COMPARITIVE STUDY OF LIPOPROTEIN (a) LEVEL IN TYPE2 DIABETICS AND NON DIABETICS WITH ACUTE CORONARY SYNDROME

DISSERTATION SUBMITTED FOR

M.D GENERAL MEDICINE

BRANCH – I

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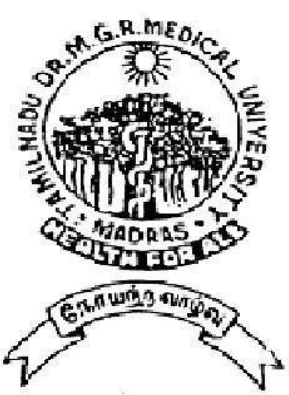

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

CERTIFICATE

This is to certify that the dissertation entitled **"COMPARITIVE STUDY OF LIPOPROTEIN (a) LEVEL IN TYPE2 DIABETICS AND NON DIABETICS WITH ACUTE CORONARY SYNDROME"** is the bonafide work of **Dr.AKILA.S** 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.AKILA.S,** solemnly declare that, this dissertation **"COMPARITIVE STUDY OF LIPOPROTEIN (a) LEVEL IN TYPE2 DIABETICS AND NON DIABETICS WITH ACUTE CORONARY SYNDROME"** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr.C.DHARMARAJ M.D.,DCH** Professor, Department of General Medicine, Madurai Medical college, Madurai.

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

Place: Madurai

Date: **Dr. AKILA.S**

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LIST OF ABBREVATIONS

ACC	: American College of Cardiology
ACE	: Angiotensin Converting Enzyme
ACS	: Acute Coronary syndrome
AHA	: American Heart Association
AMI	: Acute Myocardial Infarction
Apo B	: Apoprotein B
Apo(a)	: Apoprotein (a)
ARC	: Atherosclerosis Risk co-efficient
BMI	: Body Mass Index
β-TGF	: Transforming growth factor -β
CAD	: Coronary Artery Disease
CCS	: Canadian Cardiovascular Society
CKMB	: Creatine Phosphokinase-MB isoenzyme
CRP	: C-Reactive Protein
DM	: Diabetes mellitus
GOD-PAP	: Glucose Oxidase-phenol 4-aminophenazone peroxidase
GUSTO	: Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Arteries
HDL	: Heavy Density Lipoprotein
HGF1	: Hepatocyte growth-factor
HMG – CoA	: Hydroxy-methyl Coenzyme A
IDDM	: Insulin dependent diabetes mellitus
IDL	: Intermediate Density Lipoprotein
IL	: Interleukin
JVP	: Jugular Venous Pulse

LDH : Lactate Dehydrogenase

LDL : Low Density Lipoprotein

LMWH : Low Molecular Heparin

Lp(a) : Lipoprotein (a)

Lp(a)-C : Lipoprotein (a)-Cholesterol

LTI : Lipid tetrad Index

LV : Left Ventricle

MSP : Macrophage-stimulating protein

NCEP : National Cholesterol Education Program

NIDDM : Non-insulin dependent diabetes mellitus

NPDR : Non-Proliferative diabetic retinopathy

NSTEMI : Non-ST Elevation Myocardial Infarction

PAI-I : Plasminogen Activator Inhibitor-I R.

SD : Standard Deviation

STEMI : ST Elevation Myocardial Infarction

UA : Unstable Angina

UFH : Unfractionated Heparin

VLDL : Very Low Density Lipoprotein

VPBs : Ventricular Premature Beats

CONTENTS

Comparative study of Lipoprotein (a) level in type 2 diabetics and non diabetics with acute coronary syndrome

ABSTRACT

OBJECTIVE:

To compare the level of lipoprotein (a) level in type 2 diabetics and non diabetics in association with acute coronary syndrome.

MATERIALS AND METHODS:

This cross-sectional study was conducted on patients referred to CCU with acute coronary syndrome in Cardiology department, government Rajaji hospital, Madurai medical college. 100 subjects including 50 diabetics as test group and 50 non diabetics as control group who were matched for age and sex were enrolled in this study. We measured serum FBS, TG, cholesterol, LDL, HDL and serum Lp (a) in both groups. Data were analyzed by T-test and chi-square.

RESULTS: Lp (a) level was significantly higher in diabetics when compared with control group (Diabetic group 27.62±12.80 vs non diabetic group 12.5±5.42 mg/dl P Value <0.001). Serum TG, Cholesterol, LDL was also significantly higher in diabetics ($P < 0.001$) while HDL was lower.

CONCLUSION: Lp(a), which is an independent risk factor for atherosclerosis, has elevated levels in diabetic patients. So lowering its concentration would help prevention of CAD, a known cause of death in diabetic patients.

KEYWORDS: Lipoprotein (a), Lipid profile, Type 2 diabetes mellitus.

INTRODUCTION

Cardiovascular disease has emerged as major health problem worldwide. Coronary artery disease (CAD) has a multifactorial origin, including hereditary and acquired risk factors which may be the direct cause of the disease or merely associated with it. Changes in lipid metabolism play a relevant role in the progression of atherosclerosis and the laboratory assessment of lipoproteins is of fundamental importance to diagnose and treat this condition.

High levels of lipoprotein (a) -Lp (a) are known to be a cardiovascular risk factor associated with premature coronary artery disease. Lipoprotein (a) was described by Berg in 1963 as a genetic variation of LDL. Lp(a) presents a lipid composition which is similar to the composition of LDL, but with different protein content, since it presents the apolipoprotein (a) or Apo(a) linked to apolipoprotein B by disulfide bridges. The serum levels of Lp (a) and the molecular mass of Apo (a) vary greatly between people and are genetically determined. Lp (a) has no function in the transport of lipids and therefore its absence in the serum does not cause metabolic disruptions.

Apo (a) is highly homologous to plasminogen, the inactive precursor of plasmin - the protein that breaks up the fibrin produced during the coagulation process - due to the varied number of repetitions of amino acid sequences which are homologous to the kringle region of plasminogen. This structure allows the

binding of Lp(a) to fibrin and to the proteins of the cell surface of endothelial cells and monocyte, as well as the competitive inhibition of tissue plasminogen activator (t-PA), reducing the generation of plasmin and fibrinolysis. These characteristics provide Lp (a) with pro-atherogenic properties, in that high levels of this lipoprotein are associated with early CAD risk, cerebrovascular disease and restenosis of coronary lesions. Some authors consider Lp (a) an independent risk factor for coronary and brain artery atherosclerosis in Caucasian, Chinese, African and Indian individual.

Newer cardiovascular risk factors are of great importance in Indians, where more than 60 per cent of CAD remains unexplained by conventional risk factors. Comparative studies on newer risk factors illustrated that Indians have high levels of lipoprotein (a), CRP, homocysteine levels. Lipoprotein (a) level is consistently elevated in Indians compared to other groups.

Type 2 diabetes mellitus (DM) is associated with significant cardiac morbidity and mortality with a more than threefold increased risk of coronary artery disease (CAD). However, this increased cardiovascular risk is only partially explained by conventional risk factors, including hypertension, lipid abnormalities, central obesity, and glucose intolerance. Lipoprotein (a) (Lp(a)) is an independent risk factor for CAD. There is controversy in findings of studies regarding relation between serum Lp (a) level and diabetes. Some

reported increased level of serum Lp (a) in uncontrolled diabetic patients, while some others did not. However, it is shown that cholesterol [LDL, IDL, VLDL, Lp (a)] is a predictive factor for CHD in diabetic men and women. Therefore, this study was designed to compare the serum Lp (a) level in patients with type2 diabetes and non-diabetic individuals.

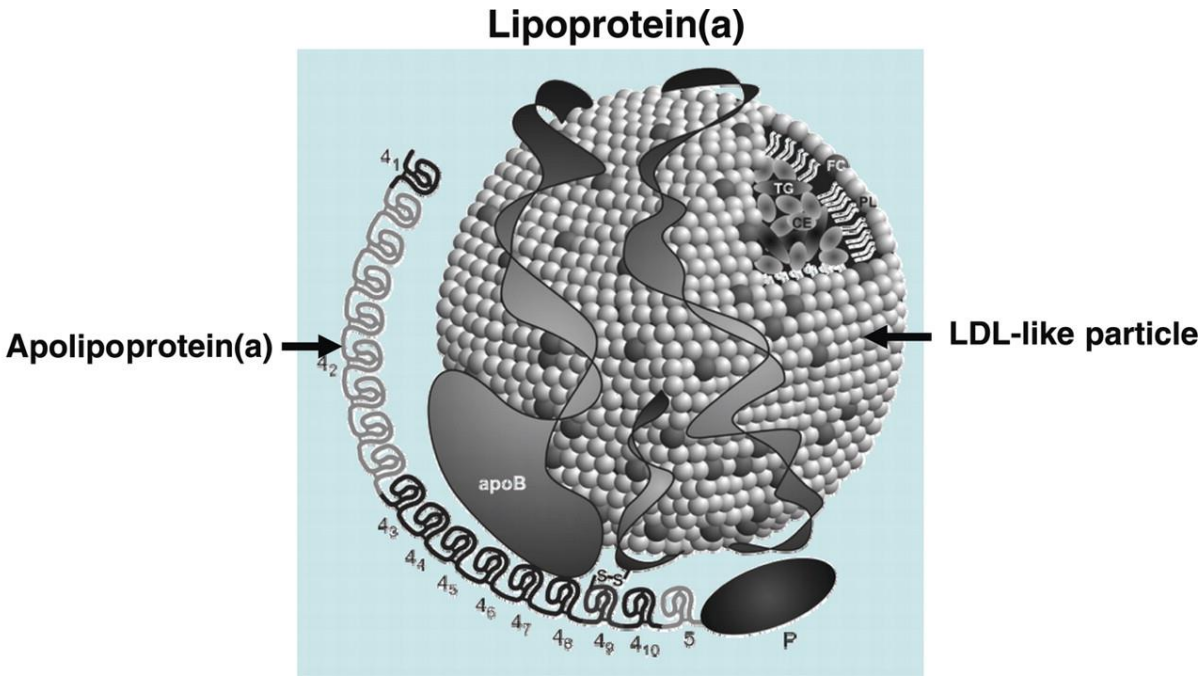
AIM AND OBJECTIVES:

- To compare the level of lipoprotein (a) level in type 2 diabetics and non diabetics in association with acute coronary syndrome.
- To assess whether lipoprotein (a) level is increased in type2 diabetics when compared to non diabetics

REVIEWOF LITERATURE

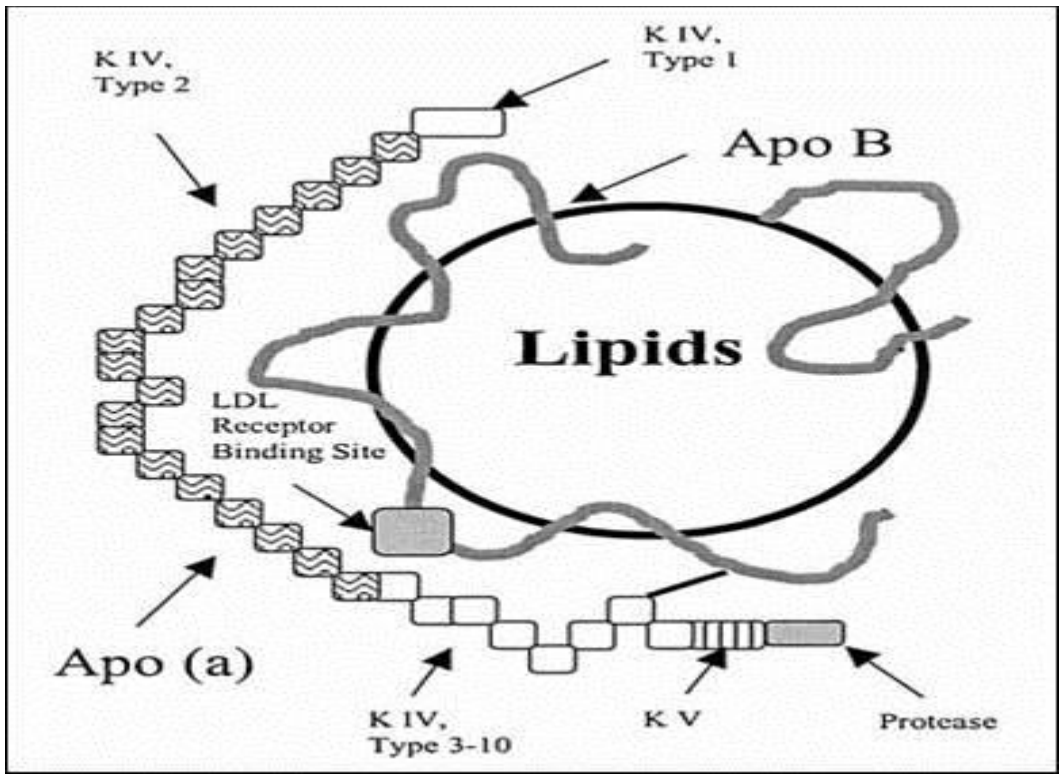
Lipoprotein (a) is LDL like particle which differ from LDL by specific apolipoprotein (a) which is covalently bound to apolipoprotein B by disulphide group. It was discovered by Berg in 1963. Lipoprotein (a) helps in transport of lipids and the gene locus for the Lp(a) is chromosome 6q(26-27). Most of the studies revealed that Lp(a) is one of the important risk factor for atherosclerotic diseases like stroke and coronary artery disease.

STRUCTURE



Lp(a) is metabolically distinct from LDL. The Apo(a), have multiple repeated plasminogen kringle (k) domains. This makes the Lp(a) isoform which determines its heterogenecity .

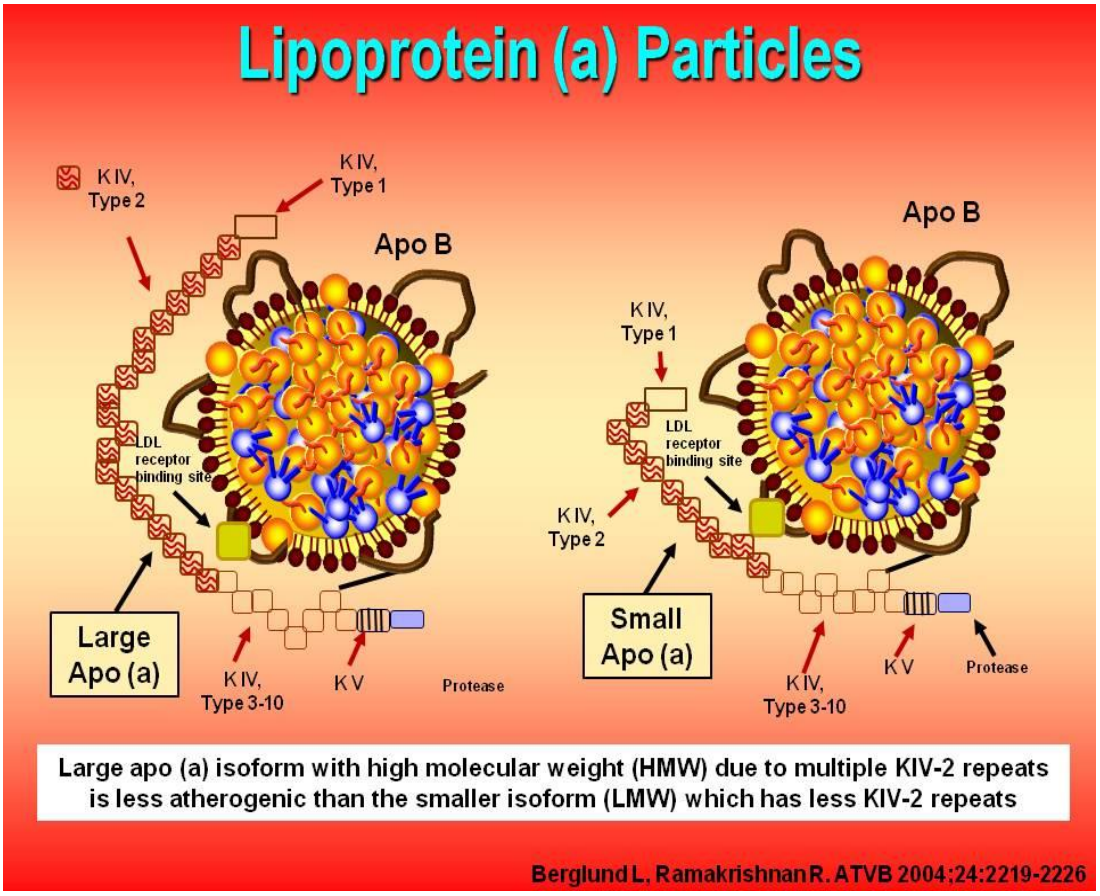
Lipoprotein(a) depends on its isoform of Apo(a) for its metabolic and physiochemical properties.



Lipoprotein (a)

The size of the Apo (a) depends on kringle IV repeats in it. The variable Apo (a) sizes are called as Apo (a) isoform and there is inverse relation between the Lp(a) plasma concentration and the size of Lp(a).

Apo (a) is produced by the hepatocyes and at the outer surface of hepatocytes Apo(a) combines with Apo(B) of LDL particles to form Lp(a). The plasma half life of Lp(a) in circulation is 3 to 4 days. The large and small LDL particles differ in the cholesterol content of lipid core. The lipid core of the LDL particle is surrounded by Apo-B 100 and unesterified



Cholesterol phospholipids. The large and small Lp(a) proteins, is due to the repeated sequence of kringle domain in apolipoprotein(a).

Apo(a) has different type of kringle IV followed by kringle V and a non functional protease domain and the Apo(a) length depends on number of repeats of kringle IV type 2, which is genetically determined.

METABOLISM

Apo (a) is predominantly synthesized in the hepatocytes of the liver. The Apo (a) has high affinity to combine with Apo-B of the LDL receptor at the outer surface of hepatocytes. The Apo(a) is covalently bound to Apo-B 100 via a disulfide bridge to the free cysteine group in k IV of Apo(a).

The binding between apolipoprotein (a) and the Apo-B makes the Lp(a) to have low affinity to uptake by LDL receptor.

The catabolism of the Lp(a) is to a large extent unknown. Initially, it was thought that Lp(a), like other lipoproteins, was degraded by LDL receptor. But in many experiments its shown that, Lp(a) has low affinity to the LDL receptor. The plasma half life of Lp(a) is higher when compared to LDL gives the conclusion that LDL receptor practically has no function in the metabolism of Lp(a).

The Apo(a) is separated from Apo-B in the blood and undergoes fragmentation in to degradation products of different molecular weight by the metalloproteinases. These are removed from circulation by different tissues and

organs and small amount of Apo(a) is excreted via urine. The other receptors that are associated with Lp(a) metabolism are galactose specific asialoglycoprotein receptor and the protein- megalin, the VLDL receptor.

The levels of Lp(a) are elevated in following conditions

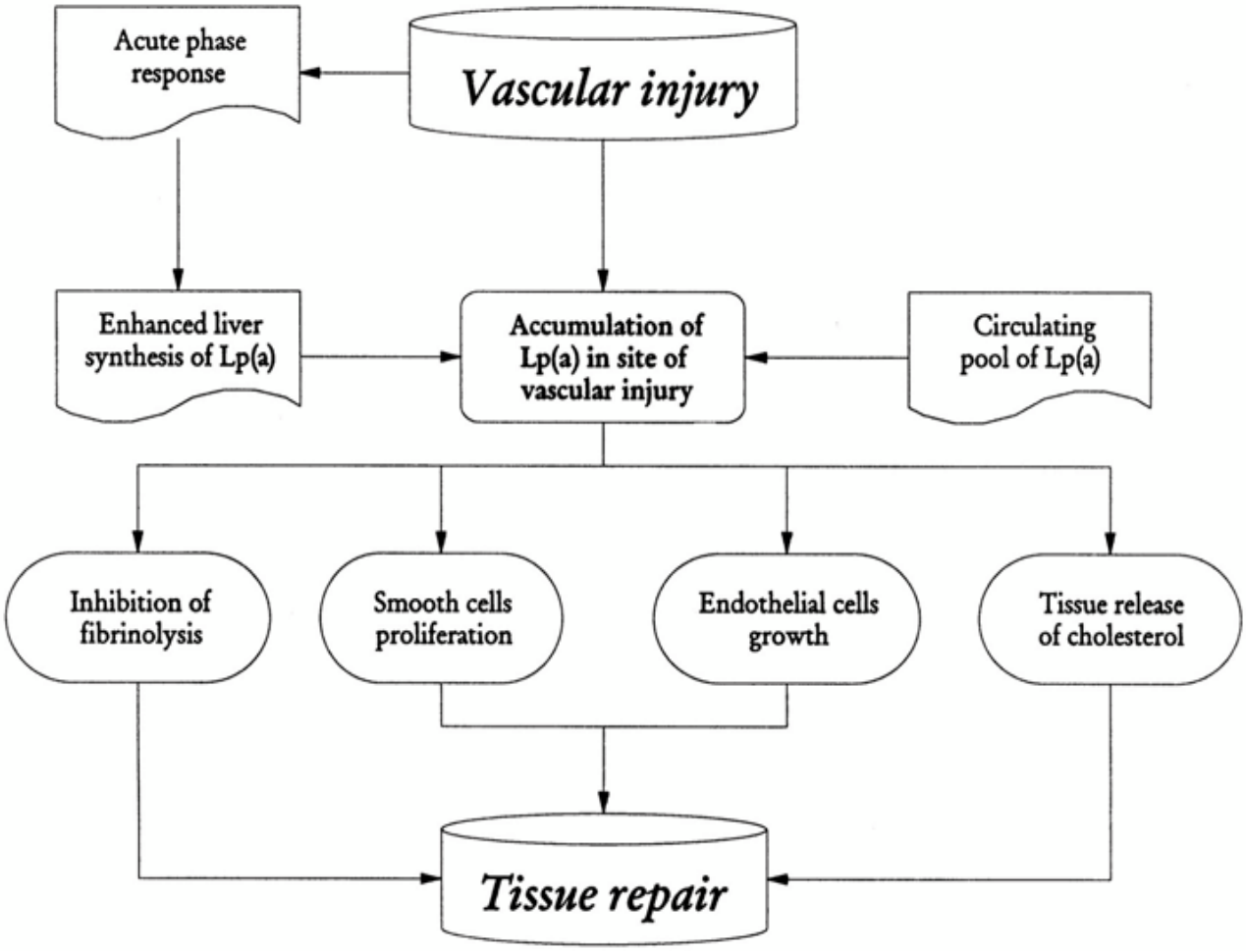
- Coronary artery disease
- Stroke
- Diabetes mellitus
- Chronic renal failure
- Nephrotic syndrome
- Severe hypothyroidism
- Familial hypercholesterolemia
- Patients receiving cyclosporine
- Oestrogen depletion

The levels of lipoprotein (a) level is low in chronic alcoholics, chronic liver disease and malnutrition.

