prostacyclin) and vasoconstrictors (endothelin-1 and angiotensin II) and nicely balancing their effects. When this delicate balance is lost, the conditions are given for the endothelium to be invaded by lipids and leucocytes (monocytes and T-lymphocytes). The inflammatory response is incited and fatty streaks appear – the first step in the formation of the atheromatous plaque which may later rupture and set the conditions for thrombogenesis and vascular occlusion. Therefore, endothelial dysfunction which is universal in diabetes is the starter in the process of atherosclerosis and many other factors are the chasers.

As a result of this, vascular NO synthesis and stability are reduced and there is an impairment of endothelium-dependent NO-mediated vasodilatation in diabetes. In the presence of endothelial dysfunction the powerful vasoconstrictors like endothelin-I and angiotensin-II replace the vasodilators, NO and prostacyclin.(14)"

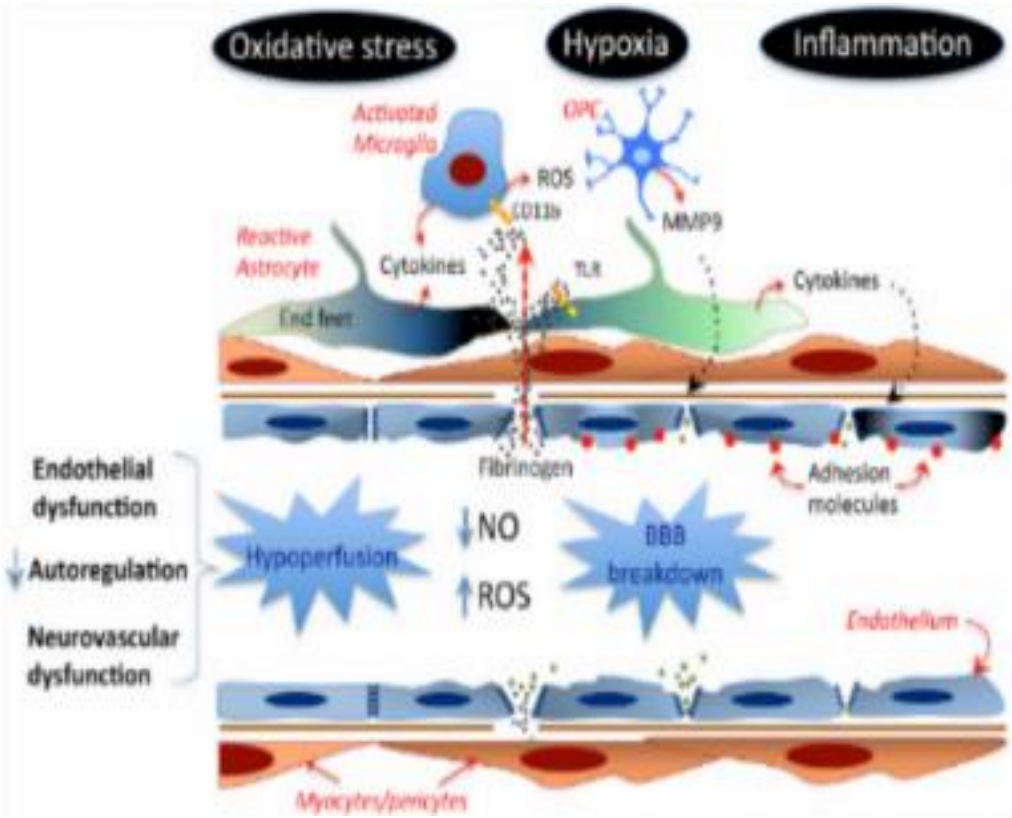
2. Oxidative Stress : "Oxidative products are produced as a consequence of normal aerobic metabolism. These molecules are highly reactive with other biological molecules and are referred to as reactive oxygen species (ROS). Under normal physiological conditions, ROS production is

balanced by an efficient system of antioxidants, molecules that are capable of neutralising them and, thereby, preventing oxidant damage. In pathological states, ROS may be present in relative excess. This shift of balance in favour of oxidation termed ‘oxidative stress’ may have detrimental effects on cellular and tissue function and the cardiovascular risk factors generate oxidative stress. Both type 1 and type 2 diabetic patients are under enhanced oxidative stress. Hyperglycaemia causes nonenzymatic glycosylation of proteins and phospholipids, thus increasing the intracellular oxidative stress. Therefore, advanced glycosylation end products (AGEs) formed later in this process are stable and virtually irreversible and generate ROS with consequent increased vessel oxidative damage and atherogenesis”.

3. Activation: “ Activation of polyol pathway and diacylglycerol (DAG), protein kinase C (PKC) cascade are the other consequences of persistent hyperglycaemia (uncontrolled diabetes). Excess of intracellular glucose is metabolised by sorbitol pathway; and there is also rise in DAG, PKC levels intracellularly consequent to persistent hyperglycaemia. This occurs in many tissues including heart, aorta, glomeruli and retina”.

4. Other Factors: “ There are many cardiovascular risk factors in diabetes and insulin resistance (IR). These are metabolic and lipid-related factors, coagulation and inflammatory factors and vascularrelated factors (Table 1). Some of them are primarily related to diabetes while others may be found in diabetic as well as non-diabetic individuals. Type 2 diabetes and IR typically occur in the setting of metabolic syndrome which also includes visceral (abdominal) obesity, hypertension, dyslipidaemia, and increased coagulability all of which lead to atherosclerosis (Figure 1). Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischaemic heart disease (IHD), stroke, and death. Among people with type 2 diabetes women may be at a higher risk for CHD than men. The prevalence of microvascular disease in itself is also a predictor of CHD”.(14). Important steps in the initiation and growth of atherosclerotic plaque are:

1. Endothelial dysfunction and injury
2. Sub-endothelial monocyte/macrophage accumulation
3. Lipoprotein infiltration
4. Smooth muscle cell proliferation



5. Influence of T lymphocytes and other inflammatory cells and protein lipid accumulation in foam cells finally leading to plaque formation and adhesion thrombosis.(14)

Hyperglycemia is the most important single cause of chronic complications in diabetes which has been proved by the diabetes control and complications trial (DCCT).Patients with insulin -dependent diabetes whose intensive insulin therapy resulted in HbA1c values of 2% lower than those receiving conventional insulin therapy, had a 76% lower incidence of retinopathy and a 60% reduction in neuropathy.

UKPDS study is the best evidence to prove that intensive drug treatment to lower blood glucose concentration is effective in reducing the risk of long term microvacular complications. This study also proved that strict control of blood pressure and lipids is also important in reducing the risk of diabetic complications.

These alterations remain reversible if good control of hyperglycemia is achieved. However if persistence of hyperglycemia and in the presence of secondary factors such as hypertension, hyperlipedemia, smoking, alcohol, environmental toxins, the functional alterations progress to early structural changes. once these set in, further progression to irreversible damage and end stage disease is apparently determined by yet unknown factors independent of hyperglycemia could be genetic.

VASCULAR CHANGES IN DIABETES:

To ensure adequate nutrition to all tissues, blood vessels must possess inherent mechanisms to regulate the flow and contractility, permeability, coagulation and regeneration following injury, depending on the needs of each tissue.

Diabetes mellitus affects all these processes leading to damage of target tissues.(16)

Reduced contractility - altered blood flow

Thickened basement membrane - altered permeability

Factor Vii , vWF, PGI - coagulability

Cellular proliferation - neovascularisation

MACROVASCULAR DISEASE IN DIABETES :

Unlike the microvascular disease which gets clicked with the onset of diabetes, the macrovascular disease antedates the development of diabetes by several years. Around 75% to 80% of all diabetic patients will die, many prematurely of cardiovascular (macrovascular) disease (CVD), particularly coronary heart disease (CHD). Diabetic foot problems (gangrene, large non-healing infected ulcers) are the commonest cause of non-traumatic lower limb amputation. In one Indian study done at Chennai, the prevalence of CHD was 21.4% among diabetic patients, 14.9% among IGT subjects and 11% among non-diabetic patients. The of PAD in the same population was 6.3%.

There is a close relationship existing between pre-diabetes, diabetes and macrovascular (cardiovascular) disease throughout life; and the substantial body of evidence supports the concept that increased risk of morbidity and mortality due to CVD is associated with abnormalities in glucose metabolism across the entire continum of glucose tolerance ranging from normal to clinical diabetes.(14,28)

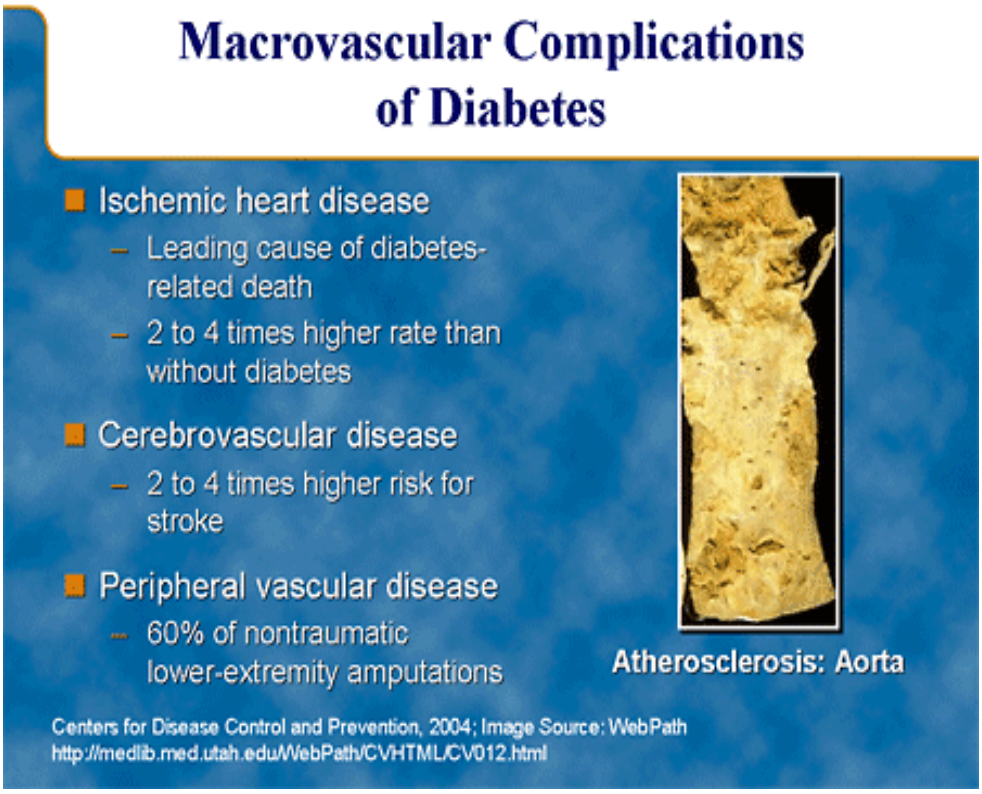
AETIOPATHOGENESIS:

The central mechanism in macrovascular disease is the process of atherosclerosis which leads to narrowing of the arteries throughout the body. Atherosclerosis is a progressive disease of the arterial wall involving the components of inflammation, vascular lipid deposition and remodelling, fibrosis, and thrombosis. Diabetes is a major independent risk factor for CHD resulting from accelerated atherosclerosis of the coronary arteries occurring at a much earlier age and advancing more rapidly to clinical cardiovascular events in persons with diabetes than in those without it.