Lp(a) in wound healing:

Normally the function of Lp(a) is transport of cholesterol to the site of the lesion and also causes vascular smooth muscle cell migration and subsequently proliferation. So Lp(a) is the necessary molecule for supply of cholesterol for

tissues which need cholesterol for tissue repair. Hence Lp(a) plasma concentration is increased as a acute phase reactant. This normal evolutionary advantage has been transferred in to pathologic mechanism for premature atherogenesis.



Lipoprotein (a) role in tissue repair

Lipoprotein (a) has Interleukin-6 responsive elements. So the Lp(a) is recognised by the interleukin receptors of macrophages, fibroblasts, platelets and endothelial

cells due to the presence of Apo(a). From the activated neutrophils, defencin is released which causes binding of Lipoprotein(a) to endothelial and the Lp(a) binds to vascular walls by lysing binding sites (LBS) of Apo(a) moiety. Lp(a) promote cell repair by transport of cholesterol. The hypothesis was supported by Yano and colleagues by markedly positive staining for Lipoprotein (a) along the surface of the fibrous cap and in endothelial cells in extra cellular space of small vessels during wound healing.

Lp(a) in angiogenesis

Lp(a) has the structure similar to that of plasminogen. Lp(a) has also anti angiogenesis effect.

Angiogenesis is defined as new vessel formation which starts with the remodelling of matrix proteins and matrix metalloproteinases as inactive zymogens. These should be activated by proteases such as plasminogen. The Apo(a) in the Lp(a) is structurally similar to plasminogen and thereby competitively inhibits the plasminogen. It indicates that Lp(a) has an anti angiogenesis effect.

In experiments, it's shown that Apo (a) leads to an inhibition of angiogenesis dependant tumour growth in the colon. As a result, the plasma concentration of Lipoprotein (a) is found to be higher in tumour patients than the healthy

individuals. The anti angiogenesis effect of Lp (a) is only little known and so it needs further investigation to prove that Lp(a) has a protective effect against tumour formation.

Lipoprotein (a) in atherosclerosis:

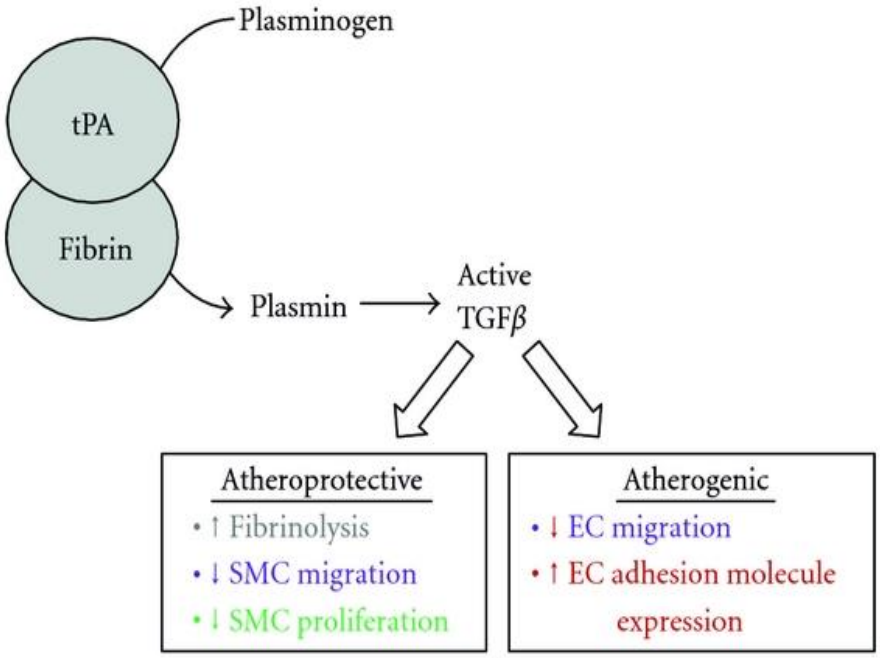
The Lp (a) particles undergoes oxidation results in forming oxidized Lp(a) which has high affinity for monocyte chemo attractant and leads to the recruitment of mononuclear phagocytes to the vascular walls results in cholesterol accumulation and foam cell formation leading to atherogenesis.

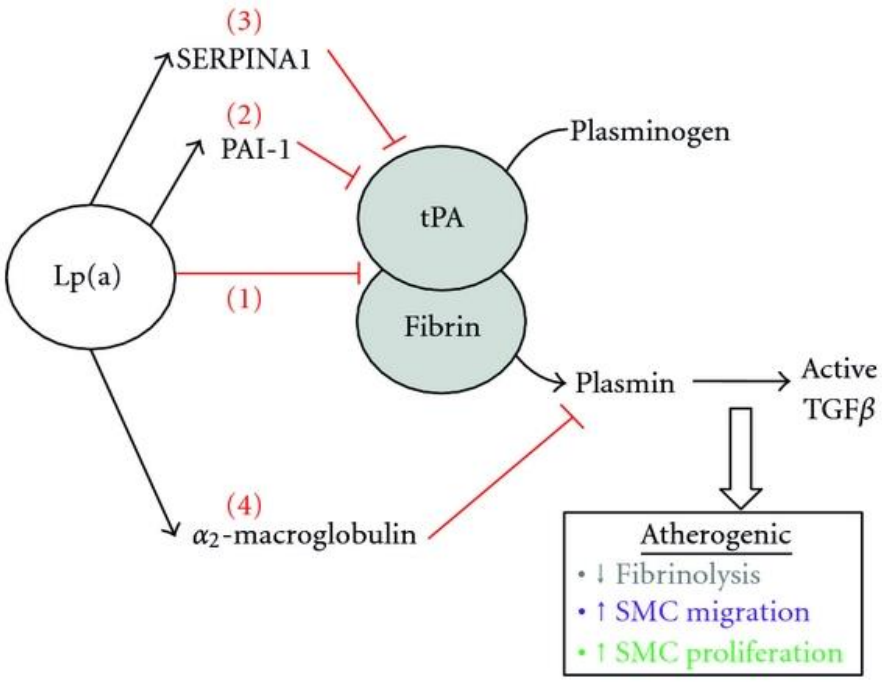
In diabetic patients patient, as a result of hyperglycemia there will be increased production of non enzymatic glycation end products. These products combine with lipoproteins undergoes oxidation which contributes to the premature atherogenesis.

Role of Lp(a) in thrombosis:

Normally the plasminogen is activated by comprising fibrin and tissue plasminogen activator. There by it encourages thrombolysis and activates TGFβ. The athero protective effect of TGFβ is by inhibition of smooth muscle cell migration and proliferation an also it causes inhibition of endothelial cell migration.

As in elevated level of lipoprotein (a), the activation of plasminogen is impaired by increased expression of plasminogen activator inhibitor-1 and SERPINIA causes inhibition of tissue plasminogen activator.





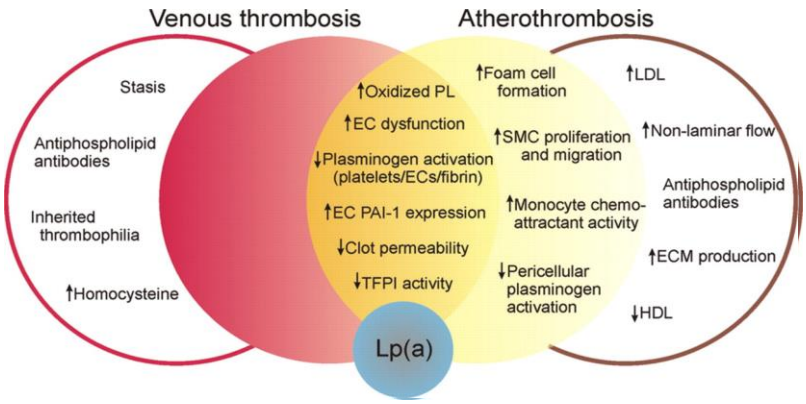
Lp(a) also enhances the activation of alpha2macroglobulin,a plasmin inhibitor there by promotes a prothrombotic effects.

Lp(a) in coronary artery disease:

In several studies ,they showed a direct relationship between increased Lp(a) levels and coronary artery disease. In asian population ,many studies revealed that Lp(a) is one of the independent risk factors for CAD compared to other populations .other conventional risk factors like cigarette smoking ,hypertension ,and hypercholesterolemia are affected by life style modification But the Lp(a) levels and the insulin resistance syndrome are not affected by drugs and life style modification.

Mechanism linking lipoprotein (a) to thrombosis and atherosclerosis:

lipoprotein(a) (Lp[a]) causes thrombosis and atherosclerosis.



Venn diagram depicts a series of factors that potentially contribute to venous thrombosis (left side) and athero thrombosis (right side). A subset of these factors that are influenced by Lp(a) is contained in the filled circles; note that all the factors potentially contributing to venous thrombosis that are influenced by Lp(a) are in common with atherothrombosis (centre). Factors that contribute uniquely to venous thrombosis or atherosclerosis, and are not influenced by Lp(a), are contained in the open circles. EC (endothelial cell) ECM, extracellular matrix; HDL- high-density lipoprotein; LDL- low-density lipoprotein; PAI-1, plasminogen activator inhibitor type 1; PL, phospholipids; SMC, smooth muscle cell; TFPI, tissue factor pathway inhibitor activity.

Cellular and molecular mechanism of Lp(a):

1. AGGREGATION OF PLATELETS:

When there is damage to blood vessels, when exposed to collagen the platelets get activated. There will be secretion of dense granules which causes aggregation of other platelets occurs by binding of fibrinogen to integrin on the surface of platelets there by clot formation is intiated.

Lp(a) promote activation of platelets via thrombin receptor activated hexapeptide and arachidonic acid. it has been demonstrated in many studies , that Lp(a) has inhibitory effect at low concentration of collagen. However the inhibitory effect was not observed in high concentration of collagen.

2. Tissue factor pathway:

Lp(a) causes increased production tissue factor (TF) which is one of the important part of coagulation system which leads to activation of thrombin increased production of TF by Lipoprotein(a) is done by activation of integrin and nuclear factor kappa B signalling cascade .Lp(a) also favour thrombosis by binding to tissue factor and thereby it inhibits the tissue factor pathway inhibitor.

3. Impairment of plasminogen activation:

The formation of plasmin is inhibited by lipoprotein (a) by competitively inhibiting the plasminogen activator such as plasminogen and fibrin. It promotes thrombosis by preventing clot lysis by inhibiting plasmin.

Lp(a) also inhibit the secretion of tissue plasminogen activator from endothelial cells. Lipoprotein(a) also increases the expression of PAI-1 (plasminogen activator inhibitor-1)in coronary artery and protein kinase c dependent mechanism.

Lp(a) also enhances production of alpha 2 macroglobulin which is a plasmin inhibitor and serine proteinase inhibitor A1 -tissue plasminogen activator inhibitor. Resulting in Lp(a) promotes thrombosis by inhibiting the association of plasminogen, fibrin and tissue plasminogen activator which impairs fibrinolysis.

4. Inhibition of TGFβ activation:

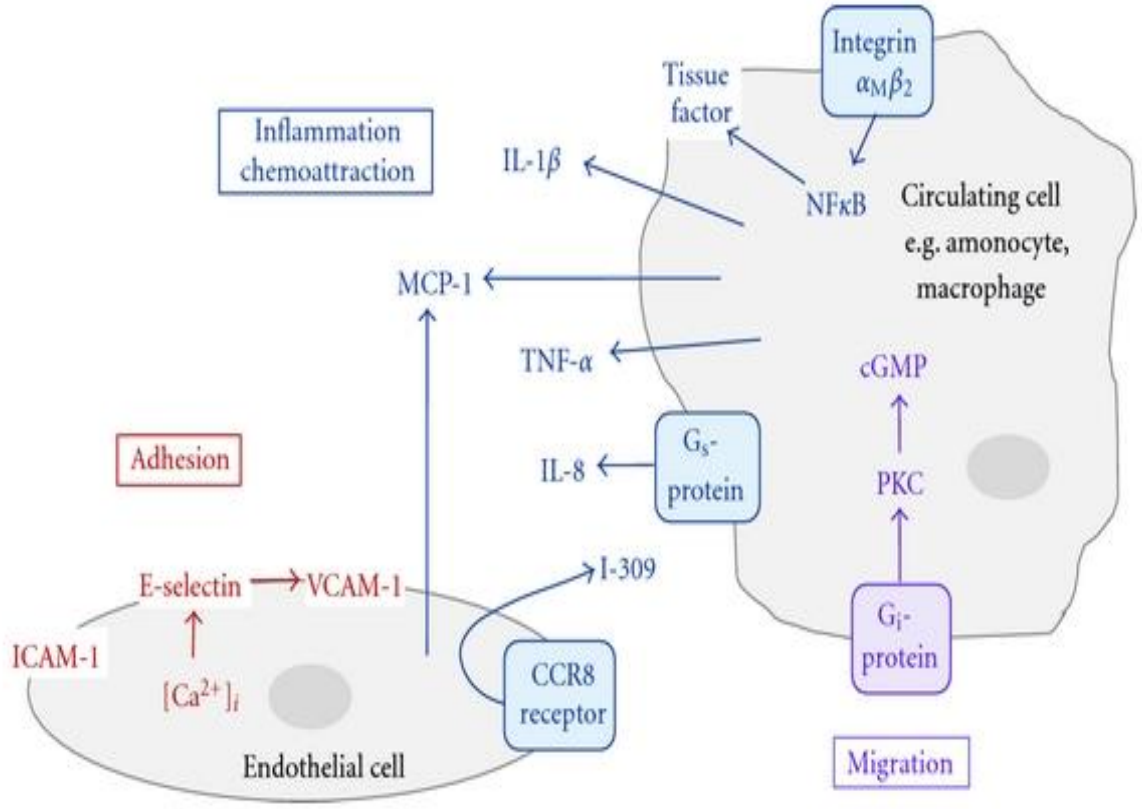
Plasmin which normally activates transforming growth factor β in clot lysis pathway causes inhibition of smooth muscle cell migration and proliferation which gives protection against atherosclerosis.

Lp(a) by inhibiting plasminogen activation also inhibits the activation of TGFβ. So the smooth muscle cell migration and proliferation within the vessel wall

occurs favouring atherosclerosis. Lp(a) also reduces the bioavailability of TGFβ favours atherosclerosis.

5. Inflammatory cell recruitment and activation;

Lp(a) levels are increased as an acute phase reactants ,as in inflammatory process.



Interleukin 6 through binding to Apo(a) of Lp(a) at multiple sites promotes production of Lp(a) as an acute phase reactants. Lipoprotein(a) has high affinity

to incoporate and take oxidised phospholipids which promote secretion of cytokines results in interaction of inflammatory cells to the injury site.

6. Transport of oxidised phospholipids:

Lp(a) binds to oxidised phospholipids preferentially which lead to their deposition within the vessel wall results in promoting atherogenesis.

7. Chemoattraction;

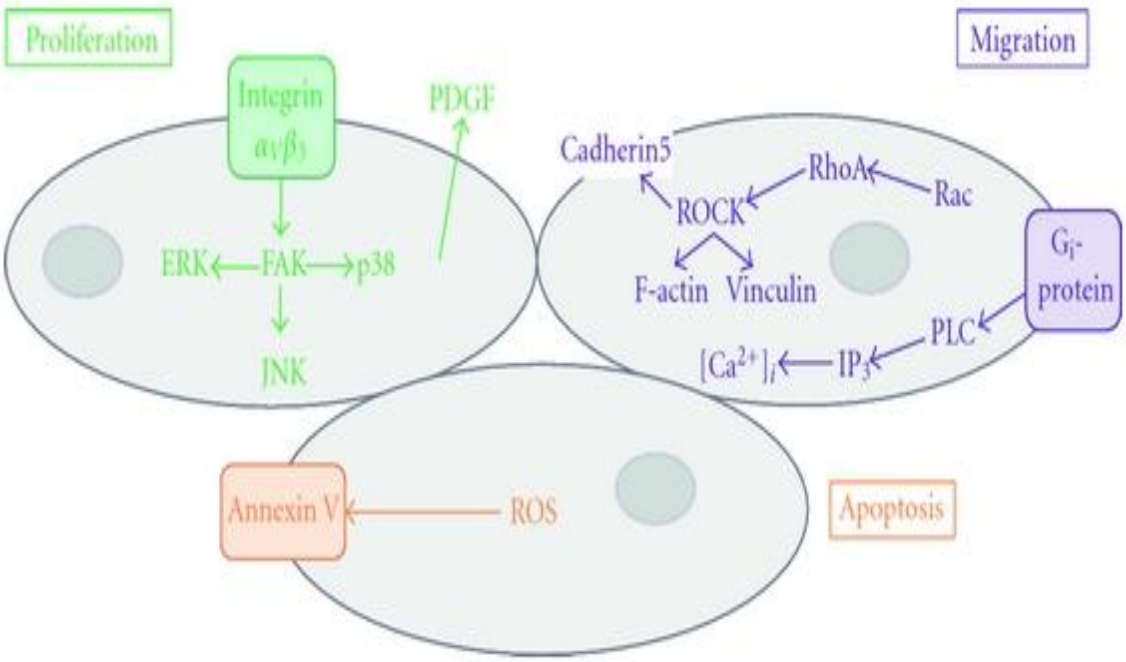
Lp(a) can induce chemotaxis and attract monocytes. Smaller Lp(a) isoforms are more potent monocyte chemo attractant which associated with greater cardiovascular risk. Lp(a) activates protein kinase c and increase intracellular levels of cyclic GMP resulting in chemokinesis. Lp(a) also promotes their migration of monocytes through the endothelium.

8. Adhesion of inflammatory cells to endothelium;

Lp(a) promotes adhesion of monocyte by binding through integrin. Lp(a) also increases the production of vascular cell adhesion molecule(VCAM-1) and E-selctin.

9. Vascular remodelling:

Lp(a) has its effect on vascular remodelling. It is done by activating multiple signalling pathways within the smooth muscle cells and endothelial cell which depends upon the oxidised state of lipoprotein(a) molecule.



The proliferation of smoth muscle cells is induced by inhibition of TGFB activation by lipoprotein(a).A common intacellular signalling pathway linked to proliferation of extracellular signal related kinase which result in smooth muscle cell proliferation.

Lp(a) also promotes smooth muscle cell proliferation within the vessel wall by increasing the expression of PDGF(platelet derived growth factor).oxidised Lp(a) is more potent mediatpr of vascular dysfunction than native Lp(a).

LIPOPROTEIN(a) in VARIOUS POPULATION:

various new cardiovascular riskfactors that are emerged in asian indians are

- Lipoprotein(a)
- C-reactive protein
- Plasminogen activator inhibitor
- Homocysteine levels

In which Lp(a) levels are consistently elevated in asian indians compared to other ethnic groups. Lp(a) is one of the most important independent risk factor for coronary artery disease. In South Indian populations also most of the studies revealed that Lp(a) levels are increased in those groups. But when compared to Asian and European population the plasma concentration of lipoprotein(a) levels are two to three fold high in African population.

It projected to rise to 80 million in the year 2030.

DIABETES MELLITUS:

Diabetes mellitus is a metabolic cum vascular syndrome of multiple etiologies characterised by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting in defects in insulin secretion, insulin action or both leading to change in both small blood vessels(microangiopathy) and large blood vessels (macroangiopathy). This disorder is frequently associated with long term damage, which can lead to failure or malfunction of organs like kidneys, eyes, ,heart and blood vessels. Diabetes is the single most important metabolic disease which can affect nearly every organ in the body and is therfore widely recognized as one of the leading causes of death and disability worldwide.

India has the dubious distinction of being called THE DIABETIC CAPITAL OF THE WORLD as it is presently estimated to have over 32 million individuals affected by this deadly disease.

TYPES OF DIABETES:

1.Type 1 diabetes

Immune mediated

Idiopathic

2.Type 2 diabetes

3.Other specific types;

a.genetic defects of beta cell function-MODY

b.genetic defects in insulin action

c.disease of exocrine pancrease

d.endocrinopathies

e.drug or chemical induced diabetes

f.infection

g.uncommon forms of immune mediated diabetes

h.genetic syndromes sometimes associated with diabetes mellitus

4.Gestational diabetes mellitus

The following are the characteristics of type 2 diabetes:

1. Associated with defects in both insulin secretion and action

2. Occurs at any age, usually diagnosed > 30 yrs

3. Age of clinical presentation may be decreasing in some ethnic groups

4. Although ~80% of patients are obese or have a history of obesity at the time of diagnosis, it can also occur in non-obese, especially the elderly

5. Type 2 diabetic patients may not present with the classic symptoms of diabetes such as polyuria, polydypsia, polyphagia and weight loss.

6. Type 2 diabetic patients are not prone for ketoacidosis except during severe stress, such as infections, trauma, medications or surgery.

7. Type 2 diabetic patients frequently present with microvascular and macrovascular chronic complications of diabetes.

Indications for diabetes screening in asymptomatic adults includes the following

A. Sustained blood pressure >135/80 mm Hg

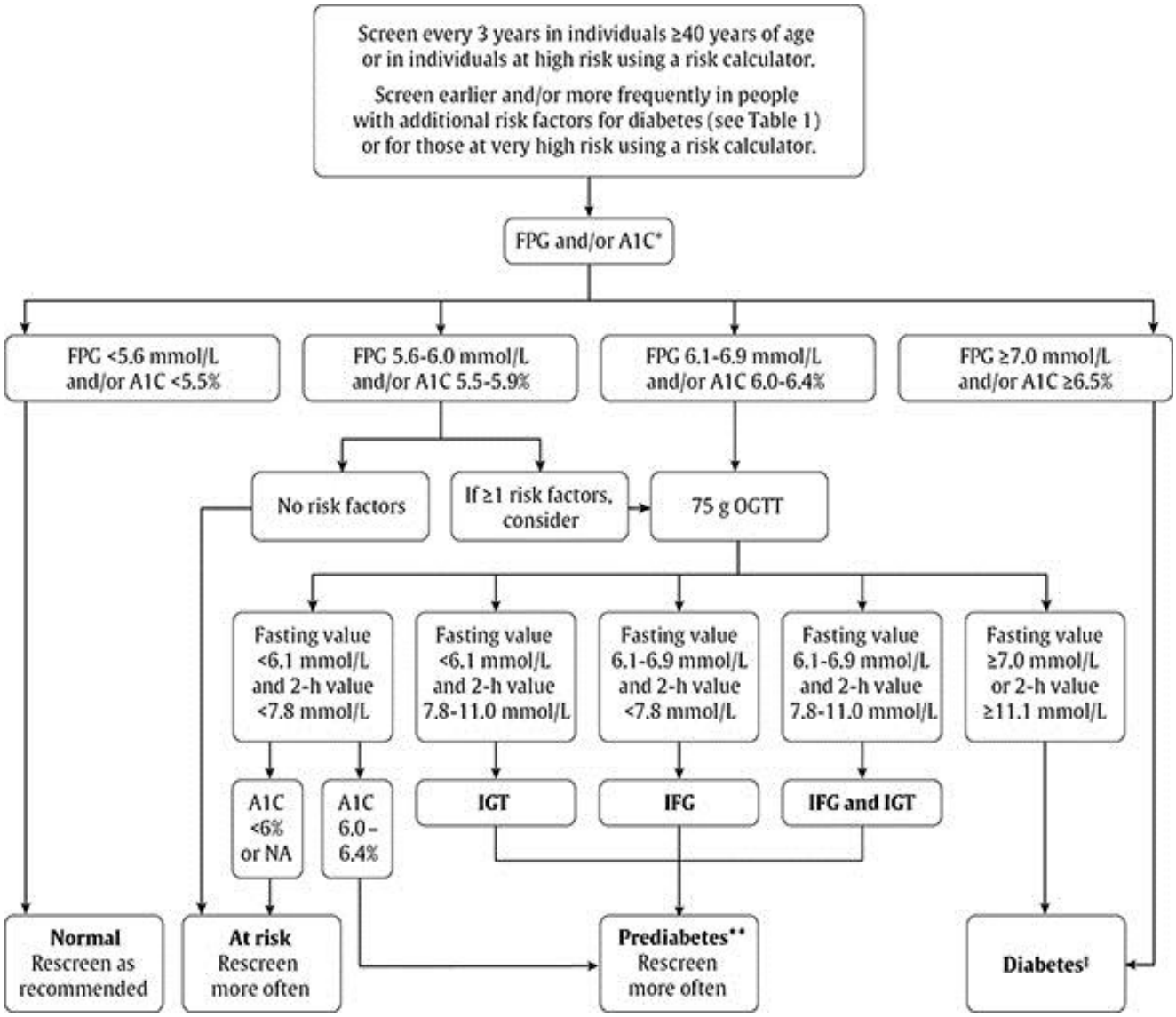
B. Overweight and 1 or more other risk factors for diabetes (e.g., first-degree relative with diabetes, BP >140/90 mm Hg, and HDL < 35 mg/dl and/or triglyceride level >250 mg/dl)

C.ADA recommends screening at age 45 years in the absence of the above criteria

Modifiable risk factors	Nonmodifiable risk factors
Overweight (obesity)	Ethnicity (African-American, Native American, Asian-American, or Pacific Islander)
Sedentary lifestyle	Family history of type 2 diabetes
Previously identified glucose intolerance (IGT and/or IFG)	Age
Metabolic syndrome	Gender
Dietary factors	History of gestational diabetes
Intrauterine environment	Polycystic ovary syndrome
Smoking	Inflammation

Lp(a) is one of the non modifiable risk factors since it is genetically determined.

DIAGNOSIS OF TYPE 2 DIABETES MELLITUS:



Metabolic abnormalities in Type 2 diabetes mellitus:

The prominent feature of type2 DM is insulin resistance. Insulin resistance is defined as the decreased ability of insulin to act effectively on target tissues like muscle, fat and liver.

Insulin resistance results in

1. Impairment of glucose utilization by insulin sensitive tissues.

2. Increased production of glucose by the liver.

Both effect will contribute to the hyperglycemia.

The obesity associated with type 2 DM is considered to be the part of the pathogenic process in developing insulin resistance. In obesity, due to increased adipocyte mass leads to increased levels of circulating free fatty acids and adipokines. They may cause insulin resistance in skeletal muscle and liver.

Impaired insulin secretion:

Initially in type 2DM, insulin secretion is increased to compensate for insulin resistance to maintain normal glucose.But in long standing type 2 diabetes, beta cell mass is decreased resulting in insulin deficiency.

Insulin resistance syndrome:

Insulin resistance syndrome is defined as collection of metabolic derangements that include hypertension, insulin resisteance, dyslipidemia, type 2 diabetes or IGF/IFG, central or visceral obesity and accelerated cardiovascular disease.

TYPE A;

-it affects young women

-have an undefined defect in insulin signalling pathway.

-they have feature of hyper androgenism, hyper insulinemia and obesity

TYPE B:

-affect middle age womem

-have autoantibodies directed against insulin receptor.

-features of hyper androgenism, hyperinsulinemia and auto immune disorders.

ACUTE COMPLICATION OF DM:

1. Diabetic ketoacidosis

2. Hyperglycemic hyperosmolar state

CHRONIC COMPLICATION OF DM:

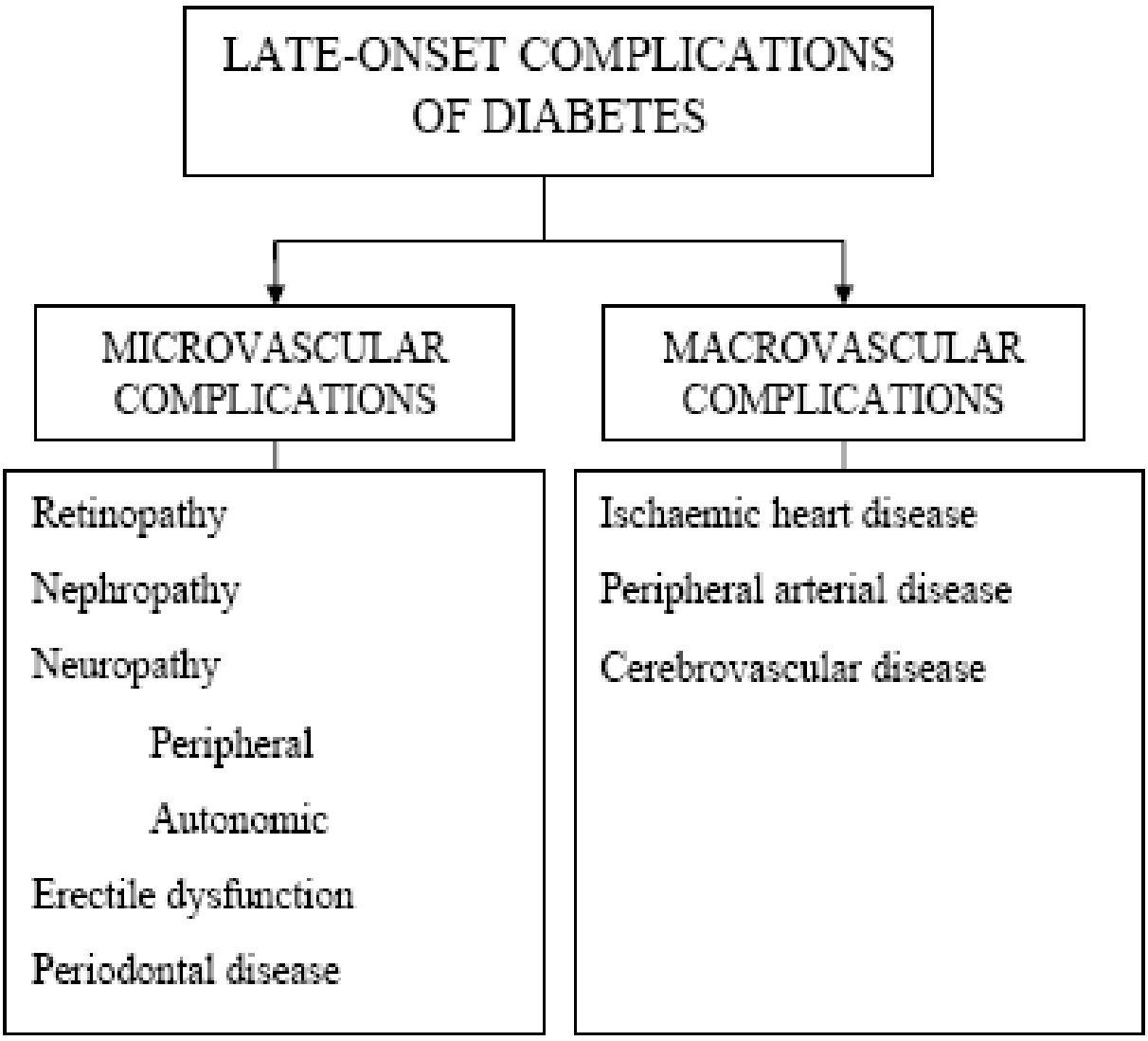


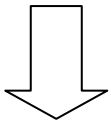
Fig. 1. Late-onset complications of diabetes.

MECHANISM OF COMPLICATION:

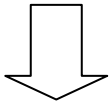
The important etiological factor in diabetes is chronic hyperglycemia which causes the complications of DM

Theories that postulated for chronic complication of diabetes mellitus

1.Increased intracellular glucose

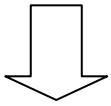


increased formation of advanced glycosylation end products

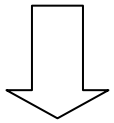


which will accelerate atherosclerosis, reduce nitric oxide synthesis, alter extra cellular matrix composition and structure, induce endothelial dysfunction and promote glomerular dysfunction.

2.Chronic hyperglycemia

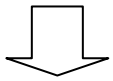


increase glucose metabolism via sorbitol pathway results in increases sorbital concentration



increases cellular osmolality and generate reactive oxygen species.

3. Hyperglycemia causes increased formation of diacylglycerol leading to activation of protein kinase c



which alters the transcription of genes for fibronectin, typeIV collagen, extra cellular matrix protein in endothelial cells and neurons.

4. Chronic hyperglycemia increases hexosamine pathway and there by increased production of fructose phosphate which alters glycosylationof proteins,TGF BETA or PAI-1.

DIABETIC RETINOPATHY:

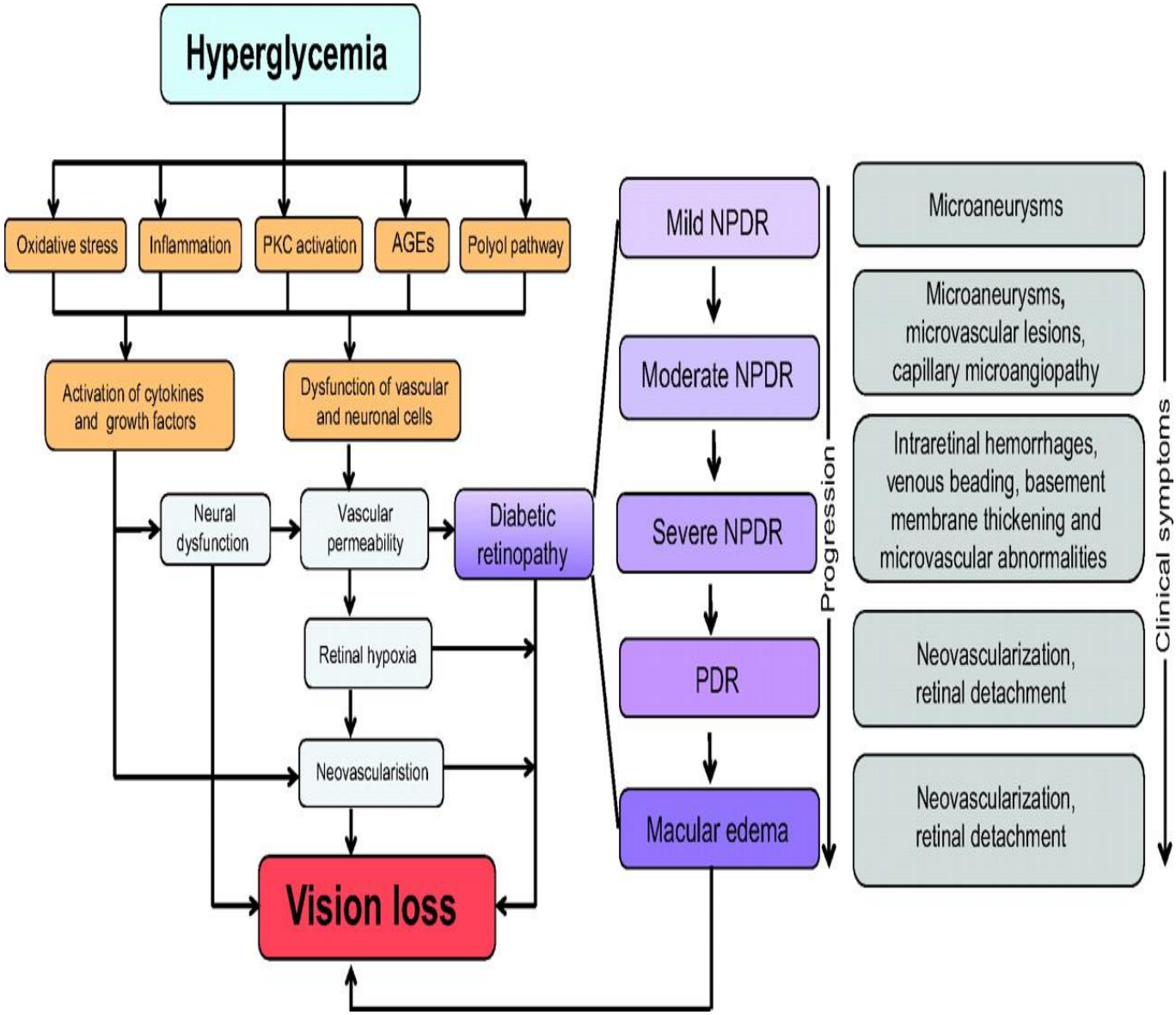
Diabetic retinopathy is a common complication of diabetes posing a serious threat to vision in diabetic patients. Diabetic retinopathy is the affection of the small vessels on the retina due to prolonged uncontrolled hyperglycemia leading to apperance of microaneurysms, hemorrhages, exudates and new vessel formation in the retina.

Classification of Diabetic retinopathy:

1. Non proliferative diabetic retinopathy

2. Proliferative diabetic retinopathy

PATHOGENESIS OF DIABETIC RETINOPATHY:



Management of diabetic retinopathy:

1. Good glycemic control

2. Medical management using aldose reductase inhibitors are being investigated in the treatment of diabetic retinopathy. This is based on the concept that glucose freely enters the cells lining the vessel wall, where it is converted to sorbitol by aldose reductase. Sorbitol in the cells exerts a harmful osmotic effect. Sorbinil, one of the aldose reductase inhibitors has shown promising prospects but the final result is still awaited.

3. Calcium dobesilate and methycobal are also found to be used in retinopathy. ACE inhibitor also retards the progress of retinopathy. PKC inhibitors are promising drugs in the prevention of progression of retinopathy.

4. **PHOTOCOAGULATION**

In situations where the vision is being seriously threatened, photocoagulation is advocated. Maximum benefit is derived when the treatment is given early when the visual acuity is reasonably good. Satisfactory results are obtained in macular edema, focal leakage and hard exudates. But when there is ischemic edema, the results are less satisfactory.

In proliferative retinopathy also, significant benefit can be derived by the judicious use of photocoagulation. Argon laser therapy is the method of

choice under these conditions.The principle behind photocoagulation is that the destruction of ischemic retina prevents the release of angiogenic factor.

5. **VITRECTOMY**

Vitrectomy is the treatment of in vitreous hemorrhage, fractional detachment and in the removal of epiretinal membranes. A visual acuity of atleast 5/200 is necessary pre operatively to achieve a favourable outcome. Vitreous hemorrhage can occur during the course of vitrectomy surgery but usually clears slowly over a period of weeks.

DIABETIC NEPHROPATHY:

Diabetic nephropathy is one of the leading causes of chronic renal failure and end stage renal disease. This is due to the increasing prevalence of type 2 diabetes, longer life span of diabetic patients and improved therapeutic options. In the case of type 2 diabete, it has slow progression and about 20 percent reach ESRD as most of the patients die due to coronary artery disease. It is the most important cause of morbitidy and mortality in type1 diabetic patients, as 35% reach ESRD

Diabetic nephroopathy is clinically defined as the presence of persistent proteinuria of more than 500 mg/day in a diabetic patient with concomitant

evidence of diabetic retinopathy and hypertension, in the absence of other kidney or renal disease.

Diabetic patients are 17 times more prone to develop nephropathy than the general population. The peak onset of DN in type 1 diabetes is between 10-15 years after onset of disease.

Pathological changes in diabetic nephropathy

The distinctive lesions seen are

1. Nodular inter capillary glomerulosclerosis(kimmelsteil wilson lesion) which is pathognomonic of diabetes mellitus

2. Diffuse inter capillary glomerulosclerosis which can lead to decrease in blood flow and thus reduction in GFR.

3. Capsular drop seen between the layers of Bowman's capsule

4. Fibrous cap seen in between the endothelial cell layer and the basement membrane

5. Arteriolar hyalinosis.

RISK FACTORS FOR DIABETIC NEPHROPATHY

1. Hypertension

2. Hyperglycemia

3. Microalbuminuria

4. Duration of diabetes

5. Family history

6. Ethnicity

7. Male gender

8. Cigarette smoking

9. Hyperlipidemia

Clinical features of diabetic nephropathy

1. Proteinuria is the hallmark

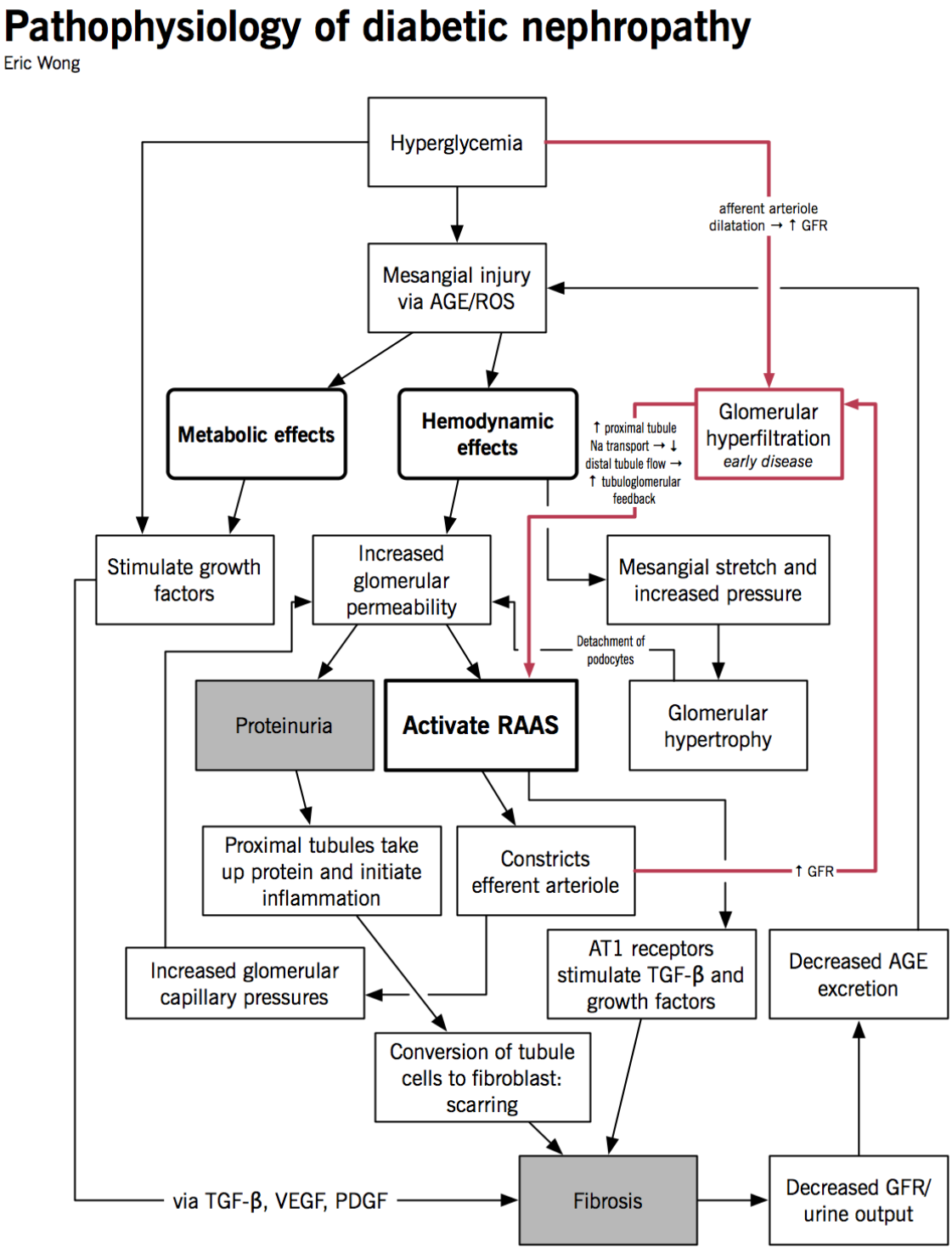
2. Fluid retention

3. Diabetic hypertension

4. Retinopathy

5. Neuropathy

6. Arterial disease



Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>380 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

STAGES OF DIABETIC NEPHROPATHY

DIABETIC NEPHROPATHY AND PREGNANCY:

The presence of microalbuminuria and proteinuria indicates poor prognosis for both mother and fetus during pregnancy as they are strong predictors of preeclamsia. Treatment with ACE inhibitors and tight glycemic control for at least 3 months prior to pregnancy reduces the risk. During pregnancy methyl dopa or calcium channel blockers can be given for control of blood pressure as ACEI are contraindicated.

Primary prevention of diabetic nephropathy

Primary prevention involves intervention before stage1-hyperfiltration hyperperfusion develops

1. Early diagnosis of diabete mellitus and strict control of blood glucose from the very begining.

2. Control of hypertension.

3. Lipid control.

4. Dietary protein of acceptable quality

5. Identification of high risk group such as those with family history of hypertension.

Management of diabetic nephropathy:

1. Control of hyperglycemia

2. Dietary protein restriction

Low protein diet (40g/day) in overt nephropathy retards the progression of renal disease. Proteins from vegetable source are preferable.

3. Control of hypertension

Normalizing the blood pressure at every stage of progressive diabetic renal disease is stressed as an important component of the therapeutic program. Blood pressure should be reduced to a standing BP of 120/70 to 130/80 mm hg. In normoalbuminuric patients, a reduction in hyperfiltration is observed by the use of ACE inhibitors. ACE inhibitors are more benefitial in the stageof incipient nephropathy. In some type 2 diabete with microalbiminuria, ACE inhibitors may increase serum creatinine if the patients happens to have renal artery stenosis or hyperkalemia. Hence serum creatinine and electrolytes should me measured after intiation of therapy, whenever the dose is changed or atleast 3to 4 times in a year. Raised arterial blood pressureaffects the renal damage in diabetics in a complex way. Intrarenal hypertension is the pathogenetic factor in the progressionof renal disease. Effective normalization of these factors by ACE inhibitors not only reduce the proteinuria but also postpones the ESRD.