Multivariate analyses of a number of large prospective studies with a followup of 12 to 20 years have shown that diabetes is associated

with 2- to 5-fold increase in CHD and premature cardiovascular-related deaths in both type 1 and type 2 diabetes. Atherosclerosis in diabetes is typically more diffuse, heterogeneous and extensive, occurring earlier and faster and more often associated with high-risk, unstable and vulnerable plaque with a large lipid core covered by thin fibrous cap which can easily rupture and result in acute coronary syndrome and death than in those without the diabetes. Diabetes, therefore, has definite accelerating impact on the pathogenesis of atherosclerosis which, in fact, is not qualitatively different from that occurring in non-diabetic individuals.

CLINICAL MANIFESTATIONS OF MACROVASCULAR DISEASE



Cardiovascular Disease :

Cardiovascular syndromes in patients with diabetes present in similar ways to those in non-diabetic population, although many patients are younger, outcomes are worse, and ischaemic events are more likely to be ‘painless’ (or rather silent) due to associated cardiac autonomic neuropathy. A cluster of cardiovascular risk factors clinically relevant are associated with diabetes, pre-diabetes, and IR and have to be looked into while evaluating the diabetic patients.

These are: 1. Abdominal obesity with increased waist circumference (> 90 cm in men and >80 cm in women) acanthosis nigricans, ‘hump’-like fatty bulge nape of the neck

2. Hypertension (>140/90 mmHg)

3. Dyslipidaemia Increased triglycerides Decreased HDL cholesterol Small dense atherogenic LDL particles Post-prandial lipaemia

4. Microalbuminuria

5. Increased levels of PAI-1 activity and fibrinogen

The clinical syndromes of myocardial ischaemia due to occlusive CAD are:

1. **Angina**

Angina may be relatively painless and can present atypically in long-standing type 2 diabetic patients, particularly the older ones with autonomic (sensory) neuropathy. Diabetic patients are more likely to remain asymptomatic while showing the ECG changes during exercise testing or ambulatory (Holter) ECG monitoring. Such diabetic patients of angina show reversible ischaemia on myocardial isotope perfusion scanning in the absence of obvious angina. Silent myocardial ischaemia carries a more ominous prognosis in diabetic patients than in the non-diabetic people.

2. **Acute coronary syndromes** :

Unstable angina, non-ST elevation MI, and ST elevation MI represent a major cause of death in the diabetic population. These may also be painless or present with other symptoms like acute dyspnoea (left ventricular failure, LVF), a variety of cardiac arrhythmias often lethal, cardiogenic shock, or sudden death. Malaise, nausea and vomiting, profuse sweating or collapse are the accompanying features. Because of loss of

normal circadian pattern of autonomic cardiovascular regulation, most acute ischaemic events occur during the evening and at night among diabetic patients.

Diabetic patients who suffer an MI have a higher mortality than non-diabetic patients both in acute phase and on long-term follow-up. Infarct expansion or/and extension and recurrence of infarction, acute LVF, and congestive heart failure (CHF) all occur more commonly in the diabetic population than the non-diabetic population. Serial determinations of CK-MB and quantitative estimation of troponins are more useful in assessing the infarct size and recurrence. All modes of echocardiography (2-D, Doppler and myocardial contrast echo) are extremely useful in assessing the LV size and function, myocardial viability, presence of any thrombus in the LV or its walls and other mechanical complications like mitral regurgitation, ventricular septal rupture or ventricular aneurysm. A major cause of adverse outcomes is the five-fold higher frequency of cardiac failure.

3. **Heart failure**:

Heart failure (HF) is 2 to 5 times more common in diabetic population than in non-diabetic population. HF can occur even in the

absence of obvious CAD. Aetiology of HF in diabetes is complex; factors include the systolic and diastolic performance of the LV affected by diabetic cardiomyopathy (diabetic heart muscle disease), the superimposed deleterious consequences of hypertension and further loss of functioning myocardium following acute coronary artery occlusion. The contractility of the non-infarcted myocardium in diabetes is much reduced which adds further to HF.

4. **Cardiac dysrhythmias**:

They are related to ischaemia, left ventricular hypertrophy or CAN and frequently occur in diabetic subjects following MI and may result in sudden death. Decreased heart rate variability and subtle changes in CV reflexes due to CAN in the diabetic patients result in lethal cardiac dysrhythmias.

5. **Diagnosis of ischaemic heart disease**:

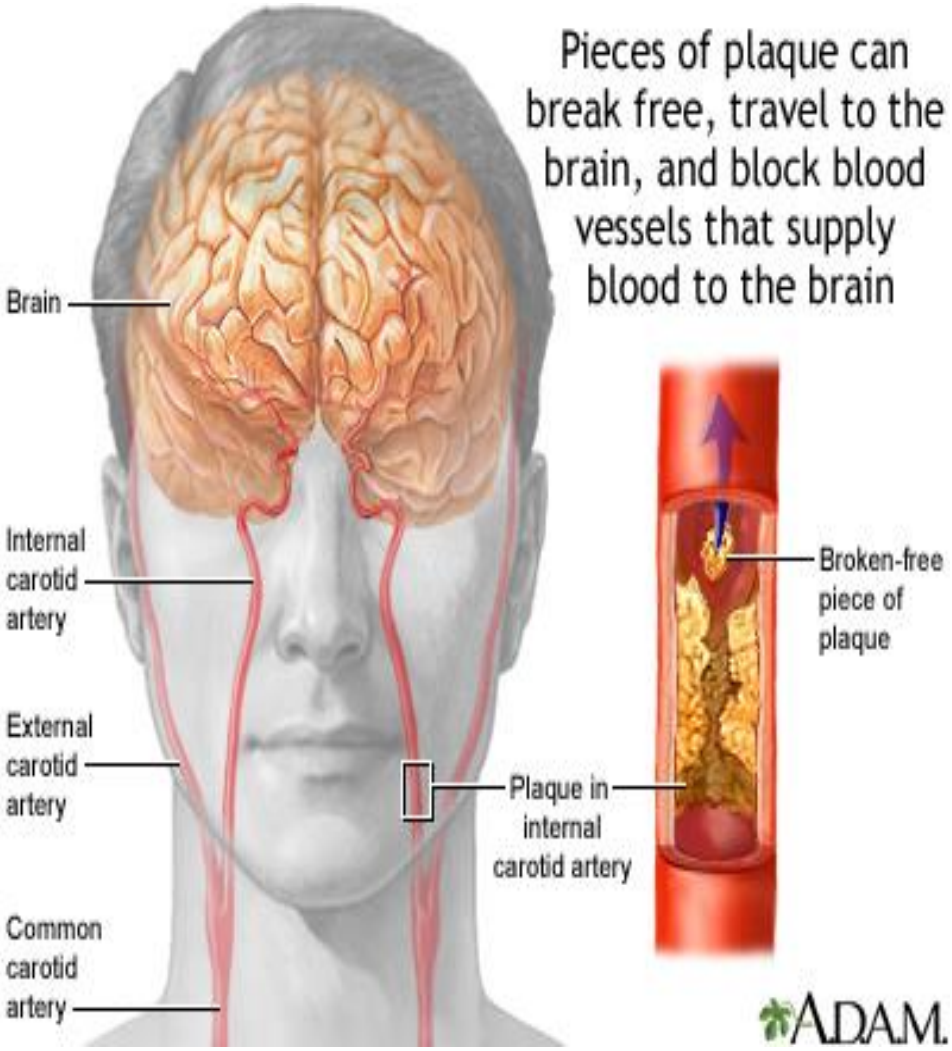
ECG, stress testing either treadmill (TMT) or pharmacologic (Dobutamine), ambulatory ECG (Holter) monitoring, echocardiography and ultimately coronary angiography should be done at appropriate times in the diabetic patients with IHD with or without symptoms. Coronary

revascularisation can be very beneficial in the diabetic patients with CAD. (14,28)

Cerebrovascular Disease

Transient ischaemic attack and stroke are more frequent among diabetic patients, than in the non-diabetic patients particularly those who had acute coronary ischaemic event earlier. Lacunar infarcts, large infarcts and multi-infarct disease occur more often among the diabetic population than in the non-diabetic population. Haemorrhagic strokes occur less commonly. The prognosis of stroke is also worse in the diabetic patients. Hypertension often coexists and worsens the situation.

Coma, convulsions and dense hemiplegias are often present. Carotid artery Doppler and B-Mode ultrasound imaging to measure the carotid intima-media thickness (IMT, abnormal if more than 1.1 mm) is an extremely simple and yet accurate indication of the diffuse atherosclerosis occurring in coronary and other arteries. The obstructive athero-plaques may be found in the carotid arteries by ultrasound and colour Doppler. CT or MRI brain and MR angiography of the brain are extremely useful in diagnosis as well as in prognosticating the stroke.



Stroke-related dementia and recurrence of stroke are more frequent in diabetic patients. Cerebrovascular mortality rate is higher in both type 1 and type 2 diabetic patients.

Peripheral Arterial Disease

PAD is 2 to 3 times more frequent in diabetic males and 5 to 6 times more common in diabetic females. Diabetes is the commonest cause of non-traumatic limb amputation. Smoking, hypertension and dyslipidaemia and associated peripheral neuropathy contribute to the increased prevalence of PAD in diabetic patients. Clinical presentation of ischaemic limb disease extends over a wide spectrum of intermittent claudication, critical limb ischaemia, and gangrene resulting from total peripheral artery occlusion. Limb pain either at rest or on walking is suggestive of occlusive PAD.

Acute limb ischaemia characterised by pain, paraesthesia, pallor, pulselessness and perishingly cold limb may also occasionally occur. Chronic lower limb ischaemia involving popliteal and tibial arteries results from atherosclerosis in the diabetic individuals. The combination of ischaemic PAD, peripheral neuropathy, injury and infection results in diabetic foot disease

CORONARY ARTERY DISEASE IN DIABETES:

Coronary Artery Disease is about twice as frequent in diabetic men and four times as frequent in diabetic women after menopause compared to nondiabetics. In fact one third of all deaths occurring in diabetics after forty years of age have been attributed to CAD. Coronary atherosclerosis in diabetic women almost equals that of diabetic men. In contrast disease has distinct male predominance compared to women among nondiabetic subjects. It has been observed that the immunity from cardiovascular mortality in the premenopausal non diabetic women is seldom encountered in the female diabetic subjects.

Coronary artery disease in diabetes is characterised by greater prevalence of triple vessel disease. The distribution of fatty streaks, fibous plaques and coronary stenosis are relatively more. A correlation between the extent and severity of coronary atherosclerosis, with the duration of diabetes has not been established. The prevalance of diffuse coronary atherosclerosis ,as evidence by postmortem arteriography and histological analysis is more often seen in diabetes subjects.

Clinically CAD in diabetic subjects is associated with prematurity and asymptomatic heart disease. In fact 75% of subjects sustaining acute myocardial infarction before 45 years of age have some form of glucose

intolerance.

An abnormal resting ECG has been documented in about 40% normotensive, ambulant diabetic subjects. Silent myocardial infarction is an entity with a greater prevalence in diabetic subjects.(16)

CAROTID INTIMA MEDIA THICKNESS

Carotid intima-media thickness (CIMT) is a well-described surrogate marker for macrovascular disease, a thickened CIMT correlates with the presence of macrovascular diseses by cross-sectional analysis. Several prospective studies have shown an association between increased CIMT and the incidence of macrovascular disease in the general population with or without prior cardiovascular disease. CIMT is significantly higher in diabetic patients than in nondiabetic subjects, and an increased CIMT is associated with angiography-evaluated coronary artery disease and predicts future events of macrovascular disease in type 2 diabetic subjects.