Other antihypertensive drugs that are effective are non-dihydropyridine, calcium blockers and angiotensin II receptor blockers. Nifidipine and amlodipine are also useful in patients who cannot tolerate ACE inhibitors.

Control of urinary infections:

Urinary infections are one of the principal causes for the worsening of renal function in an otherwise stable uraemic diabetic and require to be sought for

and energetically treated with appropriate antibiotics. Because of renal insufficiency (creatinine clearance less than 40 ml/min) potentially toxic drugs excreted by the kidneys, such as amino glycoside antibiotics must be administered in reduced dosage and monitored. Contrast agents induced renal failure occurs with increasing frequency in those with a creatinine clearance of less than 25ml/min and hence such agents are better avoided.

Diuretics

As the renal reserve declines to about 25% of normal value, chlorthiazide and hydrochlorthiazide becomes ineffective and must be replaced by a loop diuretic such as furosemide. As the creatinine clearance falls to 10-20 ml/min, as high as 480 mg of furosemide daily may be required to effect diuresis.

DIABETIC NEUROPATHY:

Diabetic neuropathy is a heterogenous condition that encompasses a wide range of peripheral nerve dysfunction and whose development might be attributed to diabetes per se or to factors associated in the disease. It is the most common and most troublesome of all diabetic complications.

Diabetic neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes the neuropathic dysfunction. It is manifested in the somatic and autonomic nervous system.

CLASSIFICATION OF DIABETIC NEUROPATHY:

Classifications	Sub-classifications/Types
Rapidly reversible	Hyperglycaemic neuropathy
Persistent symmetric polyneuropathy	-Distal symmetric sensory/sensorimotor polyneuropathy -Autonomic neuropathy -Small fibre neuropathy/Acute painful neuropathy
Focal/multifocal neuropathy/Diabetic mononeuropathy	-Cranial neuropathy -Thoracoabdominal radiculopathy/Truncal neuropathy -Focal limb neuropathy -Proximal neuropathy/Amyotrophy -Compression/entrapment neuropathy

PATHOGENESIS OF DIABETIC NEUROPATHY:

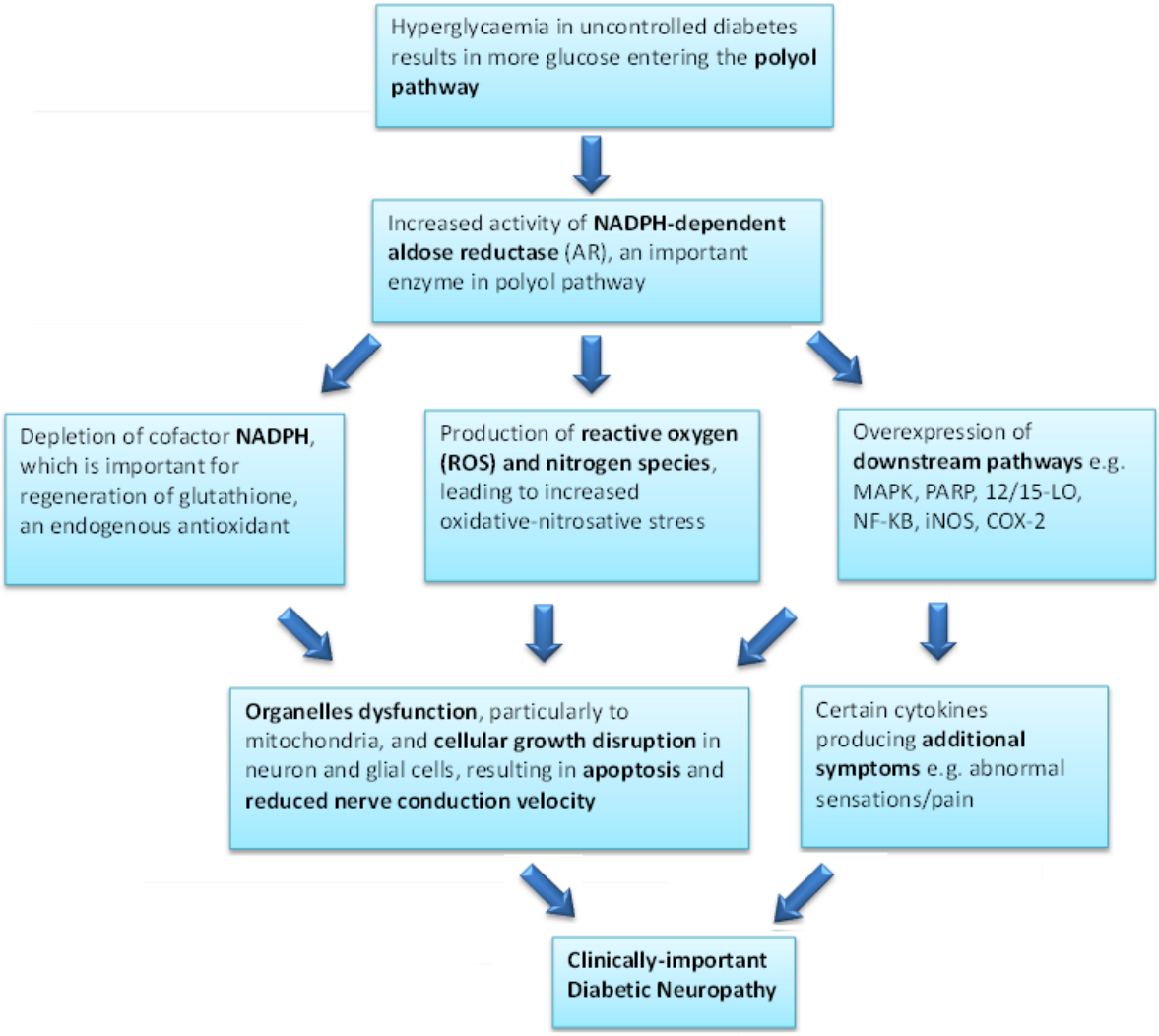
Peripheral nerves are composed of several different types of nerve fibers, each with their own function. The large myelinated A-α fibers

conduct rapidly and subserve motor power, proprioception and coordination. The thinner yet myelinated A-δ fibers subserve cold thermal detection and deep seated pain.The thin unmyelinated C fibers are responsible for warm detection threshold, heat pain and part of touch sensation nerve supply to the skin.

Axonal degeneration and segmental demyelination have been documented to be the histological hallmark of diabetic neuropathy. Intraneural vascular thrombi have also been observed. Both large fibers(mediating motor axons,proprioception and afferents for the reflex arc) and small fibers(mediating pain, temperature and autonomic outflow) are involved in diabetic neuropathy.

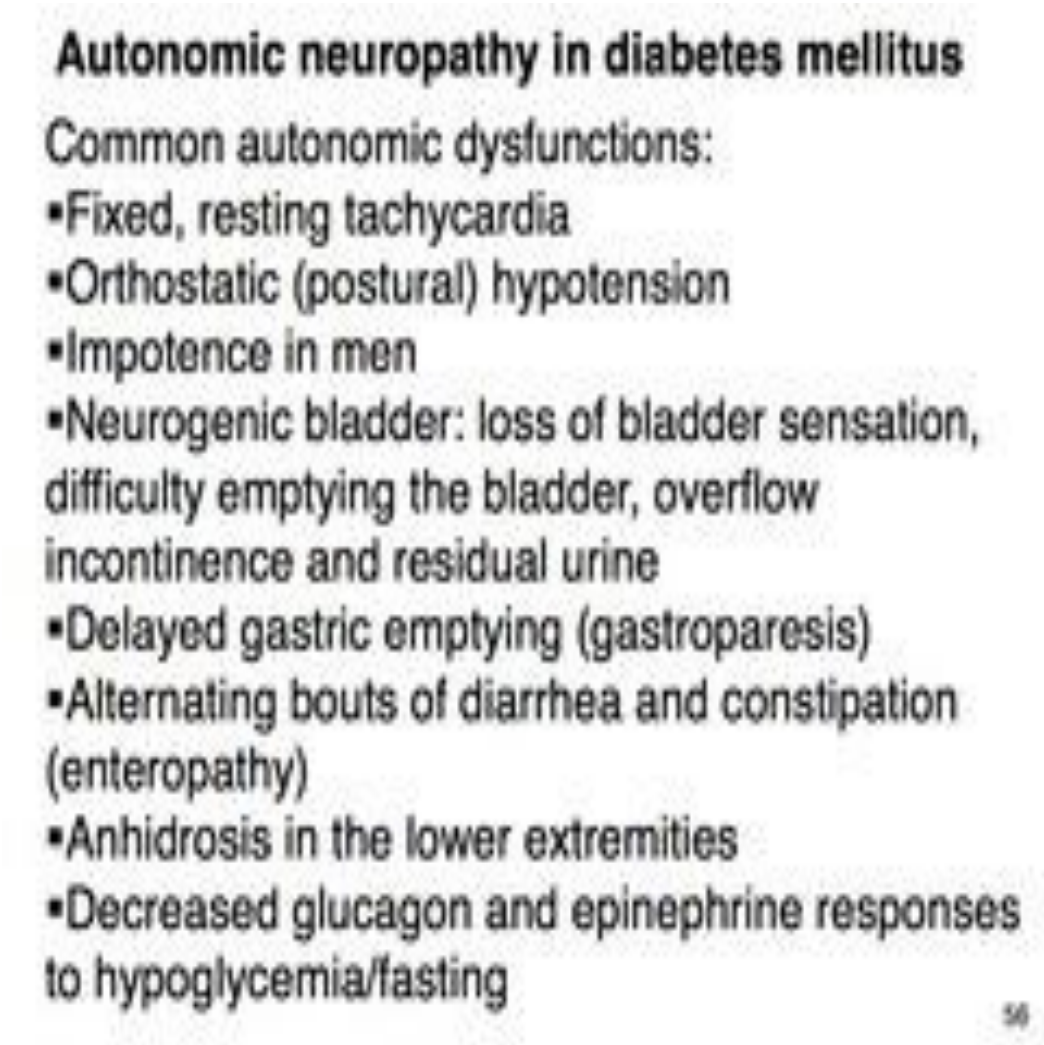
The axonal changes precede the loss of myelin, believed to be due to secondary dysfunction of schwann cells. Axonal sprouts have a large number of alpha receptors. Besides conducting nerve impulses they have the capacity to generate impulses and thus serve as pacemakers. Thus the peripheral nerve in diabetic neuropathy with a decreased axon and axonal sprouting manifests clinically as loss of sensation or of spontaneous pains due to diseased axon ,as well as occurrence of spontaneous pains(due to axonal sprouting)in the area supplied by the affected nerve. Patients experiences pain spontaneously but not when tested subjective not objective (painless painful leg).

Stages of neuropathy	characteristics
1. No neuropathy	- no symptoms and signs
2. Clinical neuropathy chronic painful	- burning, shooting, stabbing pain, and pin and needles; increased at night, absent sensation to several modalities, reduced/absent reflexes.
3. Acute painful	- severe symptoms as above(hyperesthesia common),
4. Painless with complete/partial sensory loss	-numbness/deadness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensation, absent reflexes.
5. Late complications amputation	-foot lesion, neuropathic deformity.



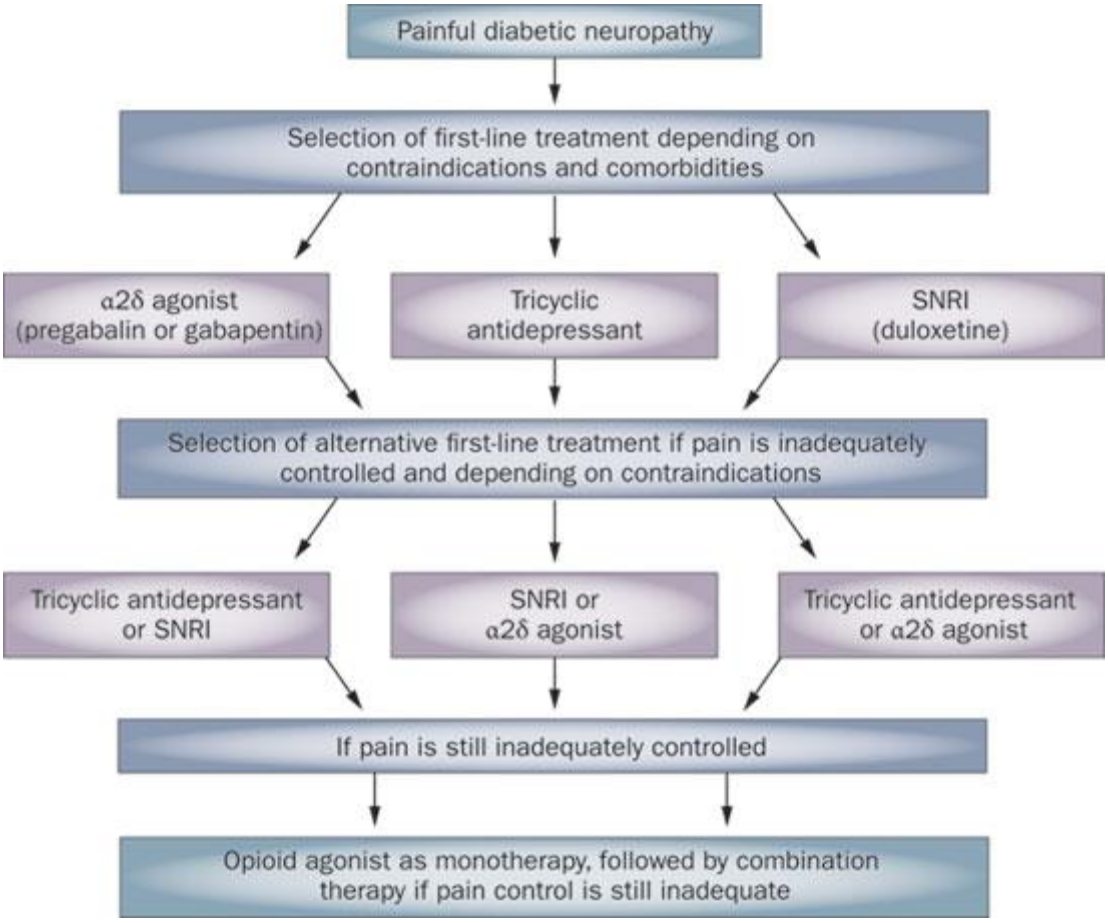
PATHOPHYSIOLOGICAL MECHANISM OF DIABETIC NEUROPATHY

AUTONOMICNEUROPATHY:



Treatment of painful neuropathy:

Many drugs have been tried to offer relief from painful neuropathic symptoms. These include simple analgesics, non steroidal anti inflammatory drugs, tricyclic anti depressants, and anti convulsants.



Treatment algorithm for the patients with diabetic neuropathy.

Dyslipidemia in diabetes

Diabetus mellitus is associated with abnormalities in lipoprotein and lipid levels referred as dyslipidemia which is more common in type 2 diabetes than the type-1 diabetes.

Normally, insulin is necessary for lipid metabolism and apolipoprotein production in liver and peripheral tissue such as endothelial cells, skeletal muscle, adipocytes and fibrocytes. Insulin by enhancing lipoprotein lipase activity helps in lipolytic pathway results in increased clearance of chylomicrons and very low density lipoproteins.

Lipoprotein abnormalities seen in diabetes mellitus

Type-1 diabetes mellitus

In type-1 diabetes mellitus patients, under good glycemic control there is no abnormalities in lipids. When there is poor glycemic control there is increased oxidation of triglycerides and low density lipoprotein. But when type-1 diabetes mellitus patient develop diabetic nephropathy, there will be high LDL cholesterol and intermediate HDL.

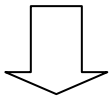
Type-2 diabetes mellitus

In type-2 diabetes mellitus patients when there is good glycemic control also patients have high triglycerides and intermediate HDL cholesterol and there will be increased small dense LDL particles which is more atherogenic.

In type-2 diabetes mellitus patients with poor glycemic control, there will be worsening of hyper triglyceridemia and high lipoprotein(a) levels. When they develop diabetic nephropathy, there will be high TGL, high Lp(a) and intermediate HDL.

Dyslipedemia plays an important role in diabetic complications and there is pronounced acceleration of atherosclerosis. In hyperglycaemia there is increased production of advanced glycation products which gives rise to reactive oxygen species. Normally endothelial cells secrete biologically active substances such as nitric oxide from nitrogen terminal of L-arginine by means of oxidation in the presence of endothelial nitric oxide synthase. Nitric oxide maintain vascular homeostasis, ensuring adequate blood flow and nutrient delivery while preventing thrombosis and leukocyte diapedesis, smooth muscle cell migration.

1. Hyperglycemia causes nitric oxide activity there by it produces increased activity of pro inflammatory chemokines and cytokines.



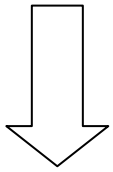
Promote monocyte and vascular smooth muscle cell migration into the intima and formation of macrophage foam cells.

2. Incresed production of super oxide anion which will inactivate nitric oxide to form peroxynitrite.

3. Hyperglycemia also causes increased production of lipid second messenger diacylglycerol which result in activation of protein kinase c.

4. There is increased free fatty acid in diabetes mellitus which will impair endothelial function. So there will be increased production of very low density lipoprotein and cholesteryl ester synthesis and there will be decreased clearance by lipoprotein lipase result in hyper triglyceridemia which will lower HDL by cholesterol transport from HDL to VLDL.

5. Increased production of endothelin



Promote inflammation and causes vascular smooth muscle cell migration and proliferation.

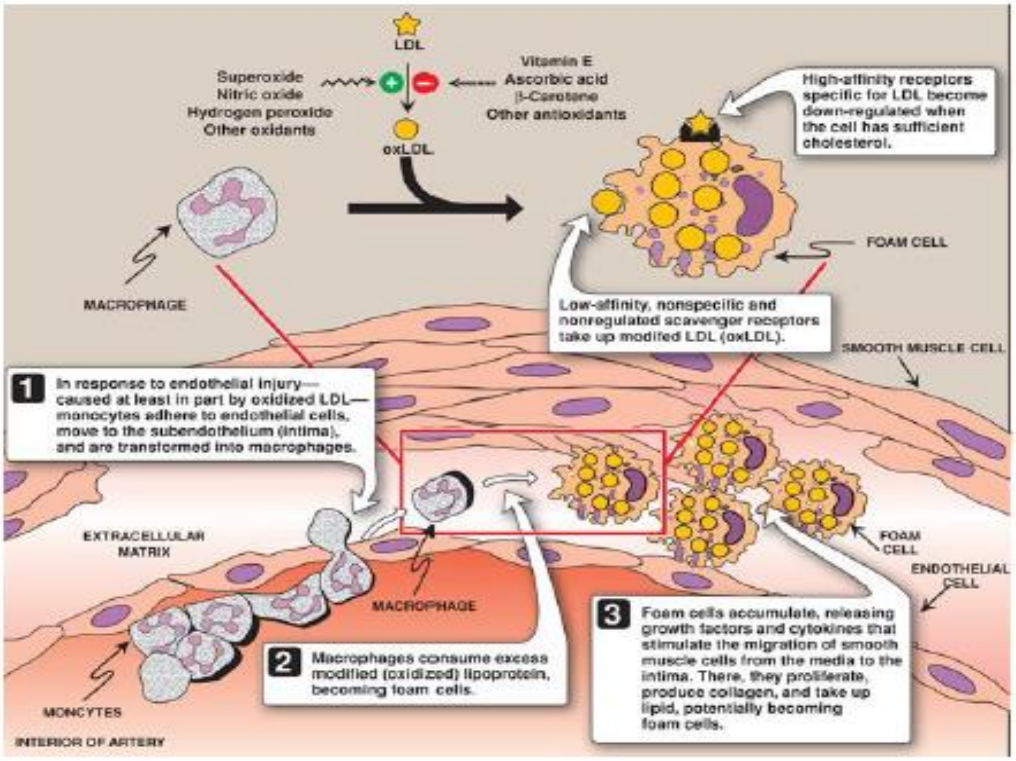
6. Platelet function is also abnormal in diabetes mellitus.

7. There is increased production of plasma coagulant factors (factor VII and Thrombin) and decreased production of anti coagulants such as protein c and thrombomodulin.

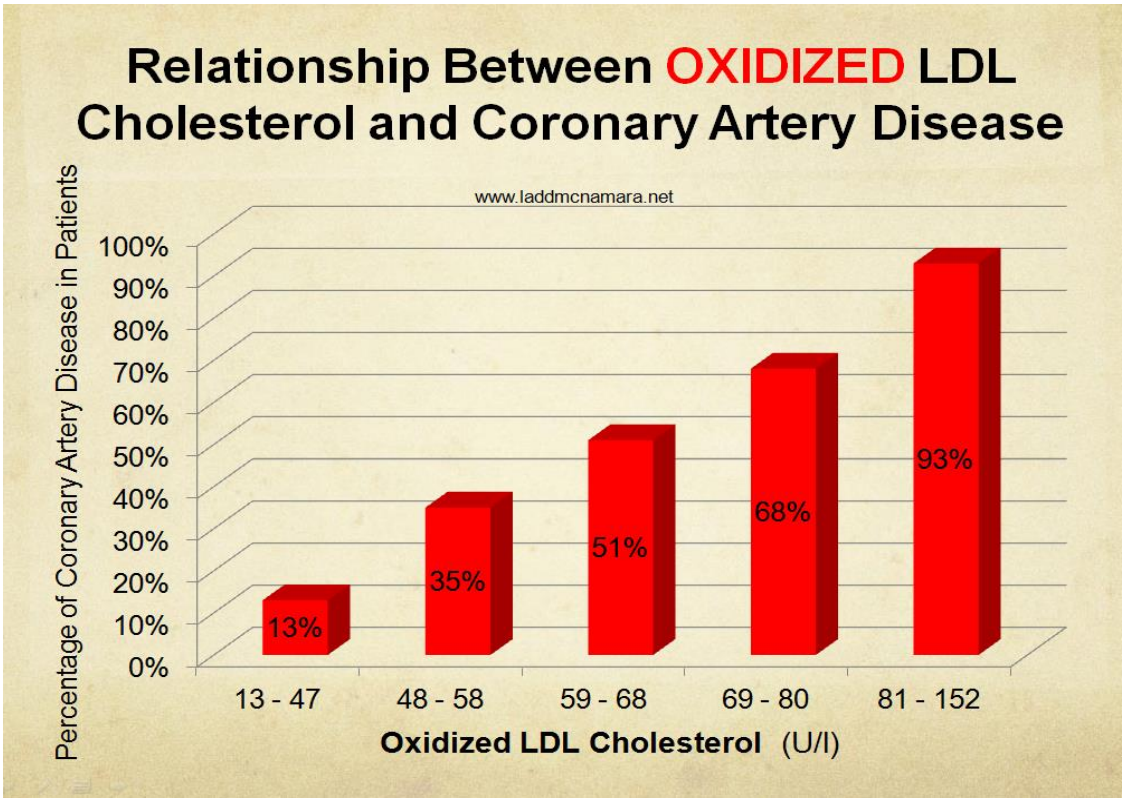
Oxidative stress in type 2 DM

In type 2 DM there is increased oxidative stress resulting in formation of super oxide anions. These super oxide anions react with small dense LDL particle which undergoes oxidation to form oxidized LDL which is more atherogenic. The oxidation of LDL is a complex process during which both the protein and the lipids undergo oxidative changes and form complex products. E.g. Non enzymatic oxidative changes in amino acids as well as proteolysis and cross links of apoprotein B occur that result in extensive alteration in the protein composition and structure.

LDL and Atherosclerosis



The peroxidised lipids decompose generating both free and core aldehyde and ketones that covalently modify amino groups of lysine residues of the protein moiety. This extensively damaged LDL creates net negative charges that were essential for its interaction and uptake by macrophages resulting in formation of macrophage foam cells.



MANAGEMENT OF HYPERLIPIDEMIA:

1.NON PHARMACOLOGICAL TREATMENT:

Diet control and regular physical activity and weight reduction in overweight persons should be aggressively perused. Total caloric intake should be decided after giving consideration to the type of work and current weight. Fats should provide 25% of the calories and the saturated fats should provide 7% of the calories.

2. Cessation of smoking:

Smoking and tobacco in any form should be totally avoided. This will help to increase HDL cholesterol in those who are tobacco consumers.

PHARMACOLOGICAL TREATMENT

All type 2 DM with overt cardiovascular disease and those above 40 years without overt cardiovascular disease but having one or more risk factors, should be started on statins, irrespective of baseline LDL cholesterol level. In those with lesser cardiovascular risk, the first goal is to reduce LDL cholesterol to the target goal. If LDL cholesterol levels are >130mg%, pharmacological treatment should be started simultaneously with life style measures. If LDL cholesterol is between 100-130 mg%, non pharmacological treatment should be started and lipids should be repeated after 3 months. If goals are not reached at that time, pharmacological treatment should be added. For isolated rise in LDL cholesterol, monotheraphy with statins should be preferred. Usually low dose of statin are used. However cardiologists use high doses of statins for short periods following acute coronary syndrome and coronary angioplasty. Higher doses are associated with increased chances of side effects such as hepato toxicity, myopathy and occasionally rhabdomyolysis. All the patients should undergo LFT and CPK before starting statin therapy.

Lipid profiles should be periodically repeated at 3 to 6 monthly interval and dosage reduced to half when LDL goals are reached.

Statins also have anti atherosclerotic properties working independently of their lipid lowering properties.

In patients having contra indications to use of statins or intolerence to statins, bile acid sequesterants can also be used. GI disturbances and tendency to raise triglycerides level are some of the limitation of these agents.

The second goal is to increase HDL cholesterol to target level. Non pharmacological measures such as cessation of smoking and physical exercise should be aggressively perused.Among the pharmacological agents, best results are obtained with nicotinic acid.

Hypertriglyceredemia:

Life style modification and abstinence from alcohol is required. Fibrates are the drug of choice if values are more than 400mgs%.

HYPERTENSION IN DIABETES:

Hypertension in patients with diabetes is divided in following sub groups.

1. Surgically curable hypertension(adrenal hypertension) as in cushing's disease, primary hyperaldosteronism and pheochromycetoma. In these conditions, both

hypertension and diabetes result from hyperfunction of endocrine organ and surgical treatment leading to correction of hyperfunction leads to normalization of both blood pressure as well as blood glucose.

Hypertension due to renal artery stenosis can also be treated surgically or by non surgical intervention (renal artery angioplasty). In diabetes, atherosclerosis is accelerated and reno vascular hypertension is more common than in general population.

2. Hypertension without diabetic nephropathy

a) Isolated systolic hypertension. Systolic BP of 160mm of Hg or more with diastolic BP below 90 mm of Hg is more common in diabetes because of associated advanced atherosclerosis and resultant loss of arterial elasticity.

In past isolated systolic hypertension was taken lightly by the medical profession due to prevailing belief that it is not as important as elevated diastolic blood pressure in pathogenesis of vascular complications. As per the current recommendations, isolated systolic hypertension should be as aggressively treated as diastolic hypertension

b) Essential hypertension. This is the commonest type of hypertension in type 2 diabetic patients. The diagnosis of hypertension may precede, follow or coincide with that of diabetes. Its pathogenesis is similar to that of essential hypertension

in non diabetics, however additional factors may operate. In recent years the role of insulin resistance in genesis of hypertension has evoked considerable interest.

Insulin resistance results in hyperinsulinemia which predisposes to hypertension through a variety of mechanism such as 1) increased sympathetic activity, 2) increased sodium and water retention, 4) altering sensitivity of vasculature to vaso active substances, etc.

3) Hypertension in those with diabetic nephropathy

Renal damage in diabetic nephropathy is responsible for hypertension. It is seen in pure form in type 1 diabetes with diabetic nephropathy. In middle aged and older type 2 diabetics with nephropathy the aetiology of hypertension is often mixed. The earliest manifestation of diabetic nephropathy is microalbuminuria. At this stage the systemic blood pressure is usually in pre hypertension range but intra glomerular pressure is elevated. Administration of ACE inhibitors and Angiotensin receptor blockers leads to reduction in intra glomerular pressure and reversal micro albuminuria.

4) Orthostatic hypotension with supine hypertension. When hypertensive diabetic develops severe autonomic neuropathy, he develops postural

hypertension but he remains hypertensive during the time he is resting in supine position.

Management of hypertension in Diabetes

Non pharmacological measures should be introduced in pre hypertension stage and continued along with pharmacological agents if by themselves, they are not sufficient to bring BP down to the target of 130/80 mm of Hg or below. Weight reduction in over weight patients by prudent diet control and appropriate dynamic exercise (30-40 minutes' walk daily at brisk pace) is very effective and proven by non pharmacological measure. It also helps in achieving goal for metabolic controls. Hypertensive patients should restrict sodium intake to 5 gm per day and refrain from smoking.

Pharmacological Agents

If non pharmacological measures do not bring down BP to target, anti hypertensive agents should be added. There are certain special considerations while selecting an agent in diabetic hypertensive individuals. The agent should not worsen metabolic control; it should have beneficial effects on vascular complications of diabetes and it should improve the quality of life; and should not cause orthostatic hypotension. There is no single agent which fulfils all these criteria in all diabetes. One has to study the needs of an individual patient

depending upon presence or absence of various vascular complications of diabetes and other conditions which could be associated (e.g. COPD/Bronchial asthma, CCF), and select appropriate agent. It to be noted that in most of the diabetes a combination of two or three anti hypertensive agents representing different classes is required to reach target BP.

Thiazide diuritics

These are the agents of first choice in stage 1 diabetic hypertensives without microalbuminuria. Hydrochlorthiazide in dosage of 12.5 mg daily is safe, effective and inexpensive. Its role in preventing vascular complications is proved beyond doubt. In the dosage mentioned above, it does not significantly increase blood glucose, cholesterol and uric acid levels. If patient has stage 2 hypertension or if monotherapy with thiazide is not sufficient to reach target BP, it can be combined with other agents.

ACE inhibitors

These agents are particularly suited for use in diabetic hypertensive patients because when given to those who have microalbuminuria, urinary albumin excretion can be reverted to nonalbuminuria. These agents can be administered even in pre hypertensive diabetic patients with microalbuminuria. At this stage intra glomerular pressure is high and its reduction leads to reduction in albumin

excretion rate. Through vasculo protection it offers action beyond blood pressure control. In diabetic hypertensive as well as pre hypertensive with microalbuminuria ACE inhibitors are the agents of first choice. They can be combined with thiazide diuritics if required. Combinations of various ACE inhibitors with 12.5mg of hydrochlorthiazide are available. Captopril, Enalapril, Lisinopril, Ramipril, Quinalapril and Trandelopril are available in our country. Advanced renal failure, hyperkalemia, bilateral renal artery stenosis, pregnancy and lactation are contra indications for use of ACE inhibitors. About 10-15% patients have to discontinue ACE inhibitors due to intractable cough.

Angiotensin Receptor blockers (ARBs)

These agents act on renin angiotensin system, at a step beyond the site of action of ACE inhibitors. They also provide reno protective action. Like ACE inhibitors, they also have the ability to convert those having micro albuminuria to normoalbuminuria. If started in diabetics who already have diabetic nephropathy, they slow down the rate of advancement of nephropathy. The time taken to reach end stage renal failure as well as double serum creatinine value as compared to baseline value at the beginning ofARB therapy is doubled as compared to those who do not take ARBs. Losartan was the prototype introduced in our country more than a decade back. In a major trial in hypertensive patients, Losartan was found to provide vaso protective action.

Candensartan, Irbesartan, Olmesartan, Valsartan and Telmesartan are other ARBs available in our country. Their indications and contra indications are same as those of ACE inhibitors. Their use does not lead to cough; hence they can replace ACE inhibitors who develop troublesome cough. Valsarta has been found to have beneficial effects in patients suffering from congestive cardiac failure. Even though ARBs have action at a site different from that of ACE inhibitors on RAAS, and even though both actions are complimentary to each other, a large trial on combination of telmisartan and ramipril was unable to demonstrate any additional beneficial effects in those on combination therapy. ("ONTARGET" study).

Beta blockers, (BB's)

They are potent anti hypertensive agents and also offer cardio protection. They are also indicated for secondary prevention of myocardial infarction. In patients with old myocardial infarction and angina pectoris with diabetes, they are preferred agents. Non selective beta blockers such as propranalol mask the symptoms of hypoglycemia and thus delay diagnosis and treatment. Thus selective beta blockers such as Metaprolol or Nebivolol should be preferred. Large doses of beta blockers can increase serum cholesterol levels. Thus if a moderate dose is insufficient to bring down BP to target, an agent from other anti hypertensive group should be added instead of stepping up the dose of beta

blockers. Beta blockers are not suitable in patients with associated broncho spastic disorders, bradyarrhythmias and several peripheral vascular diseases.

Calcium channel blockers, (CCBs)

This anti hypertensive drug class is made up of a few chemically different sub classes all sharing anti hypertensive properties but differing in other actions on cardio vascular system. (E.g. diltiazem and verapamil reduce heart rate while nifidipine tends to increase it). These agents do not have adverse metabolic effects, neither are contraindicated in broncho spastic disorders and peripheral vascular disease, but at the same time, unlike ACE inhibitors and ARBs, they do not offer any special advantage for the treatment of diabetic hypertensive. However, in some study, anti atherosclerosis effect and endothelial protection have been attributed to amlodipine. Some degree of renal protection is also provided by many CCBs. Amlodipine and Felodipine are commonly used CCBs. Edema over the feet is the commonest side effect. CCBs can be added to any other anti hypertensive agents. Even though usually they are not the agents of first choice to start the treatment, CCBs are commonly employed in combination with other agents in diabetic patients.

ALPHA BLOCKERS

These agents are metabolically neutral, improve symptoms of prostatism, and are not contra indicated in patients having broncho spastic disorders and peripheral vascular disease. However postural hypertension is a common side effect, which could be troublesome in elderly long standing diabetics having autonomic neuropathy.

Centrally acting agents

Alpha methyl dopa and clonidine belong to this class of agents. These agents are rarely used nowadays due to availability of wide range of agents which are better tolerated and equally efficacious. Drowsiness, postural hypertension and weakness are some of the common side effects of these agents. Sometimes these agents are used in combination with other anti hypertensive agents in diabetics with severe hypertension with associated problems making some of the commonly used agents unsuitable.

Macrovascular complications of diabetes mellitus:

Coronary artery disease:

Over 50% of diabetic individuals die due to CAD. Diabetes mellitus and CAD share a common soil for the development of the disease. CAD which leads to premature myocardial infarction , is the leading cause of death among diabetics and results in threefold higher mortality compared to non diabetics.

RISK FACTORS FOR CAD

Non modifiable

- Age
- Male sex
- Family history

Modifiable

- Cigarette smoking
- Obesity
- Diabetes
- Hypertension
- Elevated cholesterol
- Behavioral risk factors

Non conventional risk factors;

Atherosclerotic/thrombotic risk factors are increased lipoprotein(a), homocysteine, plasma fibrinogen, tissue plasminogen, plasminogen activator inhibitor-1, c reactive protein.

Protective factors are exercise, HDL cholesterol, stress reduction.

Factors underlying accelerated atherogenesis in diabetes:

- Insulin resistance
- Diabetic dyslipidemia
- Hyperglycemia-glyco oxidation
- Oxidative stress
- Hypertension
- Thrombogenic factors-platelet aggregation,Lp(a),PAI-1, tissue plasminogen activator and fibrinogen

TYPE 2 DIABETES MELLITUS PATIENTS WITH ACUTE CORONARY SYNDROME:

Studies by Mohan et al, Neki et al, Oshima et al, Tseng et al and Salehi et al suggest that there is a significant increase is Lp(a) in these patients when compared to the non-diabetic group. Since Lp(a) are found elevated in type 2 diabetic patients, and as it is associated with increased disruption of coronary atherosclerotic plaques, treatment of Lp(a) and associated risk factors may benefit the diabetic patients with acute coronary syndrome.

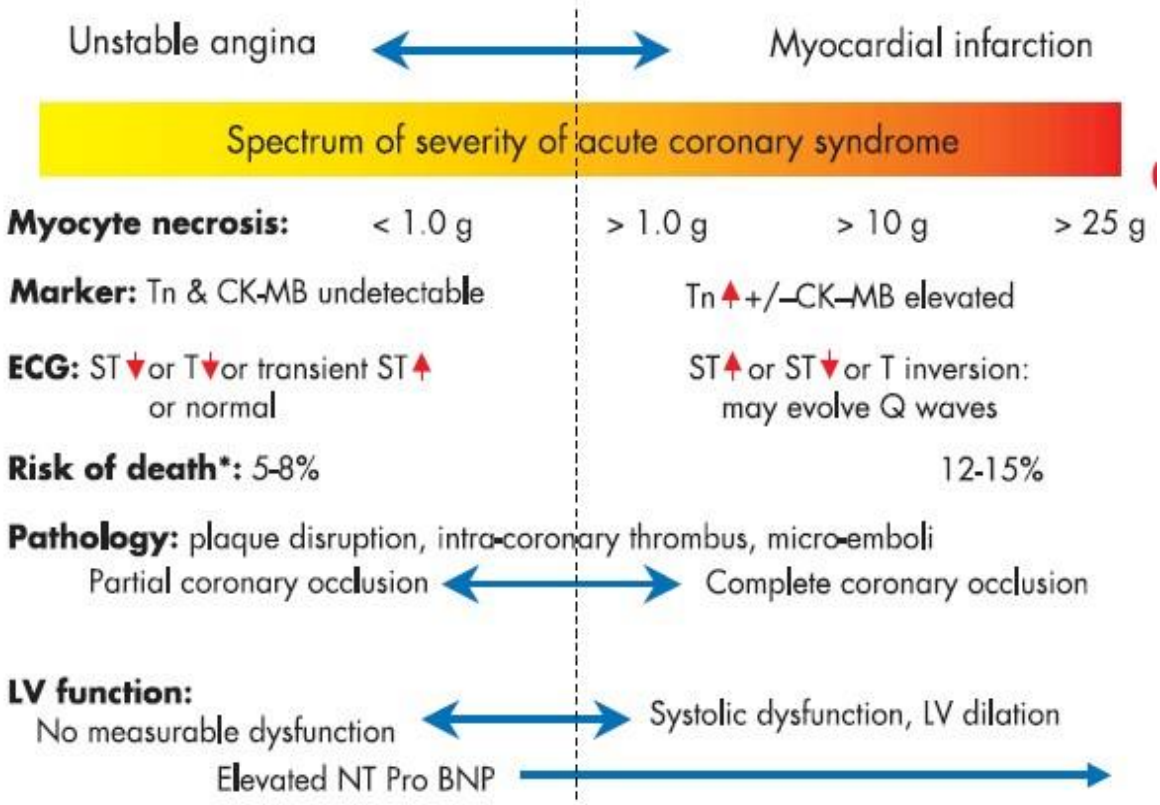
LIPOPROTEIN(a) LEVEL IN TYPE 2 DIABETE MELLITUS:

Several studies have revealed that lipoprotein(a) is a independant risk factor of coronary artery disease. Lp(a) level is genetically determined. Mohan et al, in a community- based study conducted in Chennai, had commented on lipoprotein (a) being an important risk factor in type 2 diabetes mellitus. This study was conducted with diabetic CAD patients, diabetic patients without CAD and healthy without coronary artery disease and no relationship with glycemic control. While a few other studies showed that Lp(a) levels controls. Large population studies and small longitudinal studies showed no difference in Lp(a) concentration in type 2 DM with and are noted to be high in type 2 DM especially with poor

glycemic control and some even suggested that Lp(a) may be an independent risk factor for CAD. So in type2 diabetes patients with acute coronary syndrome lipoprotein(a) level is to be evaluated and it should be treated.

ACUTE CORONARY SYNDROME:

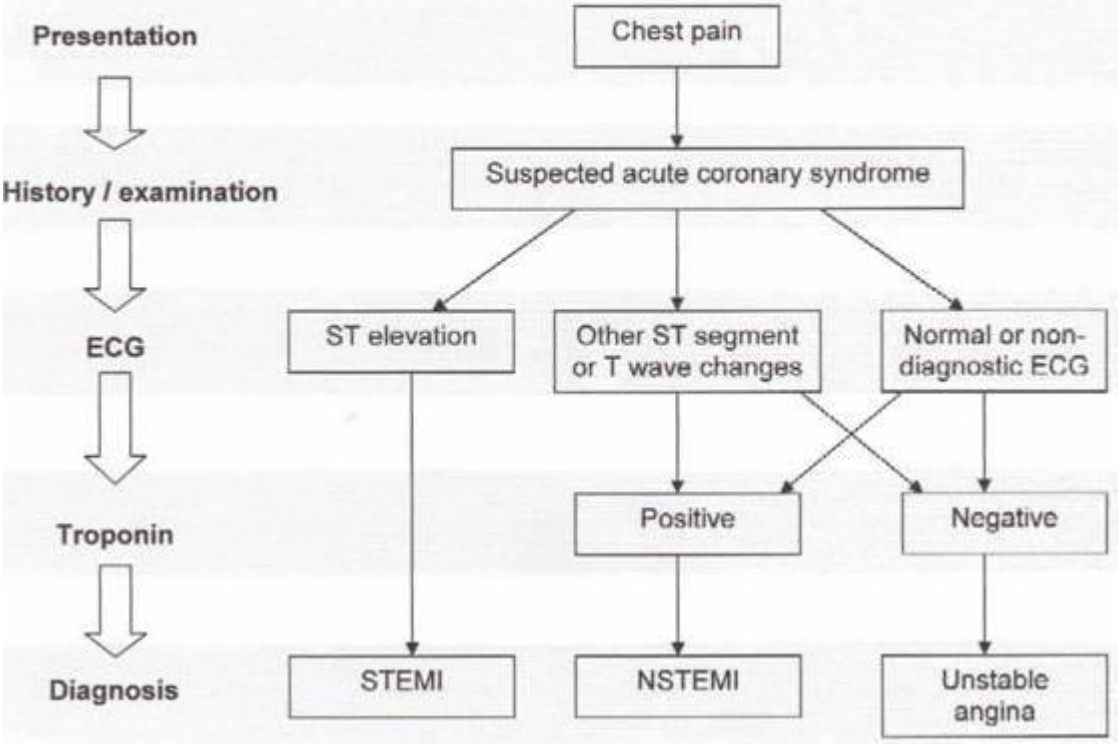
Acute coronary syndrome rages fro unstable angina to acute myocardial infarction.



ACUTE CORONARY SYNDROME:

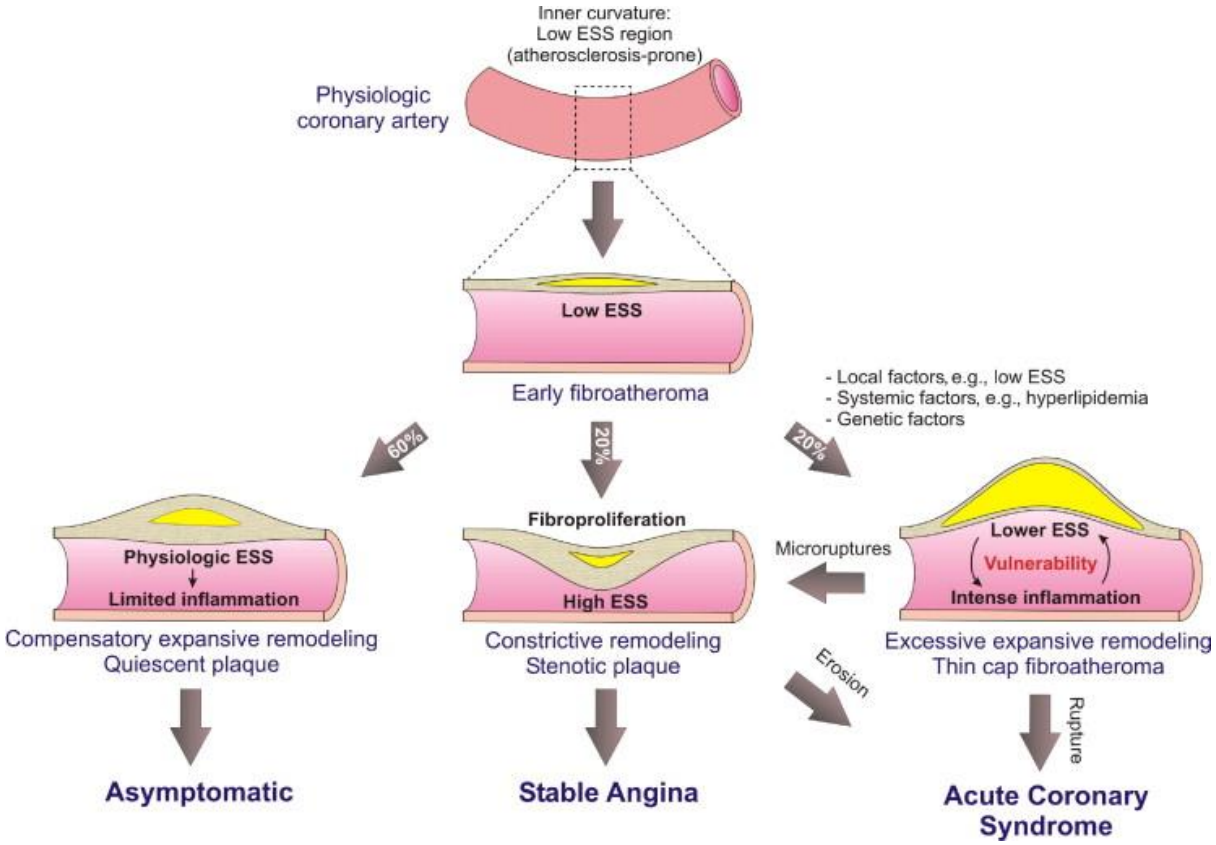
The clinical presentation of acute coronary syndrome ranges from ST segment elevation myocardial infarction, unstable angina to non ST segment elevation myocardial infarction. ACS is mainly due to the rupture of atherosclerotic plaque and complete or partial thrombosis of the infarct related artery.