CIMT measurements are used in clinical trials to evaluate the efficacy of interventions. In these trials,CIMT is used as an surrogate for macrovascular diseases morbidity and mortality on the premise that changes in CIMT reflect changes in risk of these disease. CIMT usage is an advantage in a longitudinal trial as a surrogate end point to assess progression of atherosclerosis is the considerable reduction in duration of

follow-up, and in sample size and it could contribute to investigating the cause-and-effect relationship in atherosclerosis process.(17,18)

"STUDY OF CAROTID ARTERY INTIMA-MEDIA THICKNESS BY DOPPLER ULTRASOUND-AS AN INDICATION OF ATHEROSCLEROSIS"

"High resolution B-mode ultrasound is an non-invasive technique widely used to assess atherosclerosis in the superficial arteries. It is used to assess the accurate measurement of the distance between blood -intima and media-adventitia interfaces of the carotid wall, which is defined as carotid intima-media thickness (IMT)".

Several authors have suggested the carotid IMT as a marker of atherosclerosis in vascular beds.

Increased carotid IMT has been associated with a number of atherosclerosis risk factors, with the prevalence and extent of coronary artery disease (CAD) and with the incidence of macrovascular disease. In view of these relationships, carotid IMT has been proposed as a surrogate endpoint to be used as an alternative to coronary atherosclerosis.(19,21)

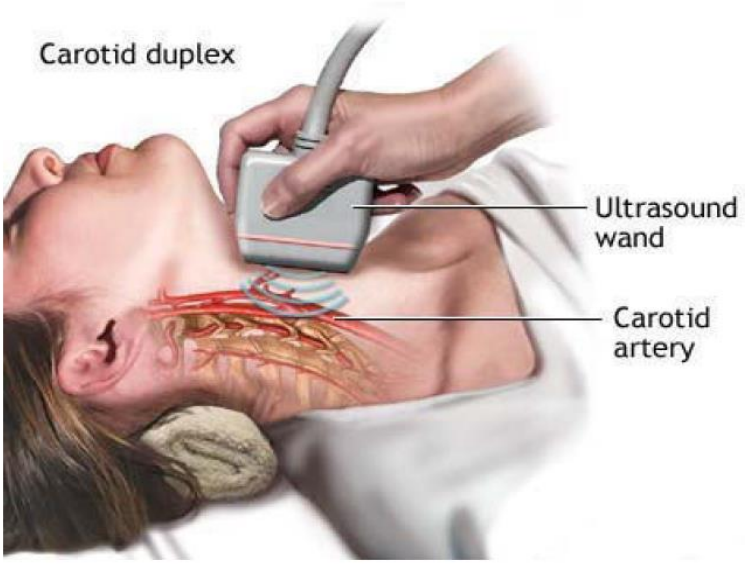


Figure 2 : Sonographic Evaluation of Carotid Arteries

UltraSonography of the Carotid arteries:

B-mode ultrasound offers advantages over angiography as it is non-invasive ,decreased risk and less expensive. By multiple serial measurements it is also used to assess progression or regression of atherosclerosis . Because of all these advantages many investigators since mid1980s have used Carotid intima media thickness by B-mode ultrasonography as an important tool to assess atherosclerosis in various clinical trials.(23,24)

Atherosclerosis is one of the inevitable accompaniment of ageing and its rate of development depends on various factors. Risk factors for accelerated atherosclerosis are hypertension, smoking, dyslipidemia and hyperglycemia. So it is necessary to identify subjects who are at early risk of developing accelerated atherosclerosis as several practical life style and pharmacological interventions for attenuating atherosclerosis development are available.

Measurement of extra cranial carotid intima-media thickness by Bmode ultrasound imaging correlated with histopathological examination. The intima media thickness is at present the best-studied ultrasonographic marker for assesing atherosclerosis. A thickening of intima-media complex not only corresponds to local alterations but also reflects generalized atheroscelerosis.

The normal intimal - medial thickness of common carotid artery as evaluated by B mode ultrasound imaging was 0.80 mm approximately. some authors have approximated the CIMT with the formula as (0.009× Age+ 0.116)

.[23]Measurement of the intima-media thickness, which increases in the early stages of atherosclerosis, is used as a surrogate endpoint for

clinical trials assessing whether lipid lowering medications might slow or reverse plaque formation.[21]

Atherosclerosis within the carotid artery occurs most frequently in the common carotid artery bifurcation and proximal internal carotid artery. Also, the carotid siphon (portion within the cavernous sinus) is also vulnerable to atherosclerosis. Old age, male gender, smoking, diabetes, hypertension and hypercholesterolemia are risk factors for carotid artery disease.

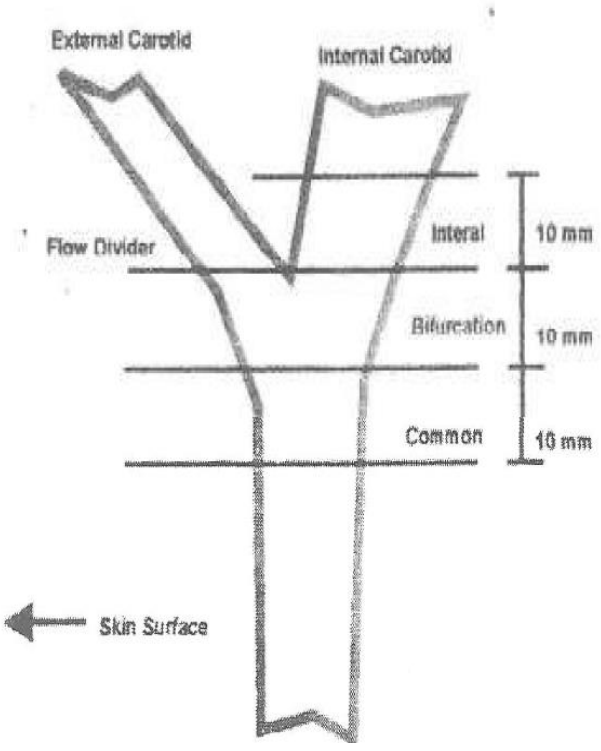


Figure 3 :"Carotid arteries are examined bilaterally in the areas of common carotid artery (1cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1cm proximal to the flow divider and internal carotid artery (1 cm distal to the flow divider) on the left and right sides"

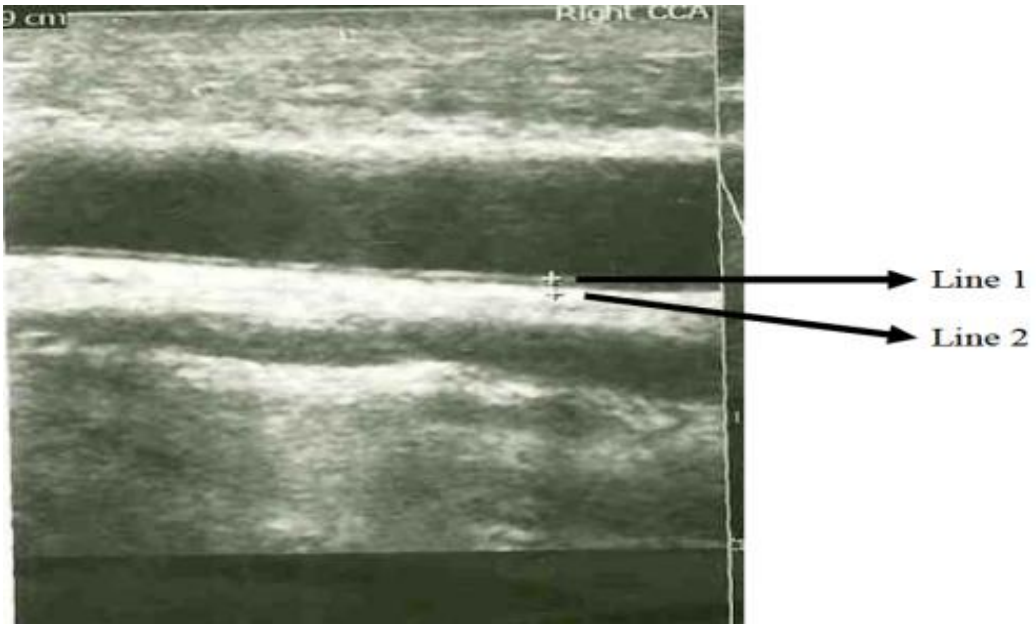


Figure 4: Showing USG guided measurement of IMT in Common carotid artery

Ultrasonographic scanning of the carotid arteries is performed by using an high resolution B mode ultrasound colour Doppler imaging and an electrical linear transducer is used.(23,24)

"Scanning of common carotid or internal carotid arteries in neck is performed bilaterally according to evading edge of second echogenic line. The first line represent the lumen intimal interface and the second line represents the collagen containing upper tunic adventitia. At each longitudinal projections three determinations of IMT are measured at the site of greatest thickness and at two points one cm above and one cm

below from the site of greatest thickness. The three values are then averaged".

APPLICATION OF CAROTID ARTERY INTIMA MEDIA THICKNESS:

Howard and colleagues, By Using B-mode ultrasound imaging examined the incidence of carotid atherosclerosis in the general population. The median carotid wall thickness ranged from 0.05 – 0.10 cm at all ages, with more than 5% of the cohort having wall thickness more than 0.20 cm. Cross-sectional analysis provide information that age-related increases in wall thickness average approximately 0.015 mm per year in females and 0.018 mm per year in males at the carotid bifurcation, 0.010 per year in females and 0.014 per year in males at the internal carotid artery, and 0.010 mm per year in both males and females at the common carotid artery.

The association of CIMT with conventional risk factors of atherosclerosis, include not only hyperglycaemia , fasting insulin and diabetes, but also body mass index, waist to hip circumference ratio, and physical inactivity (30). Abnormal glucose metabolism, abdominal adiposity and physical inactivity are associated positively with carotid IMT, in line with their believed contribution to atherogenesis. Similarly,

the atherosclerosis risk in communities (ARIC) study showed that carotid wall thickness is strongly associated with smoking , hypertension, atherogenesic lipids and tobacco ,(12), suggesting that the atherosclerosis is reflected in the IMT measurements.

The prognostic value of carotid Intima-Media Thickness has been prospectively evaluated and in many studies, increased IMT has been shown to be associated with increased macrovascular complications (31-35). In one study involving more than 4400 subjects from the Cardiovascular Health Study with age above 65 years and no known cardiovascular disease, IMT was a predictor of new cerebrovascular disease or acute coronary syndromes, even adjusting for traditional cardiovascular risk

AIM OF THE STUDY:

1. "To compare the carotid intima media thickness in case group and in control population".

2. "To find the association of increased carotid intima media thickness and CAHD/CVA/PVD".

3. "To assess the usage of carotid intima media thickness as a early predictor of macrovascular complications in type 2 Diabetics".

Justification for study:

"Atherosclerosis typically occurs over a period of many years, usually many decades. After a generally prolonged silent period, atherosclerosis may become clinically manifest. Evaluation of intimal medial thickness is considered as surrogate marker of Atherosclerosis. B mode ultrasound was found to be a suitable non-invasive method to visualize the arterial walls and to monitor the early stages of the atherosclerotic process".

METHODS AND MATERIALS

Study Design: Case control Study (type 2 dibetes mellitus patients with macrovascular complications as cases and without macrovascularcomplications as control group)

Study population: Type 2 DM patients presenting with macrovascular complications admitted in the medical ward will be included in the study. An equal number of age, sex, BMI and comorbid conditions[Systemic Hypertension] matched persons not having macrovascularcomplications attending OPD and in ward will be included in the study as control group

INCLUSION CRITERIA

1. Patients aged 35 TO 75years with type 2 diabetes mellitus
2. CAHD/CVD/PVD Diagnosed through medical history, clinical examination and appropriate investigation including Electrocardiogram, EchoCardiograms, and Computer Tomography scan

EXCLUSION CRITERIA:

- Patient with type 1 diabetes mellitus
- Patient with hemodynamic instability – bp<90/60 mm hg
- Patients with renal disease and liver disease both acute and chronic and connective tissue disorders.