Figure 1: The Classification of Acute Coronary Syndromes



STEMI occurs, when coronary blood flow stops suddenly by a thrombotic occlusion of a coronary artery which is previously affected by atherosclerosis. Coronary artery thrombosis develops rapidly at a site of vascular injury, which

is facilitated by factors such as hypertension, lipid accumulation and cigarette smoking. STEMI occurs due to the disruption of an atherosclerotic plaque. at the disrupted site, mural thrombus is formed which occludes the blood flow completely results in ST elevation myocardial infarction.



After disruption, there is initial platelet aggregation at the site of the disrupted plaque by various agonists like collagen, ADP and serotonin. There will be activation of thrombaxane -A2, potent vasoconstrictors which causes further platelet aggregation.

The thrombaxane-A2 and various agonists cause changes in glycoprotein-IIb/IIIa receptor, which has high affinity for fibrinogen, binds to platelets and resulting in platelet cross linking and aggregation.

At the site of disrupted plaque, coagulation cascade is activated in damaged endothelial cells. So factor X and VII are activated leading to conversion of prothrombin to thrombin which leads to conversion of fibrinogen to fibrin.

The damage to myocardium caused by the coronary artery occlusion depends on

1. The duration of occlusion.

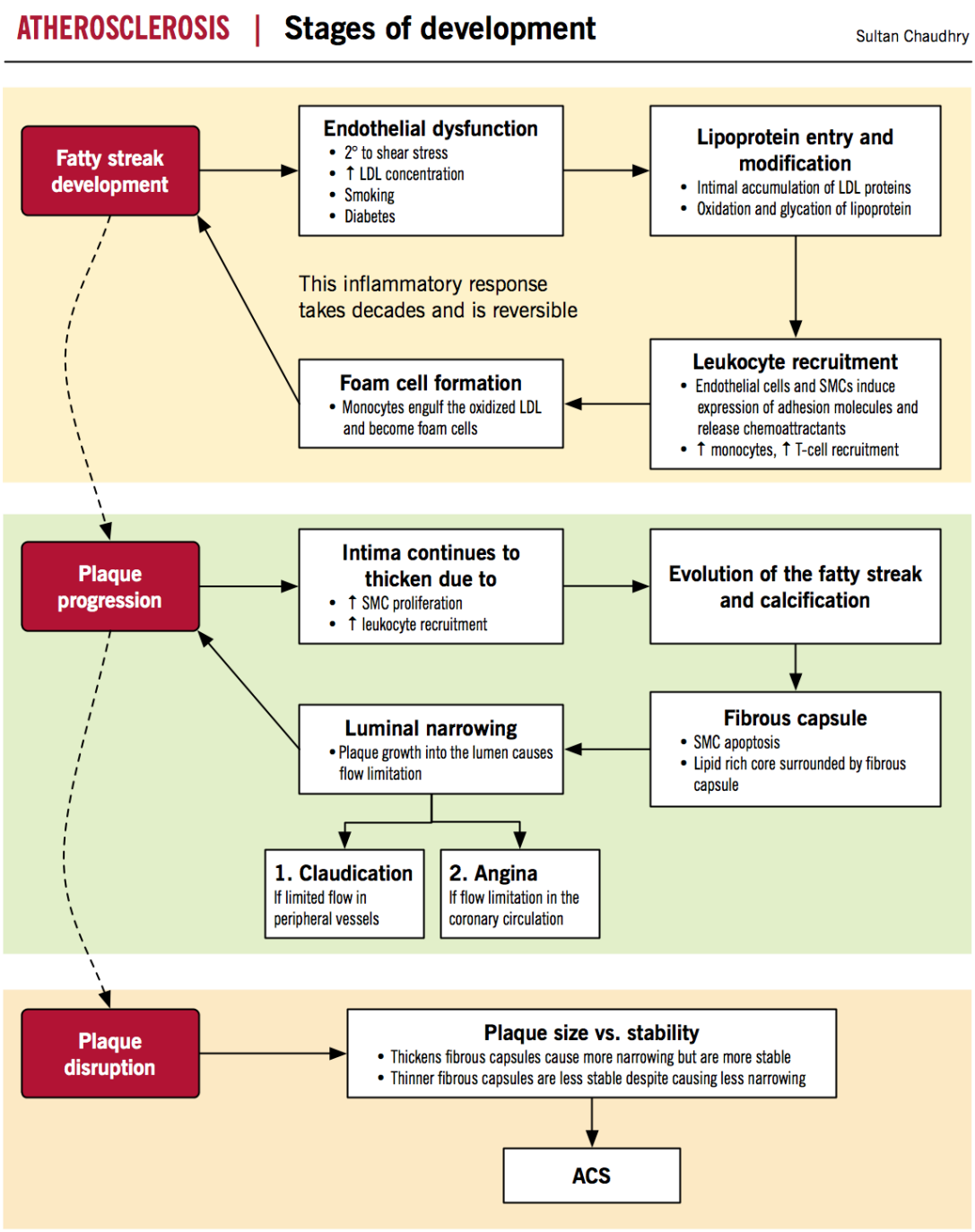
2. Total or partial occlusion of the artery.

3. Quantity of blood supplied by the collaterals to the affected myocardial tissue.

4. The demand for oxygen by the myocardium.

5. Factors that produce spontaneous lysis of occlusive thrombus.

6. Adequacy of myocardial reperfusion in the infracted zone.



Unstable angina

Unstable angina is defined as angina pectoris or equivalent ischemic discomfort with at least one of these features.

1. Angina at rest

2. New onset angina (with in prior 4-6 weeks)

3. Pain which is more severe, prolonged or frequent than previous.

NSTEMI is unstable angina features with elevated cardiac biomarkers. Both unstable angina and STEMI are due to reduction in oxygen supply, usually by an atherothrombotic coronary plaque.

The pathological process that associated in the development of unstable angina/NSTEMI

1. Rupture or erosion of the plaque.

2. Dynamic obstruction (coronary spasm as seen in prinzmetal's angina)

3. Rapidly developing coronary atherosclerosis or restenosis following primary coronary intervention.

4. Unstable angina secondary to increased oxygen demand or decreased oxygen supply such as anemia/tachycardia.

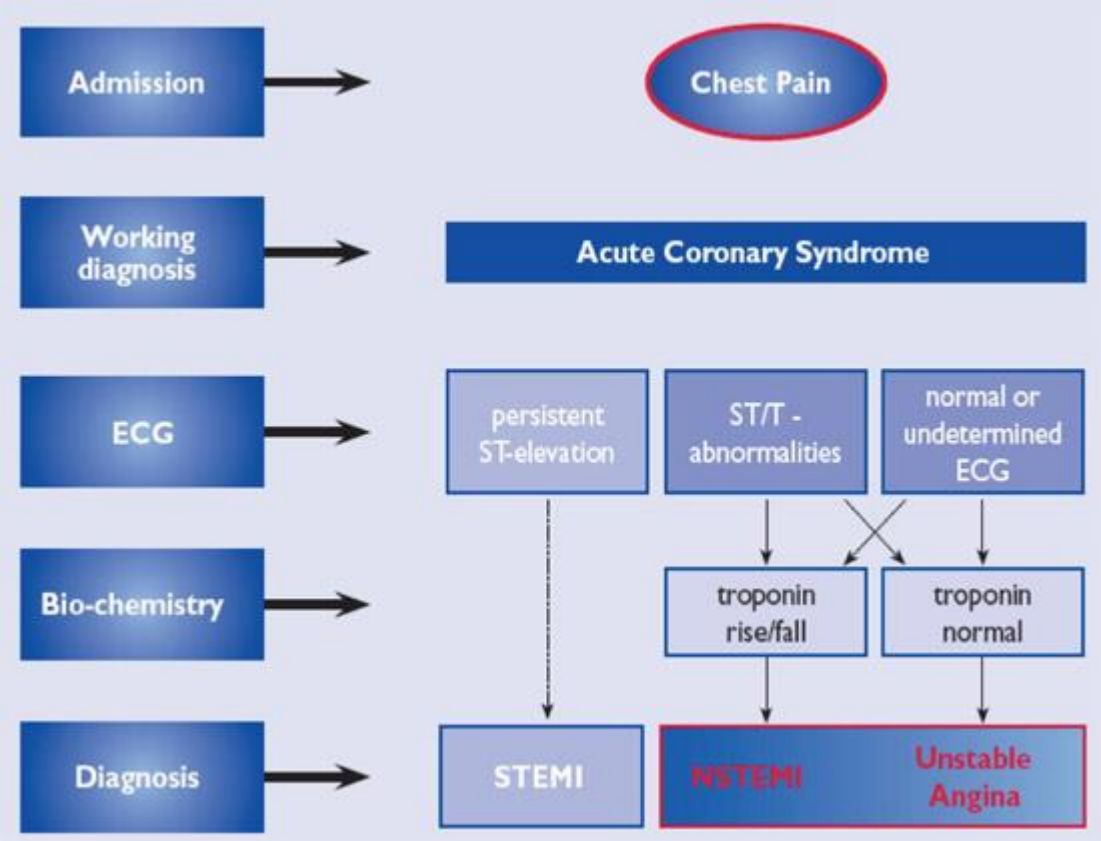
Major goals of treatment:

-increase coronary artery perfusion

-decrease myocardial workload

-prevent myocardial infarction disability or death

-intervention in cases of unstable angina



Approach to case of ACS

Clinical presentation:

Myocardial ischemia or infarction may be silent because of blunted appreciation of pain. Most often, the symptoms are atypical such as confusion, dyspnoea, fatigue or nausea. These atypical symptoms alter the patient's perception of the nature of his or her illness. Autonomic neuropathy in diabetics is an ominous sign. The resting tachycardia is due to an unopposed sympathetic activity due to parasympathetic denervation. Loss of parasympathetic activity is also responsible for exaggerated and inappropriate vasoconstriction. Autonomic neuropathy leads to ischemia or infarction by several routes 1) by reduction in myocardial blood flow due to increased coronary vascular tone at the sites of coronary stenosis 2) increase in resting heart rate leads to increased myocardial demand and 3) reducing the coronary perfusion pressure during orthostatic hypotension.

PROGNOSIS:

The mortality due to cardiovascular disease is doubled in diabetic men and quadrupled in women. Diabetics with symptomatic peripheral vascular disease are likely to have significant coronary artery disease though asymptomatic.

The prognosis for acute myocardial infarction in a diabetic is rather poor compared to anon diabetic. In fact the mortality recorded in coronary care units is about 40% compared to 20% in non diabetics. Even when the patients have been shifted from critical care unit after coronary care, the mortality is higher in diabetic subjects. Hyperglycaemia due to poor metabolic control is a single factor related with excess mortality in diabetic myocardial infarcts. The prognosis is also influenced by a very high prevalence of cardiogenic shock and congestive heart failure complicating acute infarction in diabetic subjects. Severe atherosclerosis with impaired coronary collateral circulation, frequent association of small vessel disease, microangiopathy and the proneness for ketoacidosis possibly contribute to the excess mortality in diabetic subjects.

MANAGEMENT:

The management of acute myocardial infarction is similar in diabetics and non diabetics subjects expecting that therapy with insulin is mandatory for ensuring metabolic control in diabetes for improved outcome. DIGAMI study has proved that intensive treatment with insulin glucose infusion targeted to achieve a tight control of glycemic level improves survival rate. This intensive treatment was also associated with lower one year mortality and morbidity, and the beneficial effect was also seen on long term follow up. One has to be cautions in trying to achieve a tight glycemic control as this may require a committed teamwork.

sThe association of diabetic ketoacidosis with acute myocardial infarction enhances the mortality rate to about 85%. Angiography done within the first few hours demonstrates total occlusion with thrombosis in about 90% of subjects, and intracoronary streptokinase has been found to restore the patency of the occluded vessels in two thirds of such subjects. The procedure of angiography precipitating acute renal failure due to dehydration in a diabetic subject must be kept in mind. In subjects undergoing coronary bypass graft surgery the patency of the graft and the post operative morbidity and mortality are similar to the non diabetic group.

THROMBOLYSIS THERAPHY:

Atypical symptoms in diabetic delay the initiation of thrombolytic therapy. In elderly diabetic patients thrombolytic therapy is associated with high incidence of hemorrhagic complication and hence its use is limited to life threatening myocardial infarction. Though proliferative retinopathy is a relative contraindication for thrombolytic therapy, there have been no recorded incidences of retinal hemorrhages in controlled trial studies. Anti thrombotic agent abciximab is effective in preventing restenosis in non diabetic subjects compared to diabetics.

INVASIVE MANEGEMENT:

Revascularization of the myocardium is considered in patients who have ongoing ischemia despite medical therapy. Diabetes needs a large number of bypass grafts because of their extensive atherosclerosis. Per operative mortality is higher in diabetics due to poor wound healing and associated renal failure. Coronary angioplasty is an attractive treatment option because of low associated morbidity.

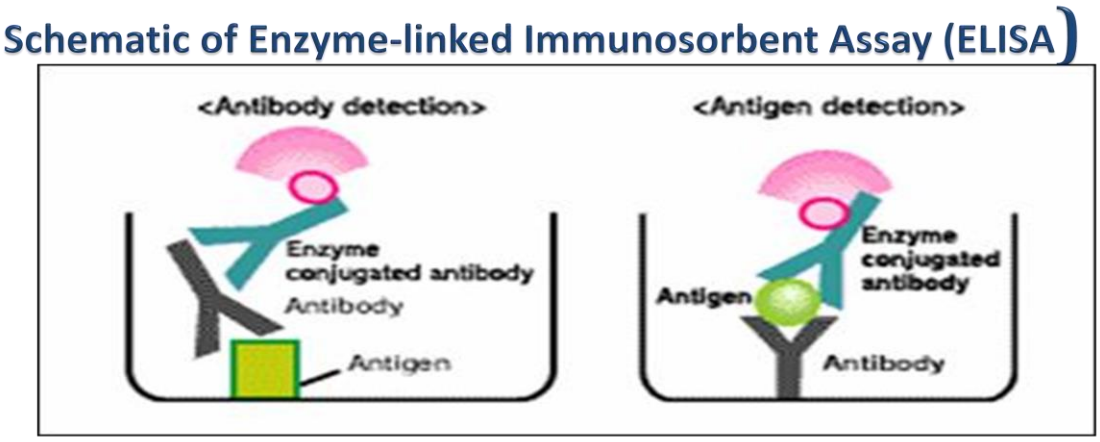
LIPOPROTEIN (a) MEASUREMENT:

A standardized international reference material has been developed and is accepted by the WHO Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine.

Lipoprotein(a) - Lp(a)

- Desirable: < 14 mg/dL (< 35 nmol/l)
- Borderline risk: 14 - 30 mg/dL (35 - 75 nmol/l)
- High risk: 31 - 50 mg/dL (75 - 125 nmol/l)
- Very high risk: > 50 mg/dL (> 125 nmol/l)

ELISA METHOD TO MEASURE LIPOPROTEIN(a):



- Samples are added to a microwell coated with antigen (or antibody), allowing antibody (or antigen) in samples to react with the immobilized antigen (or antibody) in the microwell (sample incubation). After washing to remove any unbound serum proteins, enzyme-conjugated antibodies are added and incubated (conjugate incubation). Following a second washing step, the enzyme substrate is added and allowed to incubate for an additional period of time (substrate incubation). Acid solution is then added to each well to terminate the enzyme reaction and to stabilize the color development. The assay can be quantified by measuring the produced reaction photometrically.

Among the many technique used to separate lipoprotein, the following are important.

1. **Ultracentrifugation**

There are two principle ways of using ultracentrifugation to determine lipoproteins. They employ two different instruments, the preparative and the analytical centrifuge.

a) **Preparative Ultracentrifugation**: Plasma has a salt density of about 1.006. Ultracentrifugation of plasma without adjustment of its density

for a short period brings the chylomicrons rapidly to the top of the tube. Longer ultracentrifugation at this density allows the VLDL to be collected on the surface. Addition of salt to plasma will further raise the density to selected levels and permit isolation of other lipoproteins. Those lipoproteins, which are separated below a density of 1.006 constitute VLDL, 1.006 to 1.063 constitute LDL, 1.063 to 1.21 constitute HDL.

b) **Analytical Centrifugation:** In this instrument, plasma fraction usually prepared at salt density of 1.063 is centrifuged at high speeds and the moving bands of the floating lipoproteins are photographed and later used to determine the concentration that are referred to certain standard conditions.

2. **Electrophoresis:**

If the plasma is examined by paper or agarose gel electrophoresis at pH 8.6, it is possible to demonstrate, by means of fat stains, the existence of four bands. Three of these move towards the anode and one remains at the origin, that is, the line of application of the serum, the faster moving band occurs approximately in the same position as alpha-I globulin. It is known as alpha-lipoprotein and corresponds to the HDL fraction, demonstrated by ultracentrifugation floatation technique. The next band appears at

approximately the position of beta-globulin and is known as beta lipoprotein, which corresponds to LDL fraction. Another band appears between the position of alpha globulin and beta globulin. It is known as pre-beta lipoprotein which corresponds to VLDL fraction. The band, which remains stationary at the origin, consists of the chylomicrons. The five principal lipoprotein classes are defined according to their density on ultracentrifugation and by their mobility on agarose gel electrophoresis. In addition, they can be classified on the basis of size and relative concentration of cholesterol or triglyceride and by their apoprotein content.

METHODS TO REDUCE LIPOPROTEIN(a) LEVEL:

At the current time, the recommended treatment for an elevated lipoprotein (a) is niacin, 1-3 grams daily, in general in an extended-release form. Niacin therapy can reduce lipoprotein (a) levels by 20-30%. Aspirin may be beneficial, as well. A recent meta-analysis suggests that atorvastatin may also lower Lp(a) levels. In severe cases, such as familial hypercholesterolemia, or treatment resistant hypercholesterolemia, lipid aphaeresis may result in dramatic reductions of lipoprotein (a). The goal of treatment is to reduce levels to below 50 mg/dL.

Other medications that are in various stages of development include thyromimetics, cholesterol-ester-transfer protein (CETP inhibitors), anti-sense oligonucleopeptides, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors. L-carnitine may also reduce lipoprotein a levels.

Gingko biloba may be beneficial, but has not been clinically verified. Co enzyme q10 and pine bark extract have been suggested as beneficial, but neither has been proven in clinical trials.

The effect of estrogens on lipoprotein (a) levels is controversial. Estrogens replacement therapy in post-menopausal women appears to be associated with lower lipoprotein (a) levels. However one large study suggested that there was a decreased association between lipoprotein (a) levels and risk. In other words, it is unclear what a high lipoprotein (a) level means in a woman on estrogens therapy. An estrogen as a prevention strategy for heart disease is current topic of much research and debate. Risks and benefits may need to be considered for each individual. At present, estrogens is not indicated for treatment of elevated lipoprotein(a).

METHODOLOGY

Fifty type 2 diabetic patients and fifty non diabetic patients admitted with acute coronary syndrome were selected after matching forage and sex, during the study period between july 2014 to September 2014. Lipoprotein(a)was studied in these patients.

SOURCE OF DATA

Patients admitted with acute coronary syndrome in cardiac ICU, government Rajaji Madurai medical college, Madurai, during the study period of July 2014 to September 2014.

SAMPLE SIZE

100 cases

DURATION OF STUDY

July 2014 to September 2014

INCLUSION CRITERIA

Patients with angina, occurring at rest (CCS class IV) of duration more than 30 minutes, but within 24 hours from onset of angina were included in the study. Among them, fifty patients had type 2 diabetes. Fifty age and sex matched non

diabetic were included as the other group. Diabetes was ruled out in non diabetic group with fasting and 2-hr post prandial blood glucose measurement.

EXCLUSION CRITERIA

- Severe hypothyroidism
- Treatment history of taking oral contraceptive pills.
- Type1 diabetes
- Renal failure

METHOD OF COLLECTION OF DATA

In the present study hundred Acute coronary syndrome patients, who were divided in to two separate age and sex matched groups; one with type 2 diabetes mellitus and one without Diabetes mellitus, were selected by stratified sampling, during the study period as per the inclusion and exclusion criteria.

A detailed history (with emphasis on angina/angina equivalent characteristics) was taken and a detailed physical examination was done as per the proforma to study the clinical profile of patients, blood parameters and imaging as required.

All diabetic patients are type 2. Diabetes mellitus was ruled out in non diabetic group by fasting and post prandial blood glucose which was analysed by GOD-POD (glucose oxidase-phenol 4-aminophenazone peroxidase) method.

10 ml of blood was drawn at the time of admission and lipoprotein(a) analyse done by elisa method. Samples were refrigerated till analysis was done. Serum lipoprotein (a) level, total cholesterol, LDL, HDL was done. Serum Lp(a) was calculated from the Lp(a)-C value by the following formula.

$$Lp(a)=Lp(a)\text{-}C \times 3$$

Resting electrocardiogram with 12 standard leads was taken as soon as possible and repeated serially and ST segment was monitored. Based on the findings both diabetic and non diabetic groups of patients were regrouped.

1. ST elevation myocardial infarction subgroup

Defined by angina at rest, lasting for more than 30 minutes, in past 24 hours with

a. ST elevation >2mm (o.2mv) in V1, V2, V3

Or

b. ST elevation >1mm (0.1 mv) inV4, V5, V6

Or

c. ST elevation>1mm (0.1 mV) in two contiguous limb leads

2. Unstable angina/Non ST elevation myocardial infarction subgroup

Defined by angina at rest, lasting for more than 30 minutes, in past 24 hours

a. ST depression >1mm (0.1mV) in two or more contiguous leads

b. Inverted T waves >2mm (0.2mV) in leads with predominant R waves.

Other relevant investigations are done

- ECG in all leads
- Haemoglobin%
- Total count
- Erythrocyte sedimentation rate
- Blood sugar at the time of admission
- Fasting and 2 hr blood sugar
- Blood urea
- Serum creatinine
- Serum Lipoprotein (a)
- Total cholesterol
- HDL level
- LDL level
- Triglycerides

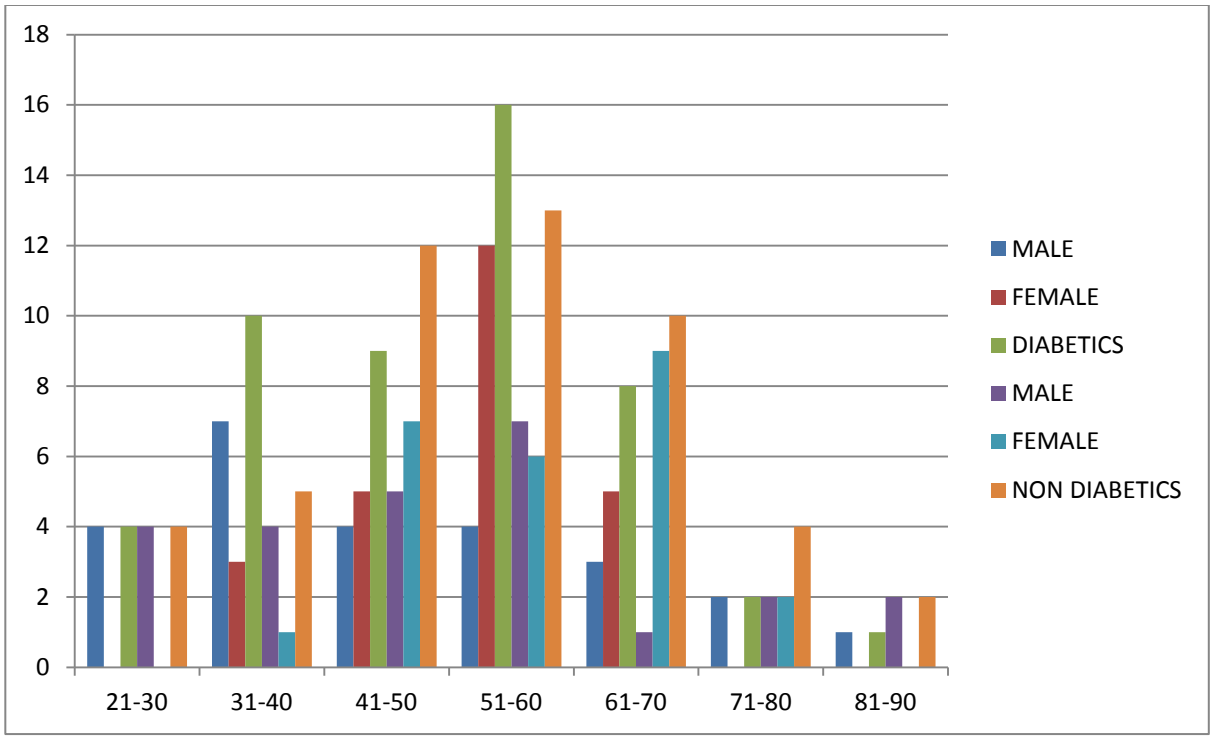
- Echocardiogram

STATISTICAL ANALYSIS:

Statistical analysis was done by using percentages, mean values, standard deviation, chi-square test, t-test and proportion test. A p-value <0.05 level was considered statistically significant and a p-value >0.05 was considered as not statistically significant.

AGE AND SEX WISE DISTRIBUTION OF CASES:

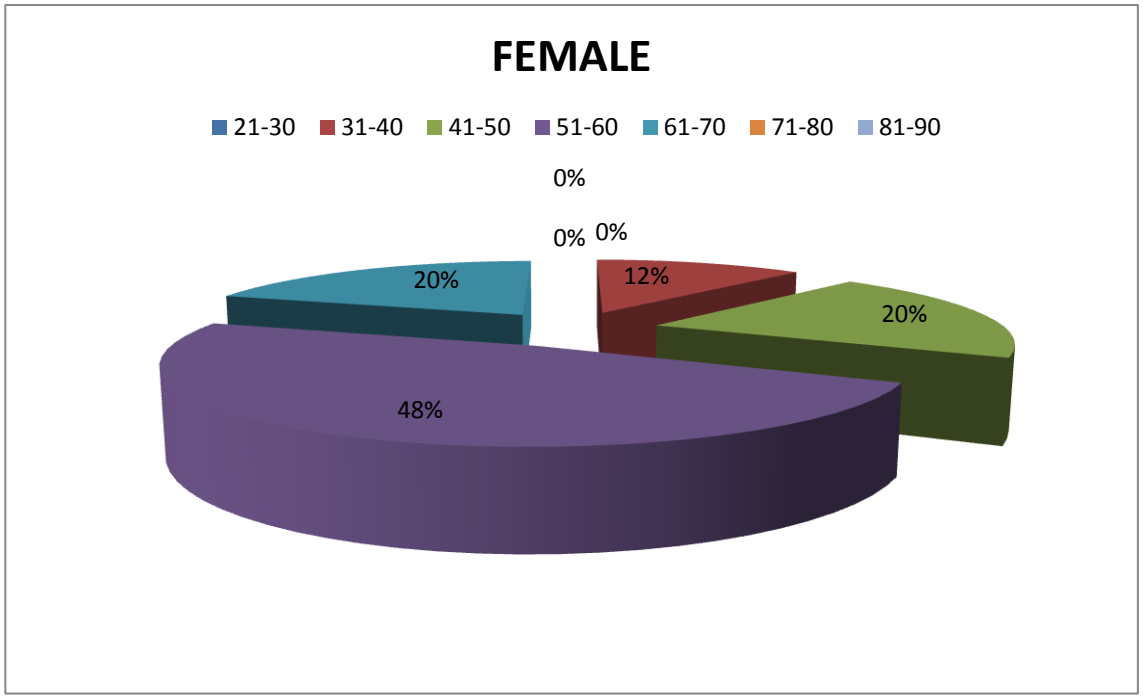
	AGE AND SEX DISTRIBUTION OF CASES						
		DIABETIC				NONDIABETIC	
S.NO	AGE	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
1	21-30	4	0	4	4	0	4
2	31-40	7	3	10	4	1	5
3	41-50	4	5	9	5	7	12
4	51-60	4	12	16	7	6	13
5	61-70	3	5	8	1	9	10
6	71-80	2	0	2	2	2	4
7	81-90	1	0	1	2	0	2
		25	25	50	25	25	50



The following observations are made from above chart

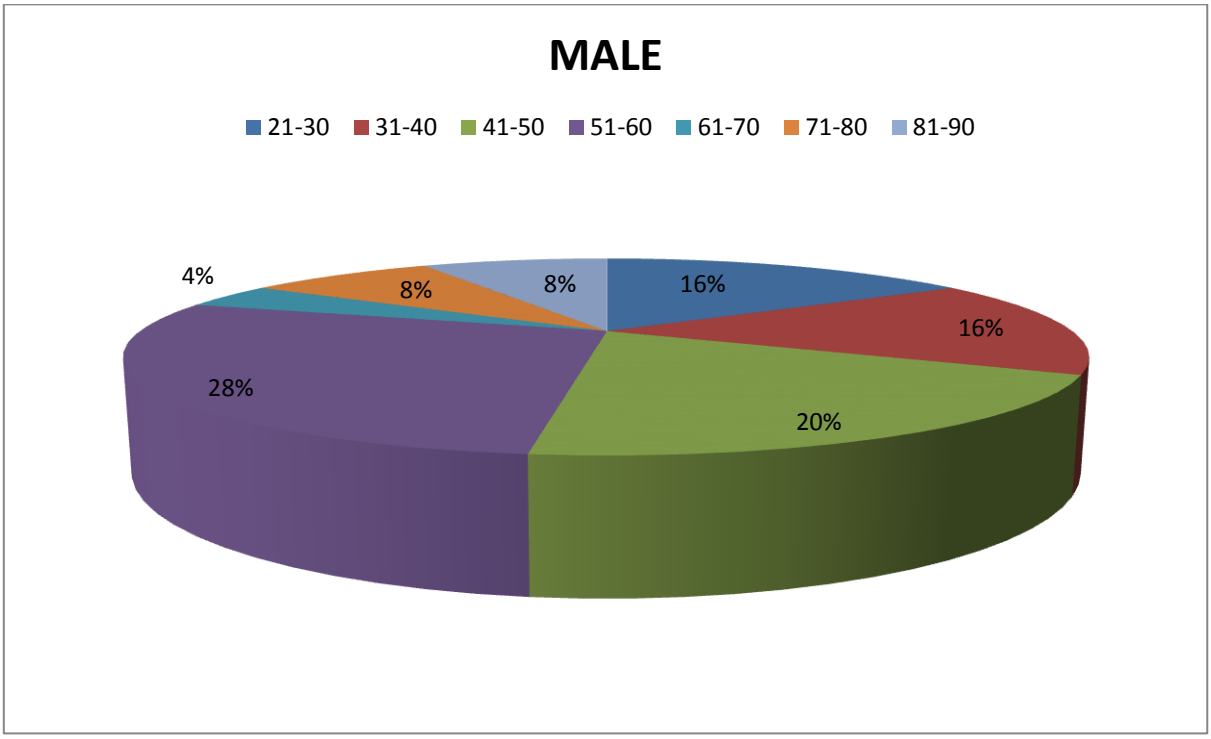
a. Majority of students belongs to the age group of 51-60 years of age.

b. There is no significant difference in age wise distribution of cases in both groups, so they are comparable $p<0.05$



SEX WISE DISTRIBUTION OF CASES IN DIABETIC AND NON DIABETIC:

In the above pie diagram shows that both in diabetic and non diabetic female groups, the incidence of disease is more common in the age groups of 51-60 years of female patients.

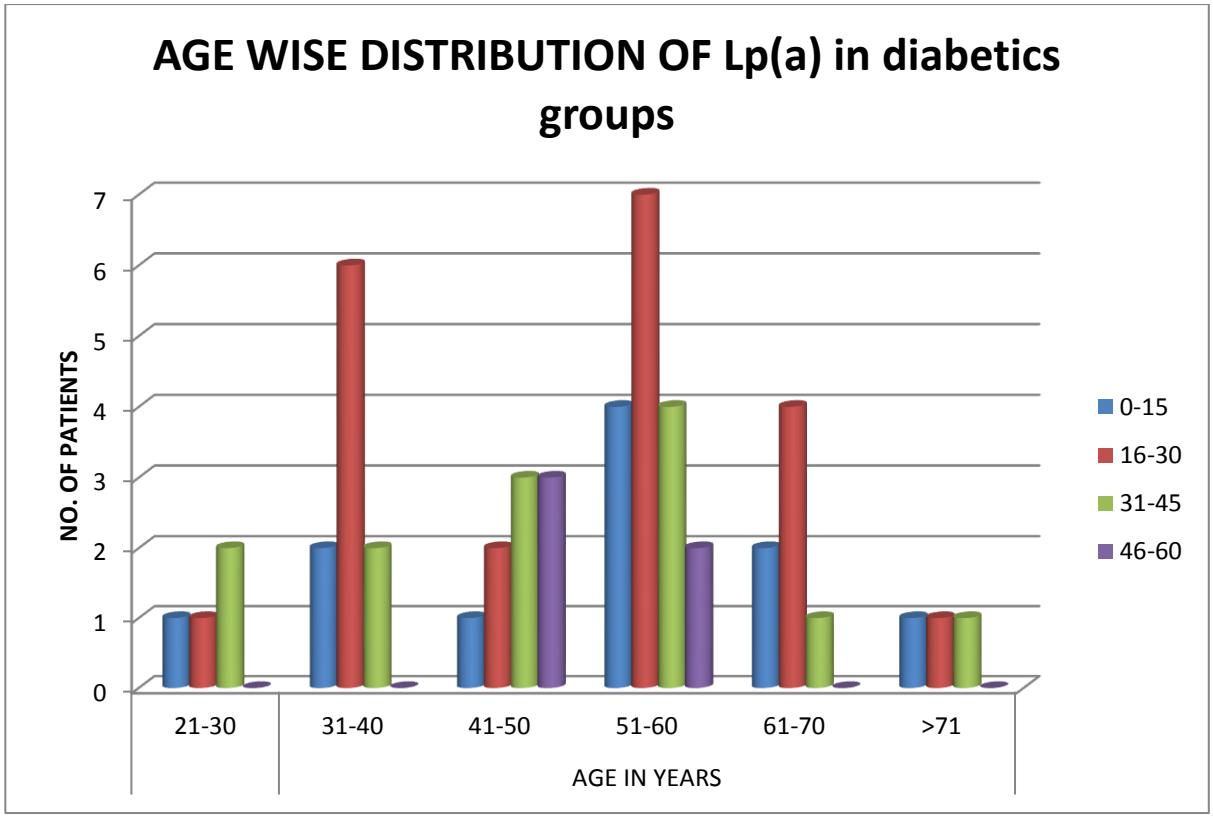


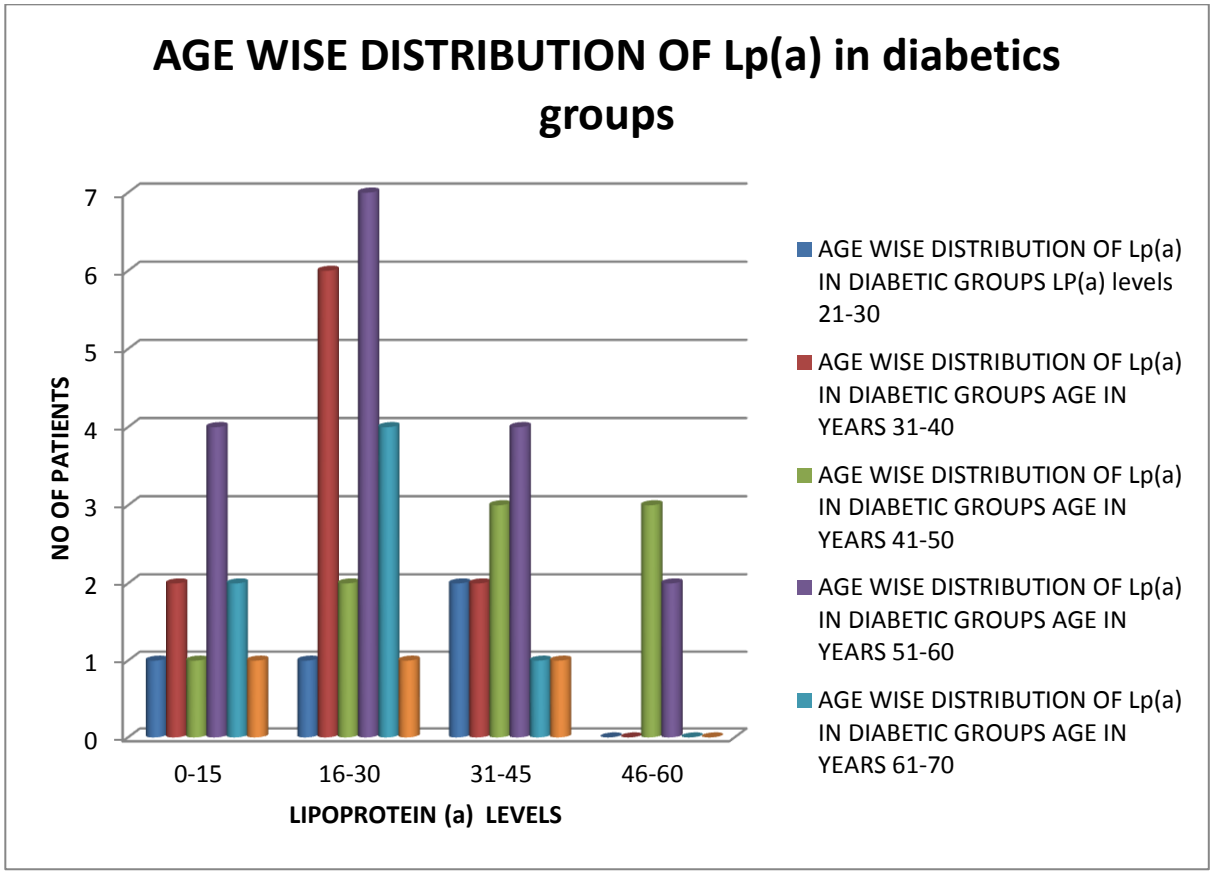
SEX WISE DISTRIUTION OF CASES IN DIABETIC AND NON DIABETICS WITH ACS;

In the above pie diagram it shows that in both diabetic and non diabetics male patients the incidence of disease is more common in age group of 51-60 years of male patients.

AGE WISE DISTRIBUTION OF LIPOPROTEIN (a) LEVEL IN DIABETIC GROUP:

	AGE WISE DISTRIBUTION OF Lp(a) IN DIABETIC GROUPS						
S.NO	LP(a) levels		AGE IN YEARS				
		21-30	31-40	41-50	51-60	61-70	>71
1	0-15	1	2	1	4	2	1
2	16-30	1	6	2	7	4	1
3	31-45	2	2	3	4	1	1
4	46-60	0	0	3	2	0	0
	TOTAL	4	10	9	17	7	3





The following observations was made from above chart

a. The maximum value of Lp (a) level seen in 51-60 age group.

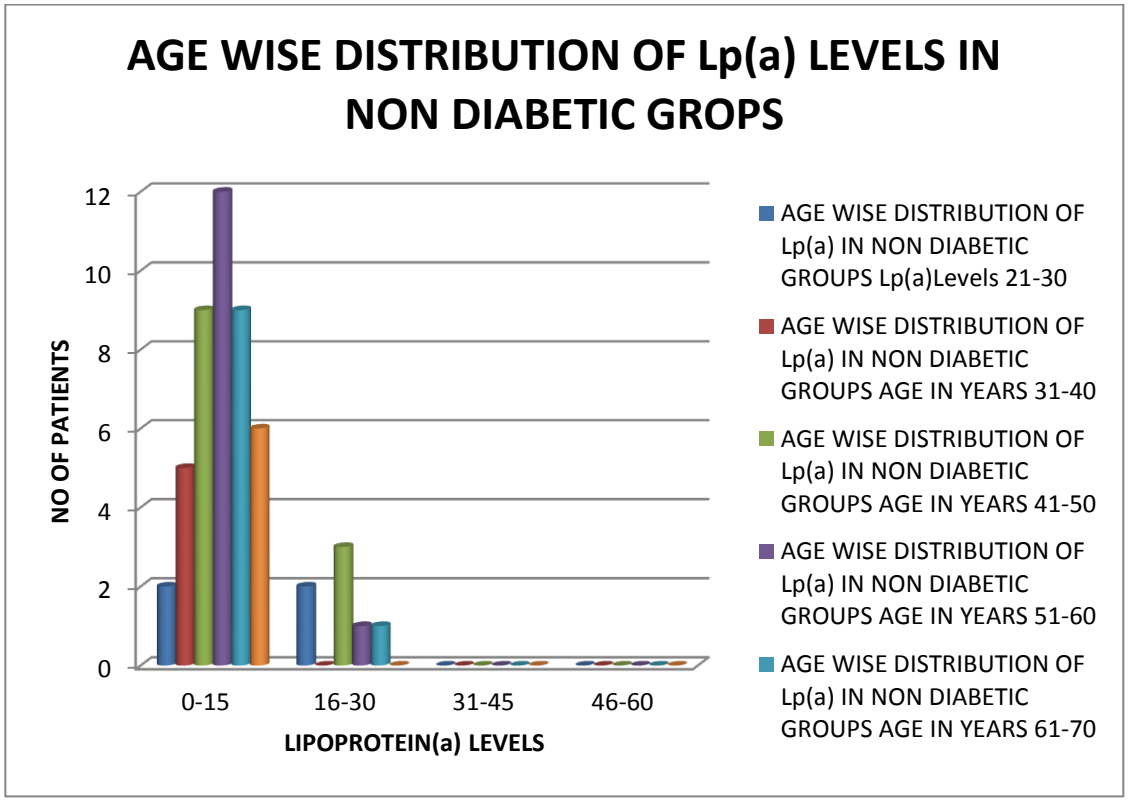
b. The minimum value of Lp (a) level seen in 21-30 age group.

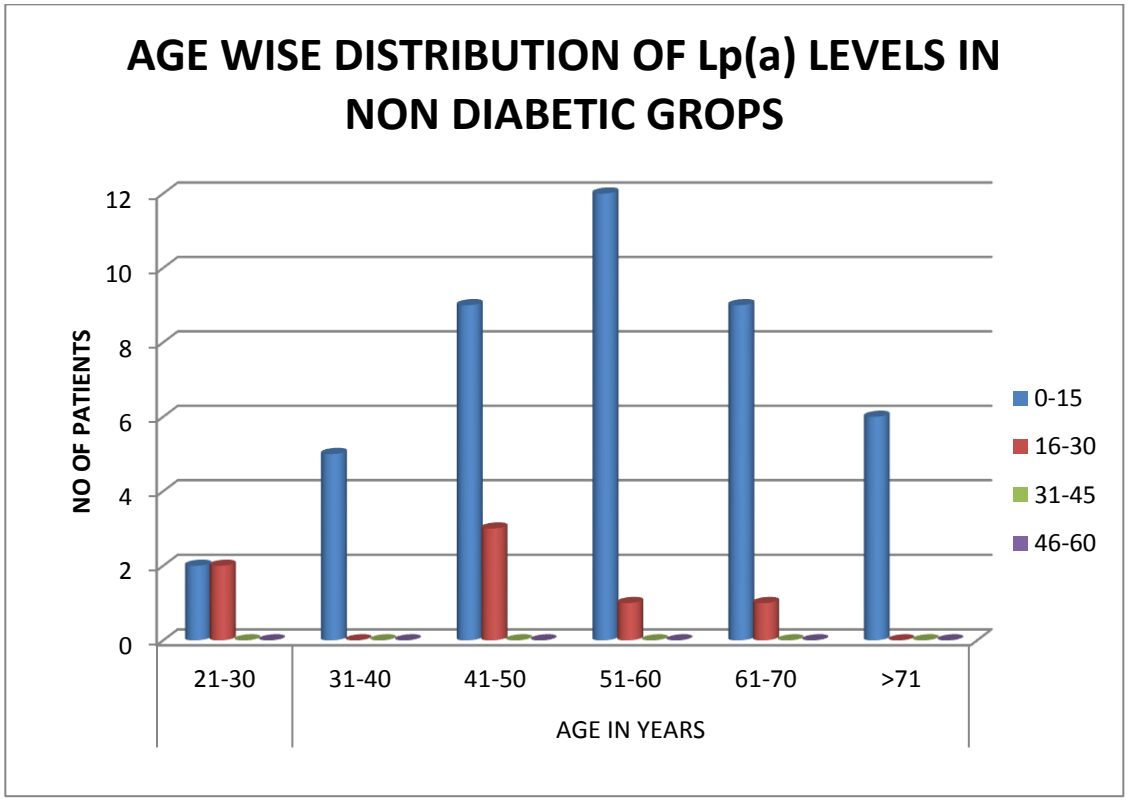
c. 90% of diabetic patients have Lp (a) levels more than 15mg/dl.

d. 32% of diabetic patients have Lp(a) level more than 30 mg/dl.