Sample Size and sampling method: Type 2 Diabetes mellitus patients 50 with macrovascular complications as CASES And 50 without macrovascular complications as CONTROLS

Formula

$$n = \frac{2s_p^2\left[z_{1-\alpha/2} + z_{1-\beta}\right]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

Where,

s_1^2 : Standard deviation in the first group
s_2^2 : Standard deviation in the second group
μ_d^2 : Mean difference between the samples
α : Significance level
1- β : Power

So, total of 50 cases and 50 controls was be included in the study.

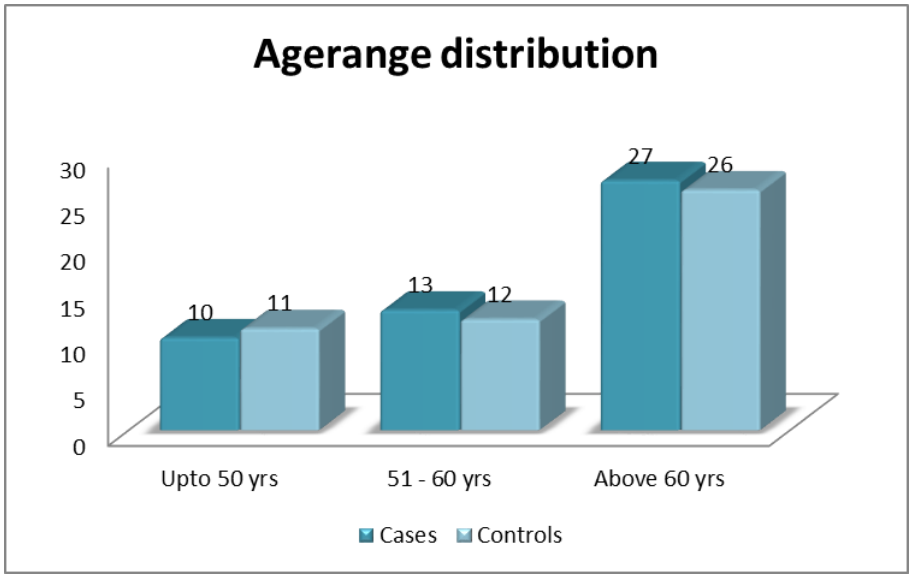
LIMITATION OF STUDY:

Due to limited source and practical constraints this study is being carried out with a small sample size. Thus the appropriate representation of the population and better outcomes could be attained by increasing sample size.

OBSERVATION AND ANALYSIS

AGE DISTRIBUTION OF CASE AND CONTROL GROUP:

Age	Cases	Controls
Upto 50 yrs	10	11
51 - 60 yrs	13	12
Above 60 yrs	27	27
Total	50	50

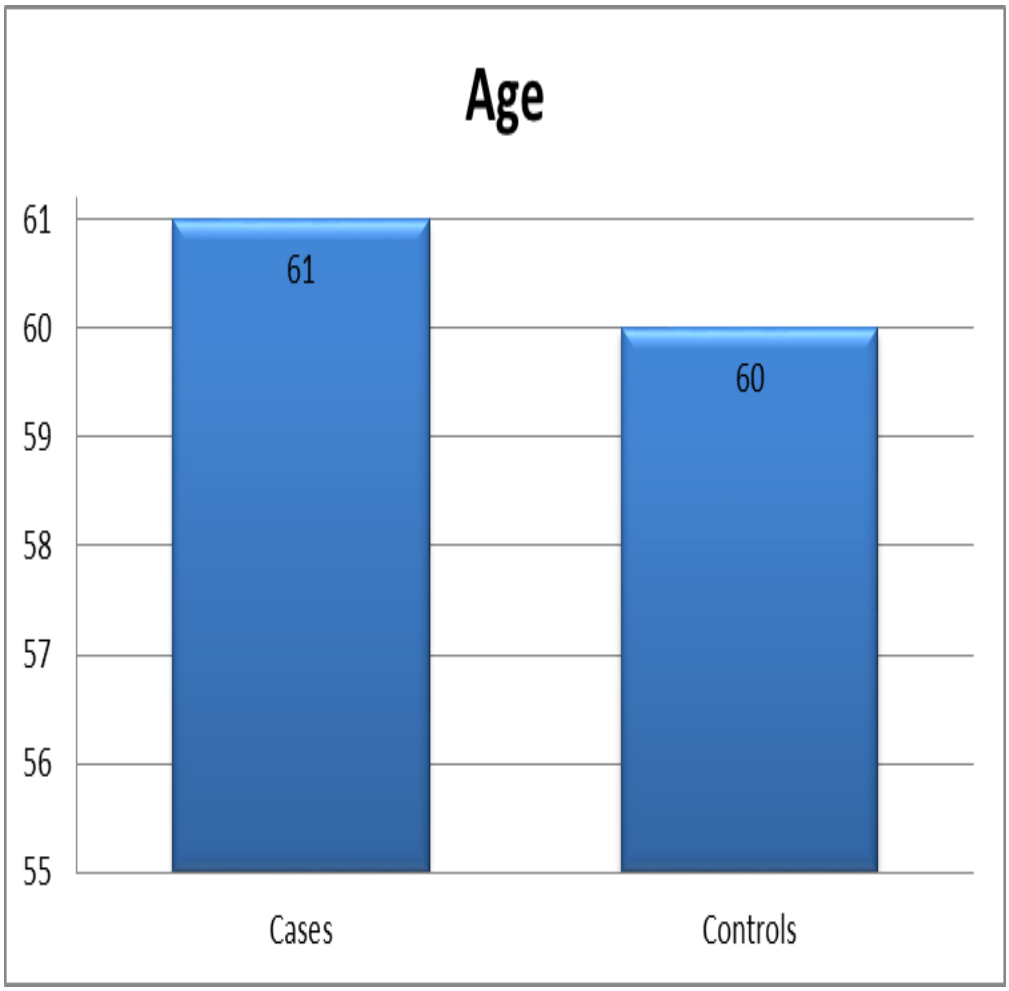


Agerange * CC Crosstabulation

			CC		
			Cases	Controls	Total
Age range	Upto 50 yrs	Count	10	11	21
		% within CC	20.0%	22.4%	21.2%
	51 - 60 yrs	Count	13	12	25
		% within CC	26.0%	24.5%	25.3%
	Above 60 yrs	Count	27	27	54
		% within CC	54.0%	54.0%	54.0%
Total		Count	50	50	100
		% within CC	100.0%	100.0%	100.0%

Chi Square value =0.096

P= 0.953



So, Equal number of cases and controls are selected in different age group

SEX DISTRIBUTION OF CASE AND CONTROL GROUP:

	Frequency	Percent
Female	27	27.0
Male	73	73.0
Total	100	100.0

Sex = F

Descriptive Statistics[a]

	N	Minimum	Maximum	Mean	Std. Deviation
Age	27	45	70	61.74	8.202
N	27				

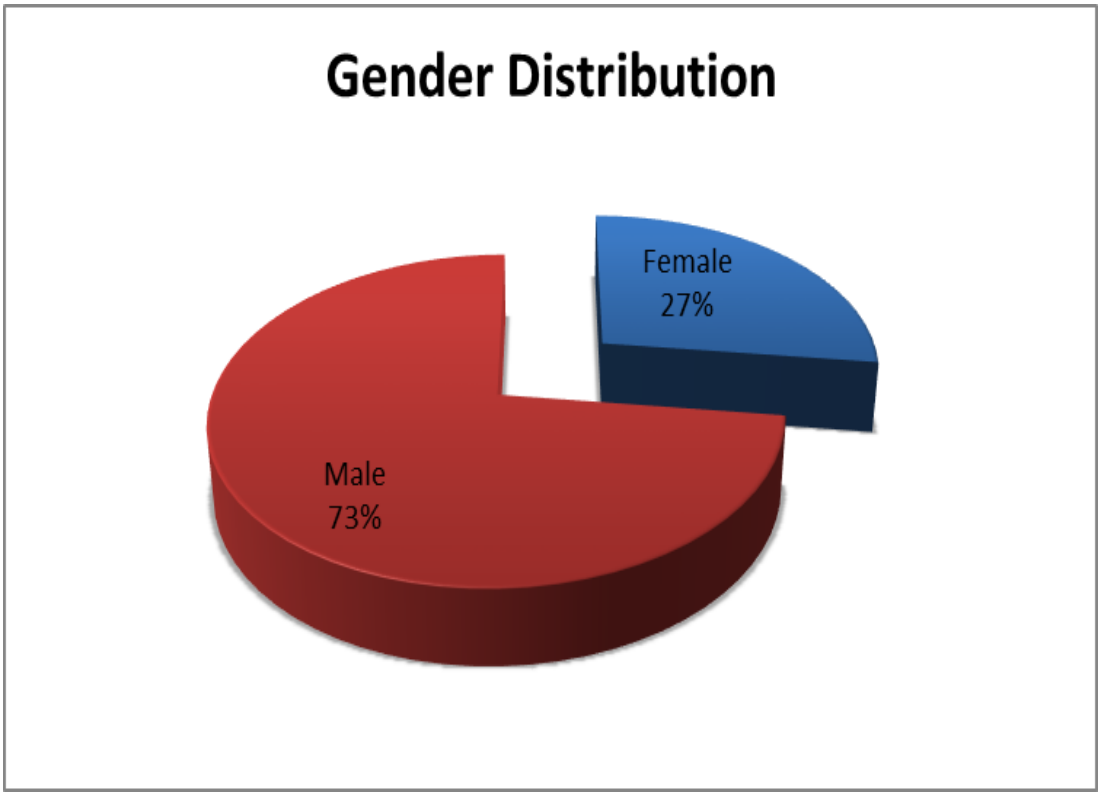
a. Sex = F

Sex = M

Descriptive Statistics[a]

	N	Minimum	Maximum	Mean	Std. Deviation
Age	73	45	76	60.07	8.571
N	73				

a. Sex = M



			CC		
			Cases	Controls	Total
Sex	F	Count	13	14	27
		% within CC	26.0%	28.0%	27.0%
	M	Count	37	36	73
		% within CC	74.0%	72.0%	73.0%
Total		Count	50	50	100
		% within CC	100.0%	100.0%	100.0%

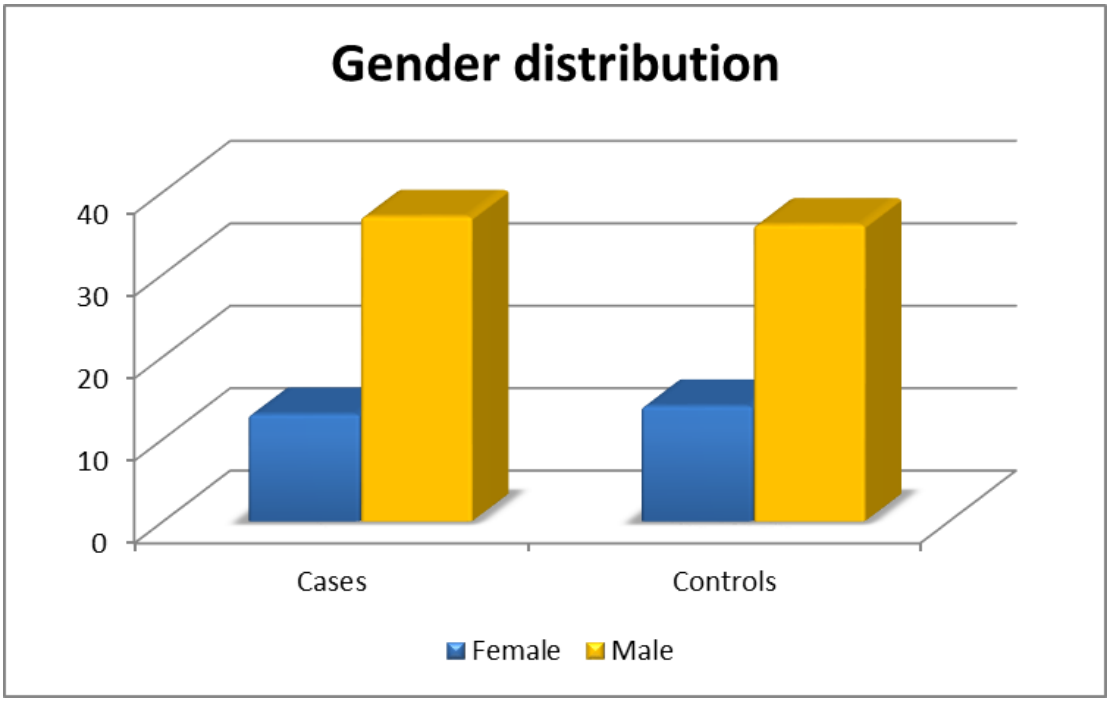
Chi-Square Tests

Chi square value = .051

p value = 0.822

p not statistically significant so sex distribution difference in case and control group

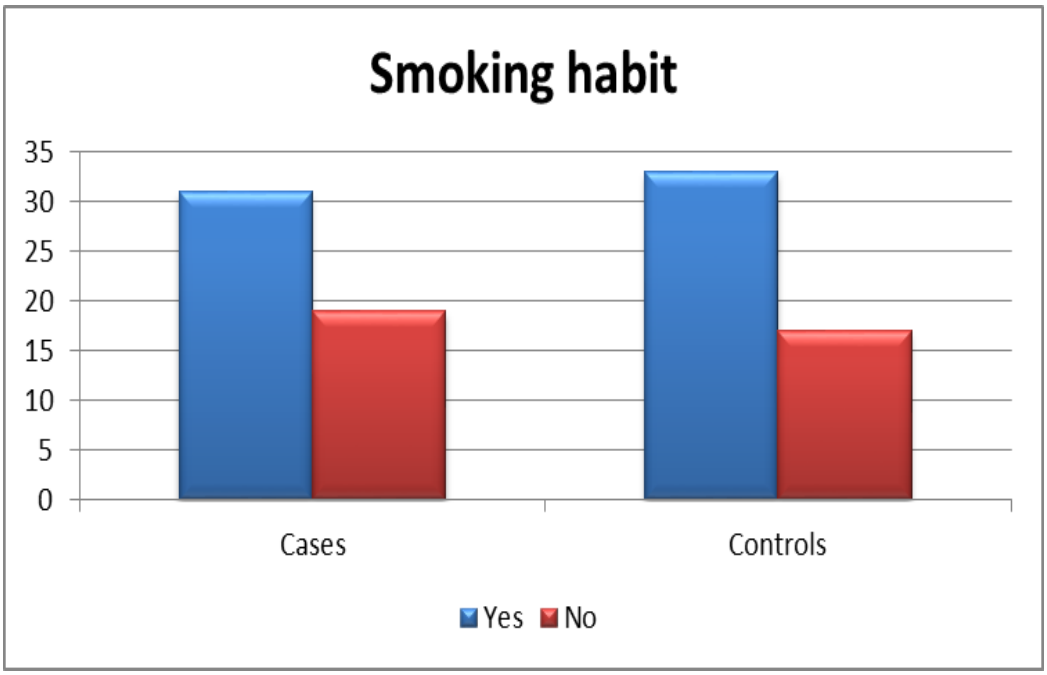
	Cases	Controls
Female	13	14
Male	37	36



So, Equal number of males and females are compared in case and control group

SMOKING DISTRIBUTION IN CASE AND CONTROL GROUP

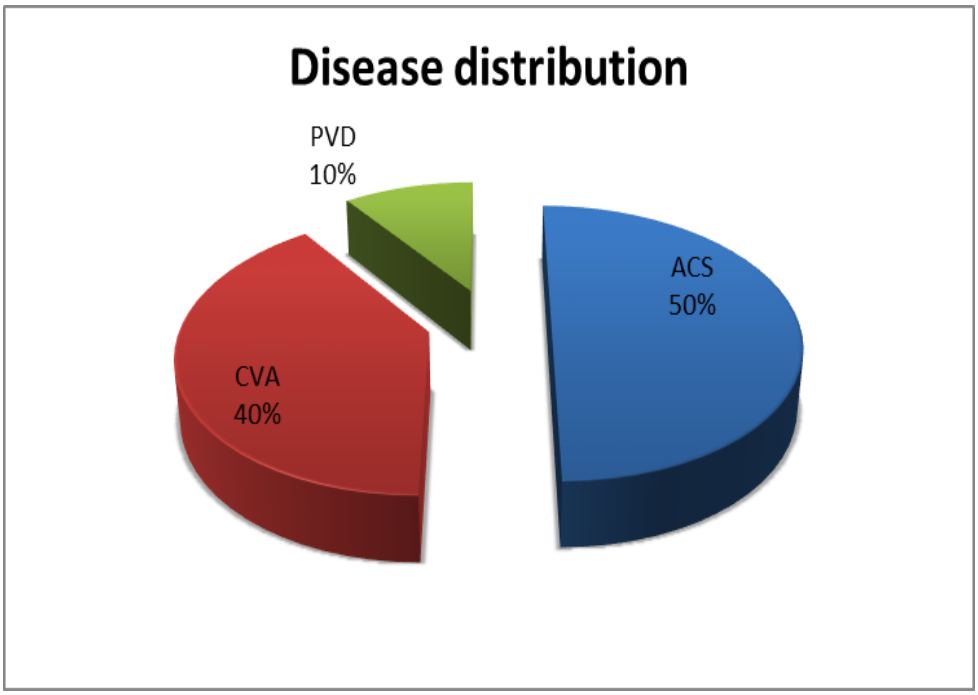
	Cases	Controls
Yes	31	33
No	19	17



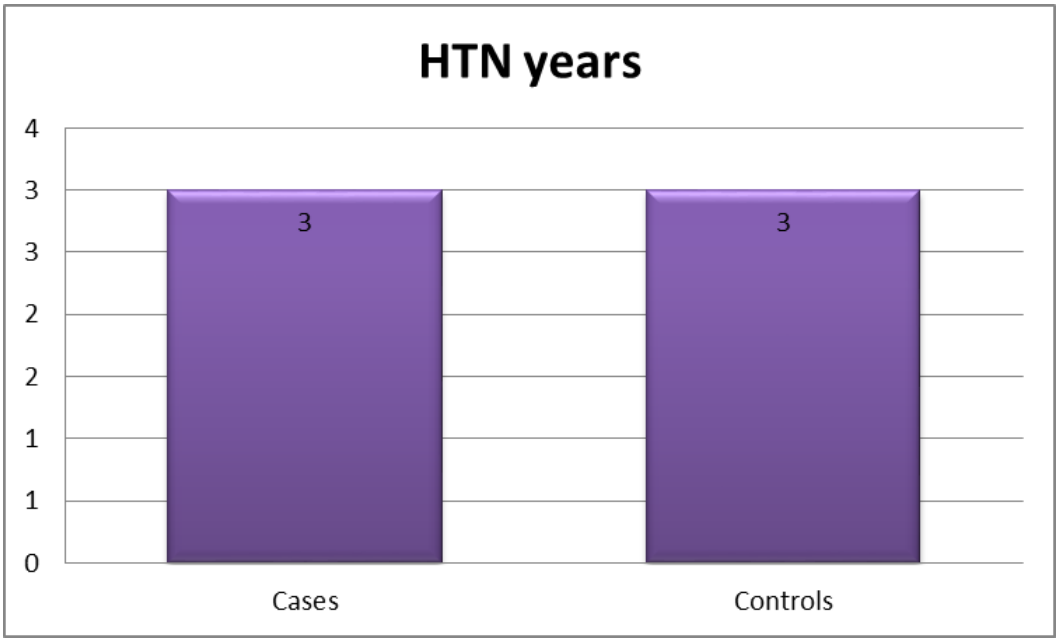
S0, smoking didtribution in case and control group matched equally.

MACROVASCULAR COMPLICATION DISTRIBUTION IN CASE GROUP:

		Frequency	Percent
Valid		50	50.0
	ACS	25	25.0
	CVA	20	20.0
	PVD	5	5.0
	Total	100	100.0

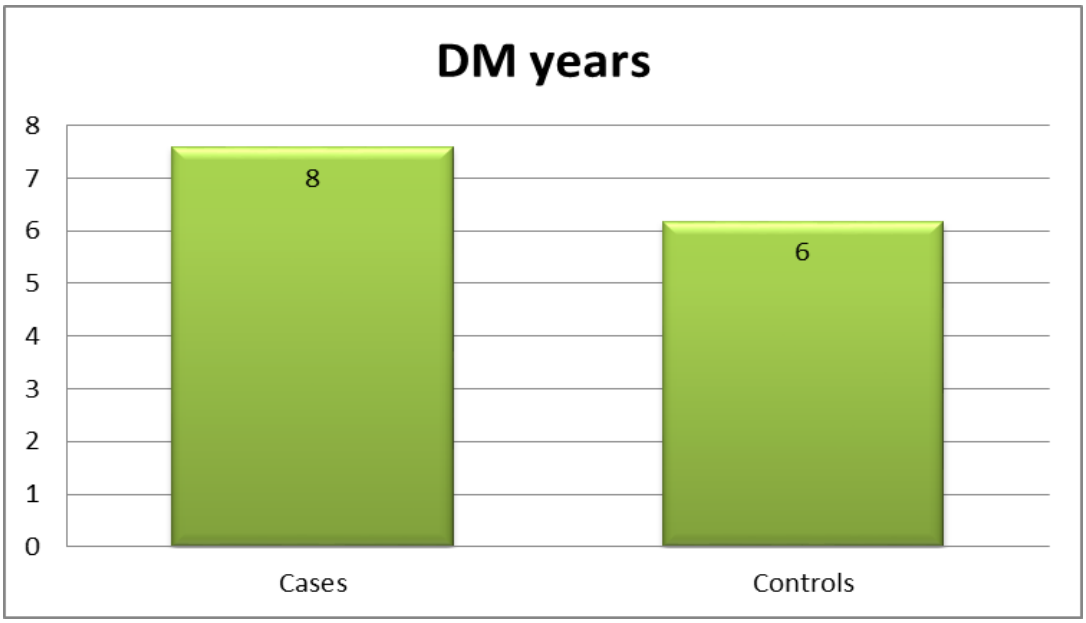


HYPERTENSION IN YEARS IN CASE AND CONTROL GROUP:



So, Hypertension in case and control group matched equally

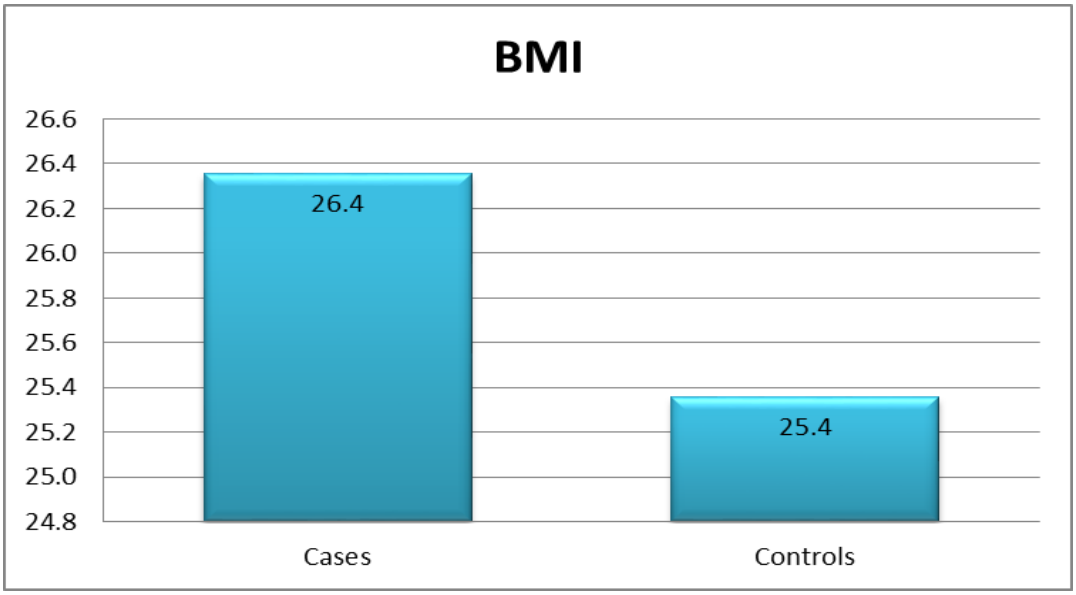
DURATION OF DIABETES IN CASE AND CONTROL GROUP:



p = 0.014 so, p is stastically significant

As, Duration of diabetes is significantly more in case group than control group

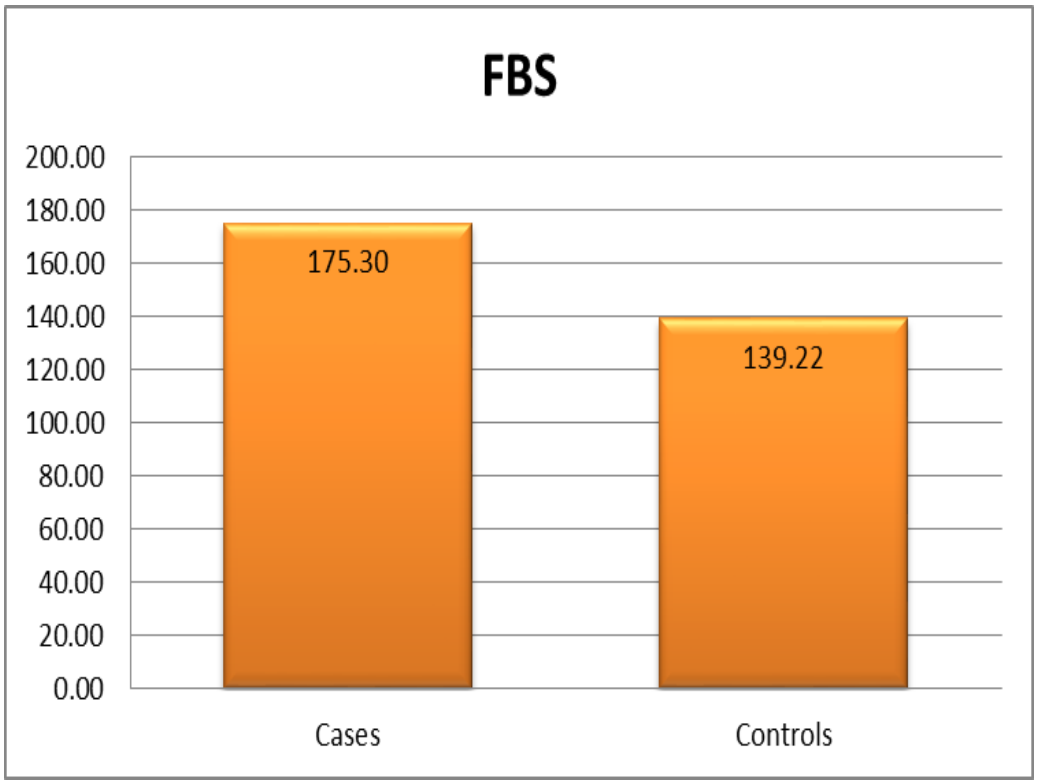
BODY MASS INDEX DISTRIBUTION IN CASE AND CONTROL GROUP:



p = 0. 188 (p > 0.05).

Body mass index is more in case than control group but not statistically significant

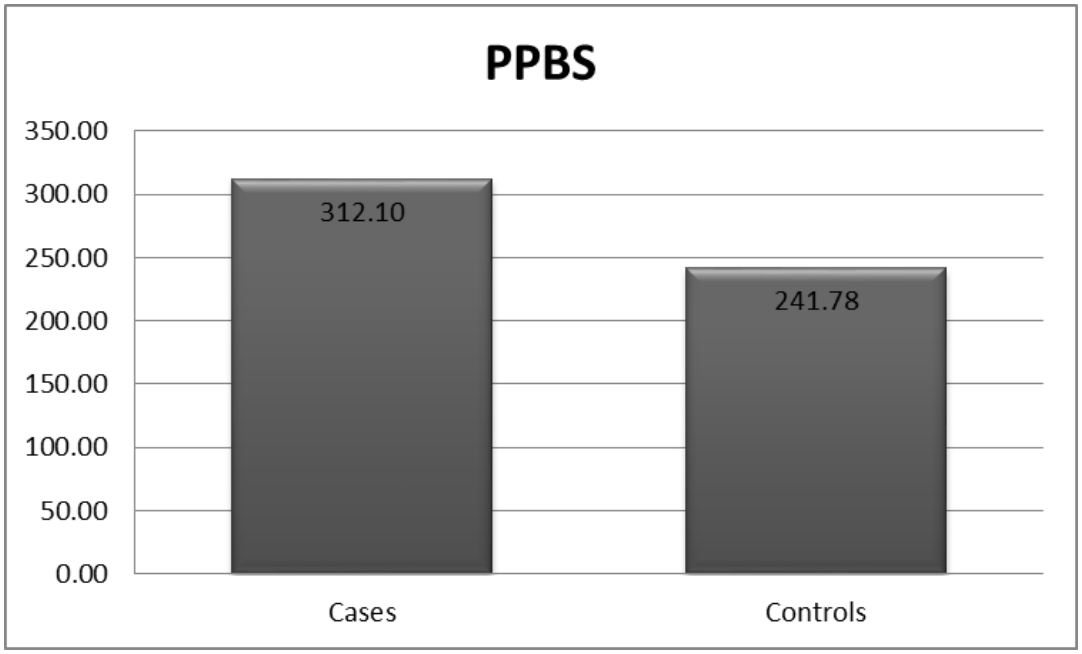
FASTING BLOOD SUGAR IN CASE AND CONTROL GROUP:



P = 0.000 (< 0.01)

Fasting blood sugar is statistically significant (p <0.01) in case than control group. So, fasting blood sugar is elevated in case than control group

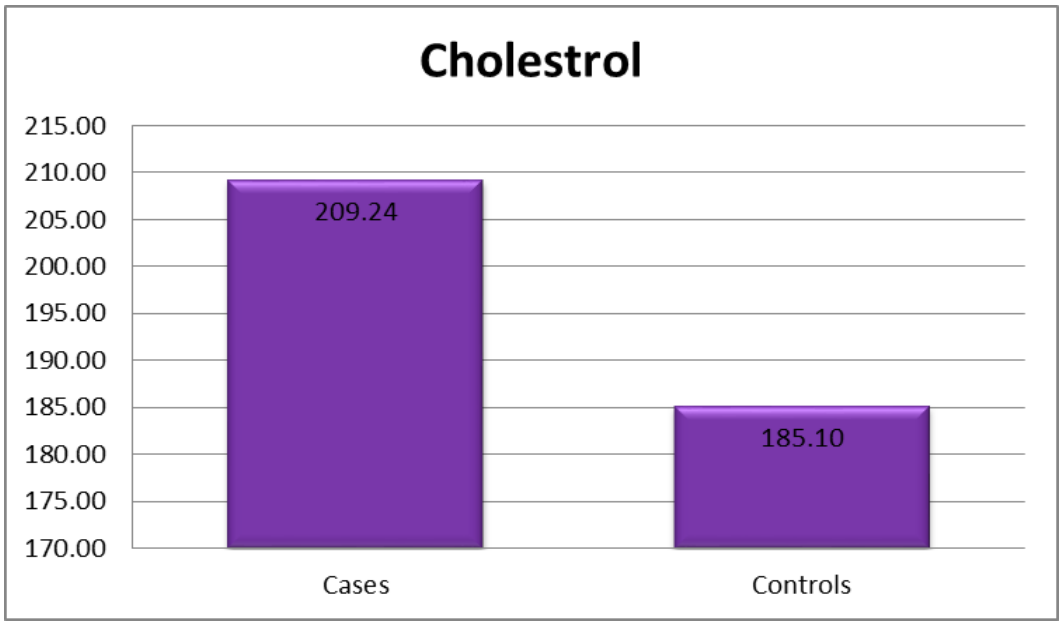
POST PRANDIAL BLOOD SUGAR IN CASE AND CONTROL GROUP:



P = 0.000

Post prandial blood sugar is statistically significant ($p < 0.01$) in case than control group so, PPBS is more in case group than control group

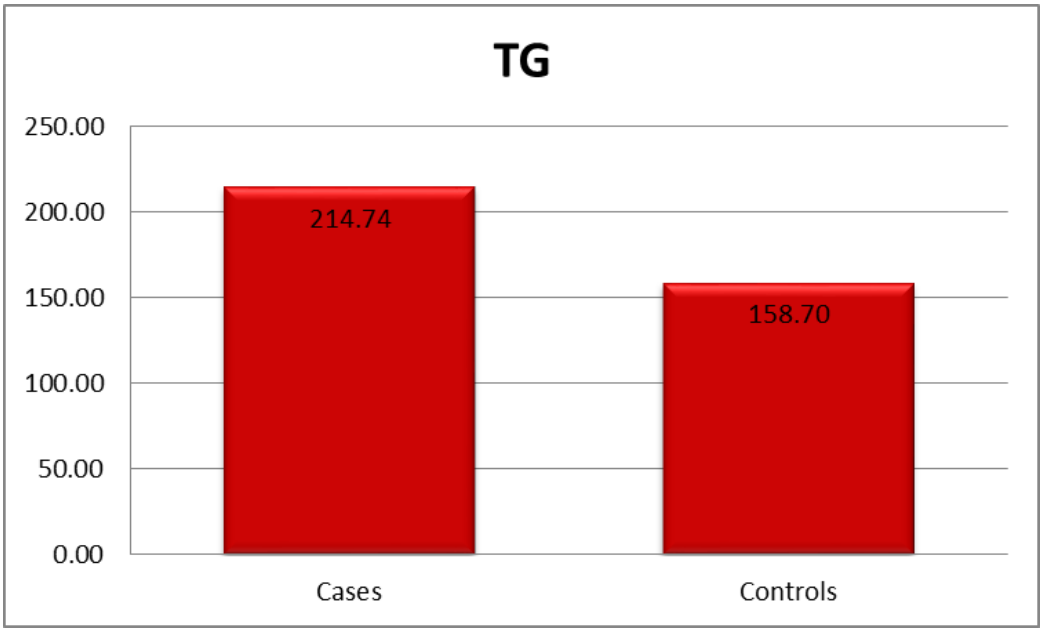
TOTAL CHOLESTEROL IN CASE AND CONTROL GROUP:



P = 0.000

Total cholesterol is statistically significant ($p < 0.01$) in case than control group, so total cholesterol is more in case group than control group people.

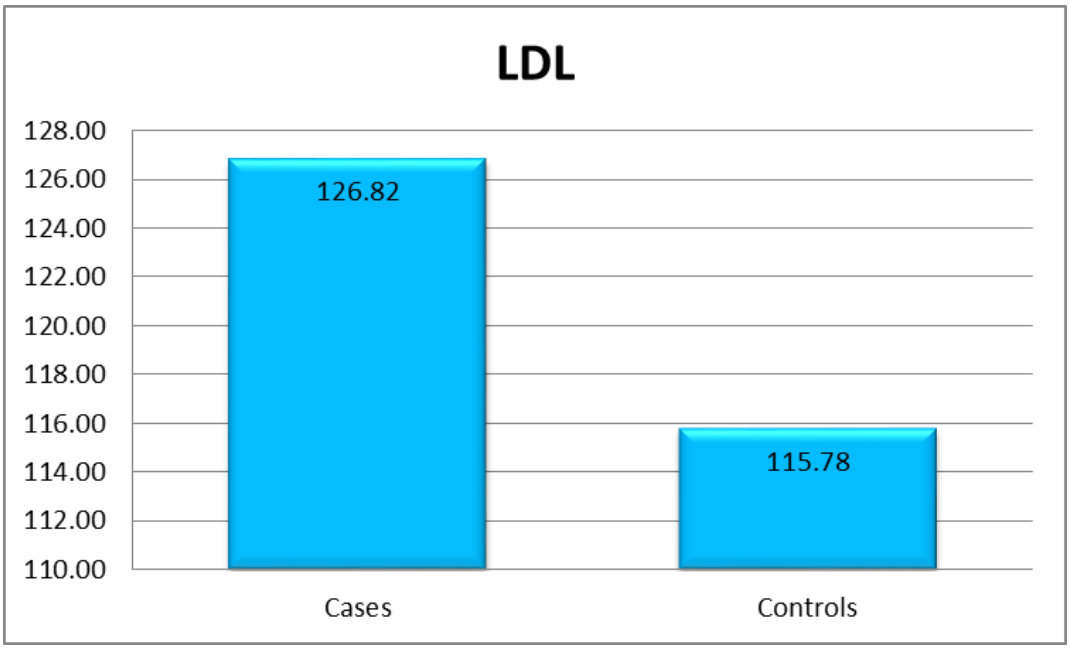
SERUM TRIGLYCERIDE LEVEL IN CASE AND CONTROL GROUP:



P = 0.000

Serum triglyceride is statistically significant ($p<0.01$) incase group than control. So, Serum triglyceride is more in cases than controls.

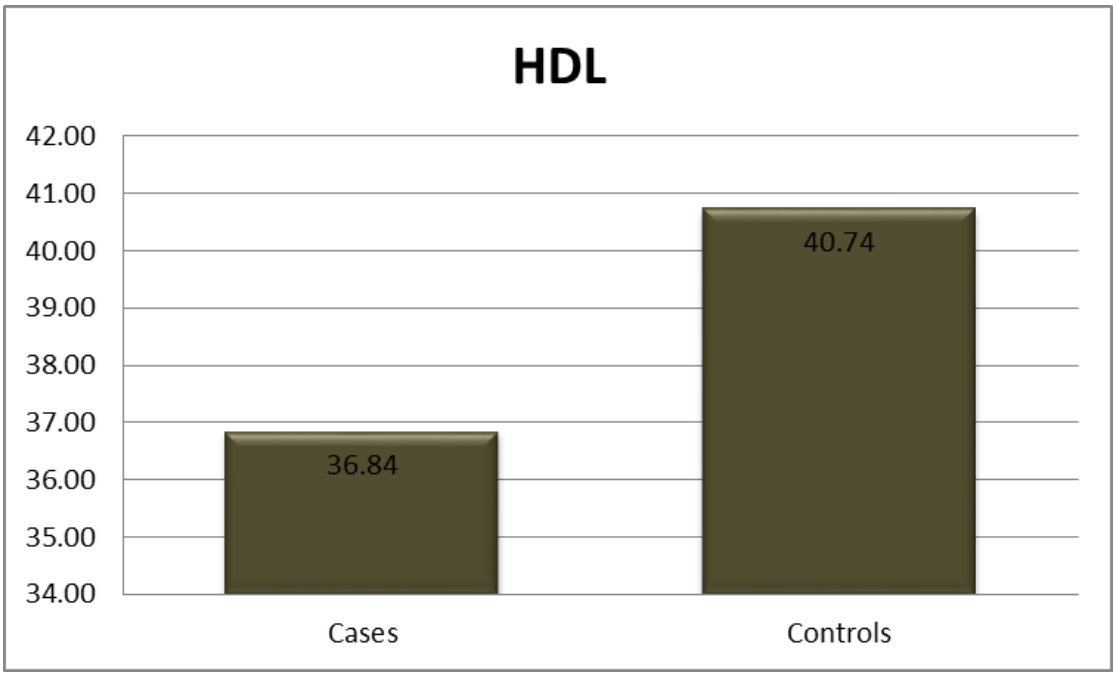
SERUM LDL IN CASE AND CONTROL GROUP:



P = 0.03

Serum LDL is statistically significant ($p < 0.05$) in case than control group. So ,Serum LDL is more in cases than controls.

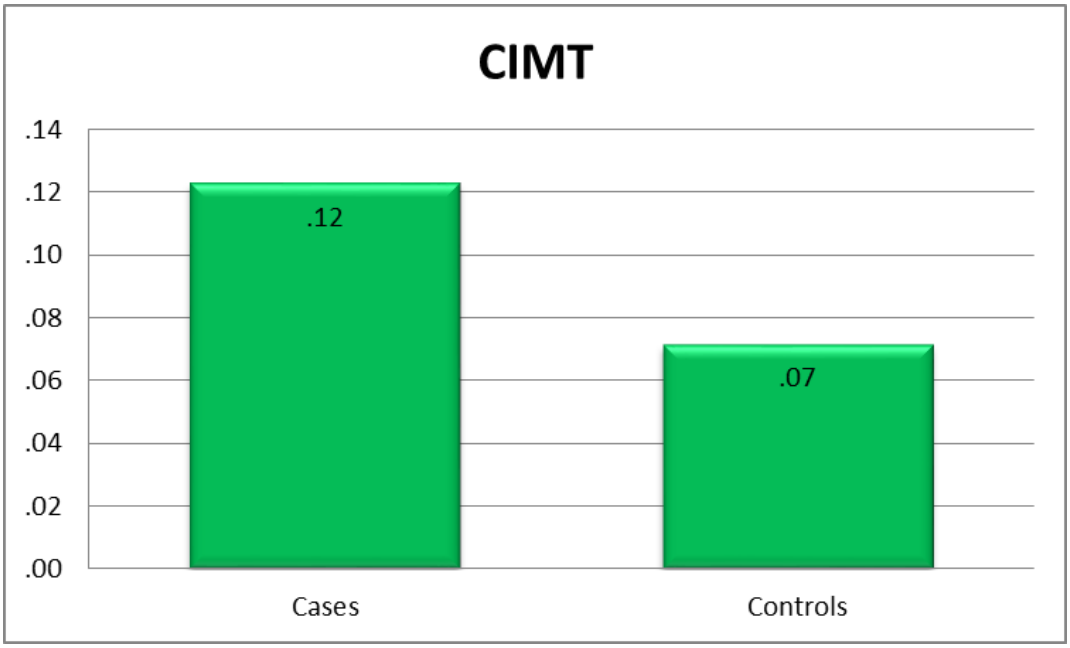
SERUM HDL IN CASE AND CONTROL GROUP:



p = 0.000

Serum HDL is statistically significant (p <0.01). So, serum HDL is significantly low in cases than controls

CAROTID INTIMA MEDIA THICKNESS IN CASE AND CONTROL GROUP:



CIMT	CASES	CONTROLS
<0.008	16	33
>0.008	34	17

So, when 0.008 mm is considered as mean, **34 cases** and only 17 controls had CIMT more than 0.008 mm.

			MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN
CIMT	Cases	50	.1226	.15471	.02188
	Controls	50	.0714	.02167	.00306

P =0.023 (< 0.05) which is statistically significant

Carotid media intima thickness is significantly elevated in case group than control group.

DISCUSSION AND SUMMARY

This is a case control retrospective study which had a sample size of 50 diabetic with macrovascular complication as cases and without macrovasvular complication as controls .This study was done to assess the value of carotid intima media thickness in patients those who had macrovascular complications in diabetes patients.

In this study AGE, SEX, SMOKING, HYPERTENSION was equally matched in cases and controls to decrease bias of these risk factors influcening result of the study.

The present study emphasized that as duration of diabetes increases there is progression of CIMT which is statistically significant.

25 acute coronary syndrome patients , 20 cerebrovascular accident patients , 5 peripheral vascular disease patients with diabetes mellitus were included in the study and 50 diabetic without complications were included in the study and carotid intima media thickness in these patients was measured in these patients using B mode ultrasonogram.

The present study has demonstrated the role of traditional risk factors like total cholesterol, LDL Cholesterol and triglycerides in the progression of atherosclerosis found to have statistical significance in cases than controls.

Serum HDL was significantly low in cases than controls.

Both fasting and postprandial blood sugar was elevated in cases when compared with controls.

The normal intimal - medial thickness of common carotid artery as evaluated by B mode ultrasound imaging was 0.80 mm approximately

Out of 50 cases 34 had CIMT more than 0.008 mm which was considered as mean

Out of 50 controls only 17 had CIMT more than 0.008 mm

On comparing carotid intima media thickness in cases and controls . cases had mean CIMT as 0.12 mm and controls had mean CIMT as 0.07 mm.

CIMT was significantly increased in case group than control group and it is statistically significant $p<0.05$ using independent t test.

Hence measurement of carotid intimal thickness using high resolution B mode ultrasonography which is non invasive well validated method is used to assess early manifestations of atherosclerosis and predictor of cardiovascular disease, cerebro vascular disease, peripheral vascular disease in asymptomatic as well as high risk patients such as dyslipidemia, DM, HTN and cigarette smoking.

CONCLUSION

The present study showed increased values of CIMT in Diabetic patients with macrovascular complication than Diabetic patients without macrovascular complications. Along with this risk factors like age, HTN, BMI, duration of DM, may actually have a correlation with CIMT either directly or indirectly influencing the disease process itself and contributing for atherosclerosis.

Ultrasound guided CIMT measurement is non invasive, reproducible method for detecting of early arterial structural changes associated with various risk factor for atherosclerosis.

Hence measurement of carotid intima media thickness by ultrasound Doppler is reliable and helps in early medical intervention to take care of risk factors and life style modification and may reduce incidence of macrovascular complications of type 2 diabetes mellitus.

PROFORMA

Name	Occupation	Hospital No
Age	Address	Op No/Ip No
Sex	DOA	

DIABETES HISTORY

1. Duration
2. Treatment history - Diet/Exercise/OHA/Insulin regular/irregular
3. Control of DM - under good control/not under control
4. Family h/o DM

HYPERTENSION HISTORY

1.No. of years and Control of hypertension-under control/ not under control

PRESENTING COMPLAINT

1. H/o giddiness
2. H/o syncope
3. H/o loss of consciousness
4. H/o polyuria
5. H/o polydipsia

PAST HISTORY

- H/o angina pain/ IHD
- H/o CVA , H/O PVD

- any other history – Renal failure , liver failure , connective tissue disorder

FAMILY HISTORY

PERSONAL HISTORY

- Diet
- Physical activity
- Smoking
- Alcohol

PHYSICAL EXAMINATION

Height: cms

Weight: Kg

BMI:

Pallor: Icterus: Cyanosis:

Clubbing: Lymphadenopathy: JVP:

Pedal Oedema:

VITALS

Temperature:

PULSE

- Rate :
- Rhythm:
- Volume:
- Character:
- Vessel wall thickening:
- Radio-radial/radio-femoral delay:
- Other peripheral pulses -

Blood Pressure:

RR:

Carotid Artery Bruit:

SYSTEMIC EXAMINATION:

Cardiovascular:

Respiratory:

PER Abdomen:

CNS Examination:

INVESTIGATIONS:

1. Blood Routine
2. FBS

   PPBS

3. B.UREA S.CREATININE
4. S.LIPID PROFILE

   S. Triglyceridres:

   Total cholesterol:

   S.HDL:

   S.LDL:

5. ECG
6. **Carotid artery Doppler**

PATIENT CONSENT FORM

STUDY DETAIL :
STUDY CENTRE :
PATIENT'S NAME:
PATIENT'S AGE :
IDENTIFICATION NUMBER :

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

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

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

I hereby consent to participate in this study.

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

Signature/thumb impression:

Patient's name and address:

Place: Date:

Signature of the investigator:

Name of the investigator:

Place: Date:

LIST OF ABBREVATIONS USED

DM	-	Diabetes mellitus
HTN	-	Hypertension
CIMT	-	Carotid intima media thickness
TC	-	Total cholesterol
TG	-	Triglyceride
LDL	-	Low density lipoprotein
VLDL	-	Very low density lipoprotein
BMI	-	Body mass index
ARIC	-	Atherosclerosis risk in communities
TIA	-	Transient ischemic attack
FBS	-	Fasting blood sugar
PPBS	-	Post prandial blood sugar
HDL	-	High density lipoprotein
SBP	-	Systolic blood pressure
Y	-	yes
HbA1C	-	Glycosylated hemoglobin
CAD	-	Coronary artery disease
PVD	-	Peripheral vascular disease
CVS	-	Cardio vascular system
CNS	-	Central nervous system
ACS	-	Acute coronary syndrome
CCA	-	Common Carotid Artery

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MASTER CHART - CASES

SlNo	Name	Age	Sex	Diease	DM in years	HTN (in years)	Smoking	BMI	FBS	PPBS	Cho	Tg	Ldl	Hdl	CIMT
1	Rajendran	65	M	CVA	7	4		25	182	300	230	200	124	37	0.09
2	Sarada	70	F	CVA	12	-		29	170	286	188	244	102	31	0.12
3	Ramakrishna	45	M	ACS	5	6		18.6	146	260	240	210	144	40	0.14
4	Kamala	70	F	ACS	9	2		24	168	380	201	172	137	30	0.12
5	Dharmalingam	65	M	CVA	7	1	Y	26	172	356	194	211	118	34	0.06
6	Shankaran	70	M	ACS	5	-	Y	27	124	292	236	356	137	28	0.06
7	Chandra	70	F	ACS	6	-		25	132	313	202	176	136	31	0.09
8	Ananth	60	M	ACS	11	8	Y	24	162	310	212	203	137	34	0.13
9	Andal	65	F	ACS	5	10		31.5	177	289	196	155	117	38	1.17
10	Ramaiya	65	M	PVD	7	4	Y	30	150	266	233	200	152	41	0.14
11	Rangasamy	70	M	ACS	8	8	Y	29	188	319	183	154	115	37	0.07
12	Venkateshan	65	M	CVA	9	15	Y	28.5	134	366	248	273	162	31	0.17
13	Shivalingam	50	M	CVA	14	-	Y	24.6	232	388	201	244	133	38	0.08
14	Janarthanan	54	M	CVA	11	3		30.5	210	462	217	310	125	30	0.12
15	Gangatharan	58	M	ACS	8	5		32.0	168	298	197	262	107	38	0.05
16	Narasaiya	55	M	ACS	6	1	Y	26	136	273	176	180	96	44	0.08
17	Babu	50	M	PVD	5	-	Y	28	171	304	202	212	120	40	0.09
18	Lingeshwaran	70	M	ACS	7	4		25	223	355	232	296	141	32	0.12
19	Munusamy	65	M	CVA	4	6	Y	24	122	256	158	144	86	43	0.12
20	Kandasamy	65	M	CVA	10	1		29	202	363	206	219	125	37	0.07
21	Balaraman	52	M	ACS	9	-	Y	28	132	312	211	198	132	39	0.08
22	Raju	56	M	CVA	7	1	Y	23.5	196	288	192	241	108	36	0.14
23	Narasimma	45	M	ACS	5	1		26	152	272	193	201	99	44	0.10
24	Subramani	45	M	ACS	8	1		22	210	314	227	186	152	38	0.08

25	Thilaga	70	F	CVA	12	6		23.5	142	376	168	214	86	39	0.14
26	Veera	70	M	CVA	6	8		20	221	396	213	267	120	40	0.09
27	Ambaram	54	M	PVD	5	1		26	184	298	230	202	152	38	0.07
28	Arumugam	70	M	ACS	9	-		18.6	142	219	181	176	106	40	0.09
29	Chinnasamy	60	M	CVA	15	1		24	168	253	219	312	124	33	0.17
30	Anamalai	58	M	CVA	5	3	Y	26	176	366	240	190	154	28	0.08
31	Subaiya	50	M	ACS	10	2	Y	27.4	156	354	221	192	147	36	0.12
32	Rathna	58	F	ACS	10	15		25	212	306	216	176	139	42	0.14
33	Singaram	69	M	ACS	7	-		31	172	289	202	256	119	32	0.13
34	Nagesh	45	F	ACS	5	-		31.5	144	224	282	148	203	38	0.07
35	Yashoda	55	F	CVA	6	-		30	268	410	198	166	127	38	0.12
36	Muniswaran	70	M	CVA	8	3		29	180	260	260	230	184	30	0.09
37	Papamma	50	F	ACS	7	-		28.5	136	288	152	190	74	40	0.08
38	Muniyandi	65	M	ACS	5	-	Y	27.5	160	250	220	268	130	36	0.15
39	Kandasamy	70	M	CVA	5	-	Y	30.5	126	242	183	175	108	40	0.05
40	Ramachandra	45	M	PVD	6	2	Y	32	178	311	190	261	94	44	0.07
41	Kumaran	70	M	CVA	7	-		26	235	331	230	136	140	43	0.05
42	Parthasarathy	57	M	ACS	8	7	Y	24	200	321	204	198	122	42	0.15
43	Nalammal	68	F	ACS	5	2		25	280	468	260	214	168	29	0.10
44	Susheelama	65	F	CVA	7	-		24	156	301	217	228	132	39	0.07
45	Kamala	70	M	CVA	10	10	Y	29	172	266	178	215	91	44	0.11
46	Maha lakshm	48	F	PVD	5	-		28	146	222	170	155	86	41	0.09
47	Rangaiah	55	M	ACS	12	-		23.5	276	362	244	296	157	28	0.17
48	Thilakan	70	M	CVA	5	-		26	186	290	219	206	140	38	0.06
49	Rajesh	62	M	ACS	8	-		22	130	252	187	196	115	33	0.09
50	Rajamma	62	F	ACS	7	-		23.5	160	328	203	223	118	40	0.09

CONTROLS

Sl No	CONTROLS Name	Age	Sex	DM(in years)	HTN(in years)	Smoking	BMI	FBS	PPBS	Chol	Tg	Ldl	Hdl	CIMT
1	Lakshmi	70	F	5	-		18.5	126	258	196	172	123	39	0.05
2	Alagan	70	M	7	8		19	130	321	163	134	89	47	0.06
3	Mary	65	F	15	5		26	178	234	176	182	106	38	0.11
4	Muthu	70	M	3	-	Y	19.5	145	317	212	146	145	37	0.06
5	Thiyagarajan	57	M	5	-		22	108	231	221	196	142	40	0.07
6	Subaash	65	M	3	2	Y	23	118	256	169	122	103	42	0.05
7	Robert	65	M	7		Y	32.3	130	259	210	136	140	43	0.05
8	Saroja	65	F	6	-		33.2	88	124	183	219	106	33	0.06
9	Jayammal	60	F	5	-		21	119	149	202	132	139	37	0.06
10	Amalraj	50	M	9	-		26	148	198	160	114	97	40	0.06
11	Ramayee	70	F	10	1		29	201	356	221	186	145	35	0.11
12	Subramani	47	M	4	4		32.7	176	333	176	146	145	37	0.08
13	Selvi	65	F	3	4		23	130	246	192	141	125	39	0.06
14	Lakshmi	50	F	5	-		25.5	150	250	206	152	136	40	0.05
15	Meenamma	70	F	9	5		30.8	192	336	198	210	126	36	0.12
16	Ramu	68	M	5	5	Y	26.1	123	184	212	146	145	37	0.09
17	Latha	65	F	2	-		24.3	96	130	173	159	102	40	0.04
18	Gangadharan	65	M	3	5		20	107	143	152	162	82	38	0.05
19	Nagaraj	70	M	4	6		27	187	224	186	170	112	40	0.07
20	Kuppammal	54	F	7	15		24.5	212	346	176	152	106	40	0.09
21	Ramachandran	65	M	15	-		27.5	188	240	177	146	104	44	0.06
22	Ranjani	62	F	12	-		20.5	173	330	184	117	119	42	0.07

23	Janartthan	50	M	5	2	Y	28.5	131	233	154	130	80	48	0.05
24	Arun	58	M	5	3	Y	25.5	112	256	209	235	121	41	0.05
25	Ramesh	60	M	8	1		23.4	107	243	173	159	102	40	0.07
26	Mahashwaran	76	M		-		25.6	124	181	142	133	68	47	0.06
27	Noorjakan	45	F	4	-		24.5	81	167	142	176	163	40	0.05
28	Vijaykumar	52	M	6	-		26.7	149	278	186	122	118	44	0.06
29	Chinnaiya	68	M	7	8	Y	29.3	117	158	192	113	124	45	0.06
30	Varadhan	70	M	13	5		28.2	163	226	210	192	133	34	0.14
31	Babu	50	M	5	-	Y	25.5	106	342	163	132	91	46	0.06
32	Antony	55	M	7	5	Y	19	138	258	173	159	102	40	0.09
33	Gangaiah	58	M	6	4		31	120	192	173	153	102	40	0.08
34	Jegan	54	M	4	3		19.5	186	258	152	133	77	48	0.06
35	Venkatesh	65	M	10	4	Y	22	252	382	180	179	111	37	0.12
36	Ramanna	70	M	8	8	Y	23	157	259	198	170	126	38	0.08
37	Loganadhan	50	M	5	-	Y	32.3	92	146	210	172	133	43	0.06
38	Ramakrishnan	45	M	7	6		33.2	138	247	198	170	126	38	0.08
39	Santhosh	65	M	5	-	Y	21	116	200	158	190	73	47	0.06
40	Durai	65	M	4	-		25.5	132	214	166	152	93	43	0.06
41	Revathy	65	F	5	-		26	114	164	221	195	137	45	0.06
42	Mohammed	50	M	4	-	Y	32.7	193	350	170	135	105	38	0.07
43	Arun	55	M	9	5	Y	25	110	246	210	222	133	36	0.11
44	Thinnaiya	58	M	3	4		22	116	250	202	132	139	37	0.09
45	Joseph	54	M	2	3		23	172	280	162	142	89	45	0.06
46	Kumaran	65	M	5	4	Y	27	103	157	135	157	58	46	0.06
47	Elumalai	70	M	7	8		26.5	148	224	202	132	139	37	0.08
48	Ramesh	50	M	5	-	Y	19	139	262	176	168	104	48	0.07
49	Shanmugam	45	M	3	6		23	92	215	221	196	142	42	0.09
50	Shanthi	65	F	7	-		28.5	128	236	232	146	163	40	0.07

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID No.13/01/2015 Dt.20. 01.2015
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval. "Study of Carotid intima Media Thickness as a Predictor of Macrovascular complications in type 2 diabetes mellitus".-For Project Work-submitted by Dr. K.Jeevitharajalakshmi, PG in General Medicine, KMC, Chennai- 10.

The Proposal is APPROVED.

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

GOVT. KILPAUK MEDICAL COLLEGE * Kilpauk, Chennai-10. * JAN 2015

20/1/15

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

29/1/2015