AGE WISE DISTRIBUTION OF Lp(a) IN NON-DIABETIC GROUPS:

	AGE WISE DISTRIBUTION OF Lp(a) IN NON DIABETIC GROUPS						
S.NO	Lp(a)Levels		AGE IN YEARS				
		21-30	31-40	41-50	51-60	61-70	>71
1	0-15	2	5	9	12	9	6
2	16-30	2	0	3	1	1	0
3	31-45	0	0	0	0	0	0
4	46-60	0	0	0	0	0	0
	TOTAL	4	5	12	13	10	6



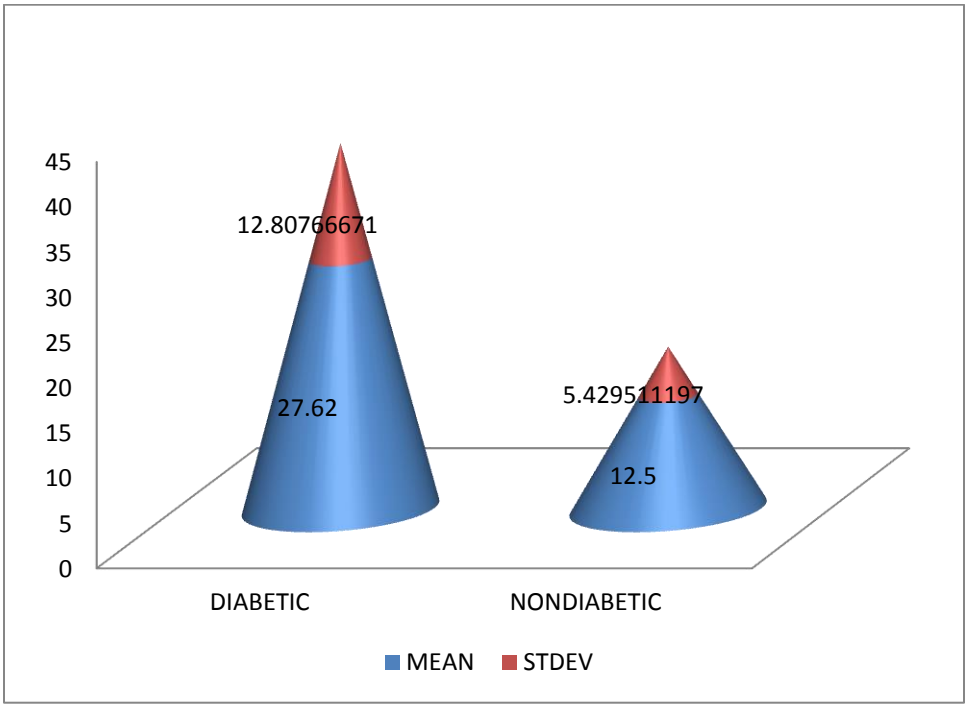


The following observation was made from above chart

A. Most of the non diabetic group patients have Lp (a) level of less than 15mg/dl.

B. Only 10% of non diabetic group have value more than 15mg/dl.

COMPARISON OF Lp(a) LEVEL INDIABETIC AND NON DIABETIC GROUP:



Comparing Lp(a) level in diabetic and non diabetic group

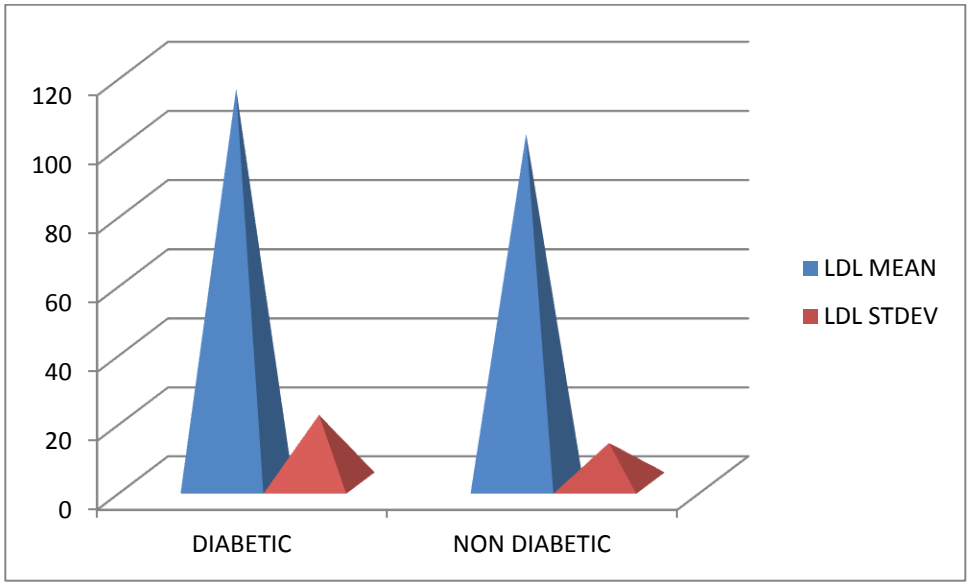
GROUP MEAN (S.D) (mg/dl)

Type 2 Diabetic - 27.62±12.5

Non diabetic - 12.5±5.42

Difference between means of serum Lp(a) level in both groups is significant($p<0.001$).Type 2 diabetic patients had a higher Lp(a) levels compared to non diabetics with acute coronary syndrome.

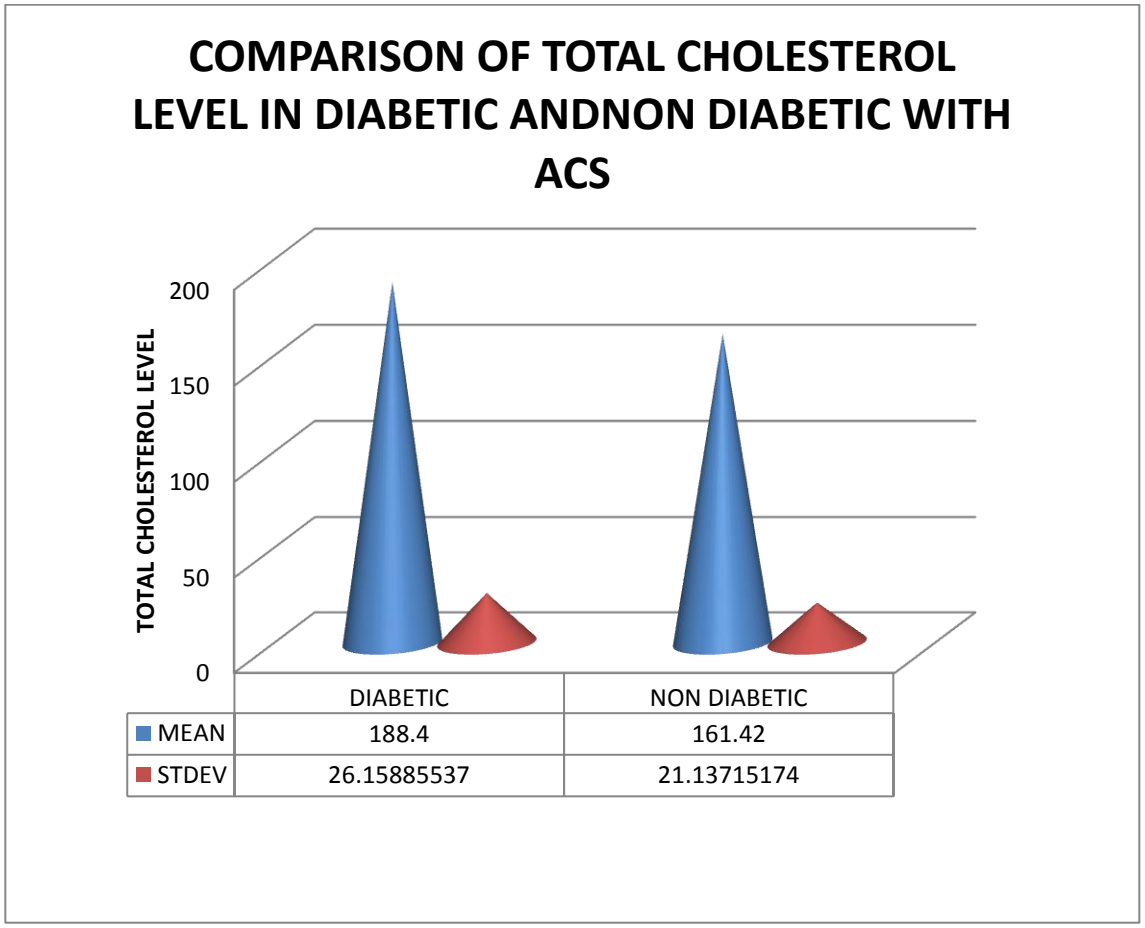
COMPARISON OF LDL LEVEL IN DIABETIC AND NON DIABETIC GROUP



GROUP	MEAN (S.D)
DIABETIC	114±19.8
NON DIABETIC	101.2±11.63

Serum LDL levels are significantly higher in diabetic group when compared to non diabetic group ($p<0.0001$).

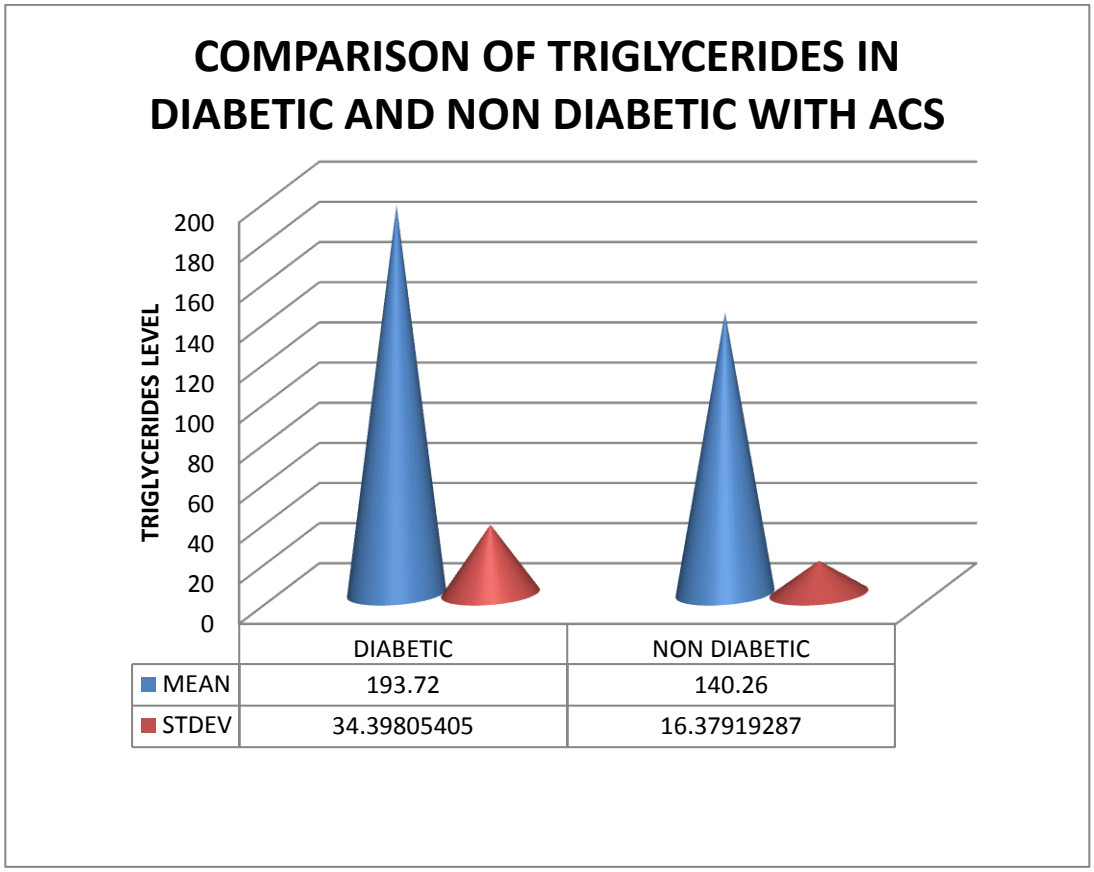
Comparison of total cholesterol in both diabetic and non diabetic group with ACS:



The following observation was made from the above chart:

Serum levels of total cholesterol in diabetics are significantly high when compared to non diabetics with acute coronary syndrome ($p<0.001$).

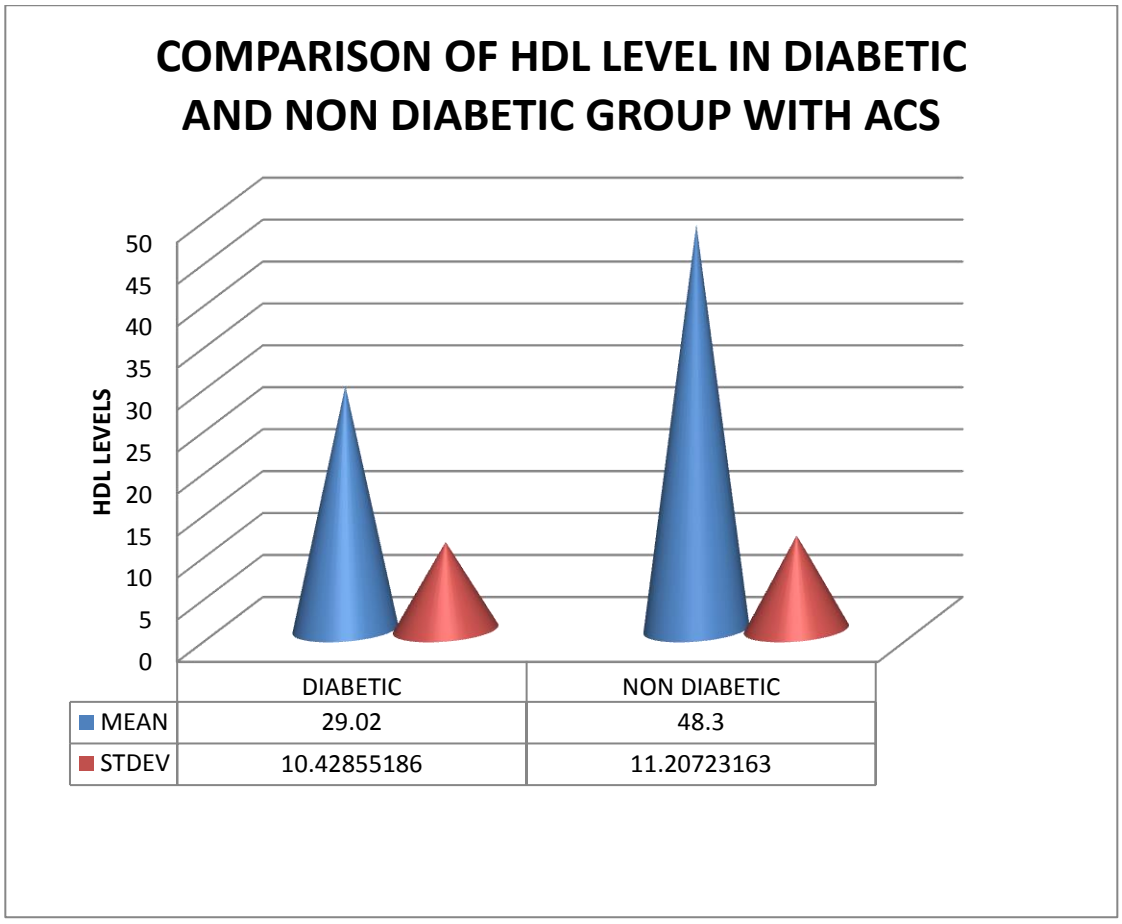
Comparison of Triglycerides Level in diabetic and non diabetic with ACS:



The following observation was made from above chart:

Serum Triglycerides level is significantly higher in diabetics when compared to non diabetics ($p < 0.001$) with acute coronary syndrome.

Comparison of HDL Cholesterol level in diabetic and non diabetic with ACS:

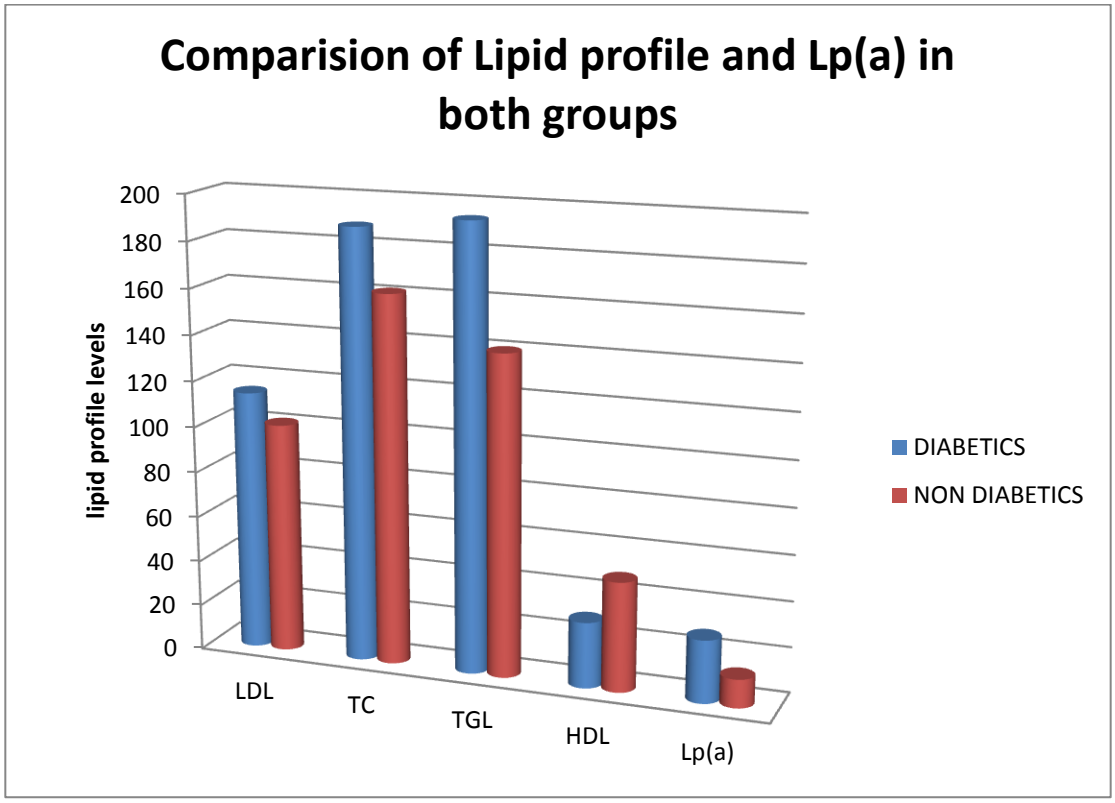


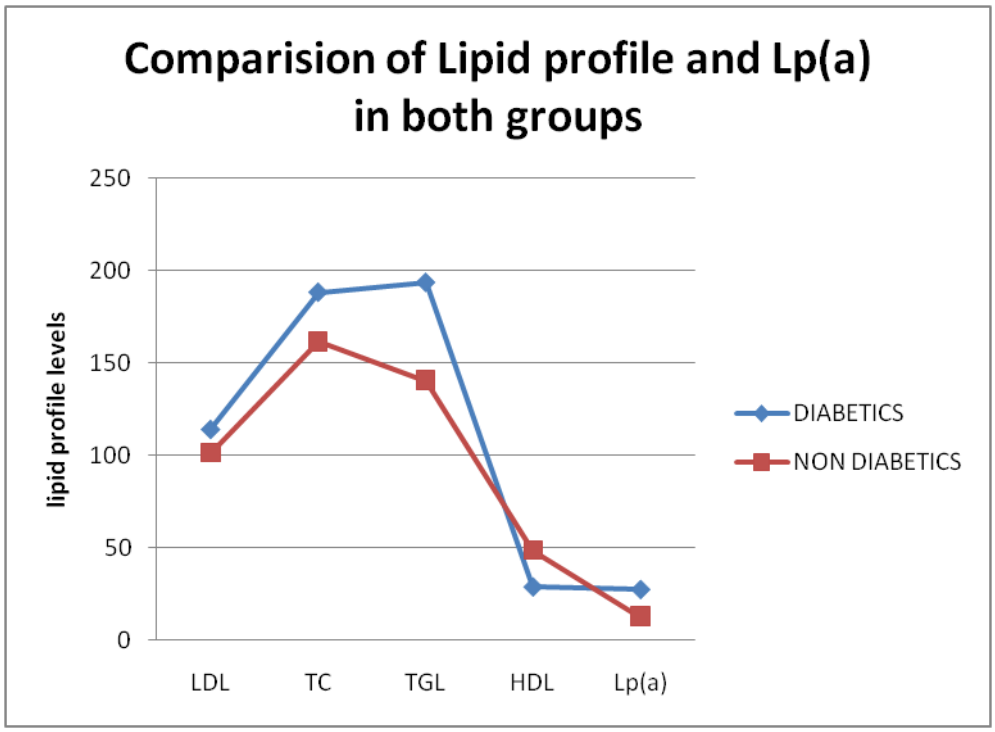
The following observation was made from above chart

Serum HDL levels was significantly lower in diabetic group when compared to non diabetic group with ACS ($p<0.001$).

COMPARING Lp(a) LEVEL AND LIPID PROFILE IN BOTH GROUP WITH ACUTE CORONARY SYNDROME:

S.NO	PROFILE	DIABETICS	NON DIABETICS	p VALUE
1	LDL	114±19.79	101.2±11.65	<0.001
2	TOTALCHOLESTEROL	188.4±26.15	161±21.13	<0.001
3	TRIGLYCERIDES	193.72±34.39	140±16.37	<0.001
4	HDL LEVEL	29.02±10.42	48.3±11.20	<0.001
5	Lp(a) LEVEL	27.62±12.80	12.5±5.42	<0.001





Serum Lp(a) level, Total cholesterol, Triglycerides, LDL were significantly higher in type 2 diabetic group when compared to non diabetic group($p<0.001$).HDL level was significantly lower in type 2 diabetic group than non diabetic group($p<0.001$).

Number of cases having significantly high Lp(a) level and odds ratio for diabetic group

Number of case	Lp(a) >15mg/dl	Lp(a)<15mg/dl
DIABETIC GROUP	39	11
NONDIABETIC GROUP	7	43

ODDS RATIO 21.77

95%CL 7.6822 to 61.7449

z statistic 5.795

p value <0.0001

RELATIVE RISK 4.16

95%CL 2.4221 TO 7.1519

Z STATISTIC 5.163

p value <0.0001

Diabetic group had an odds ratio of 21.7 when compared to non diabetic group, in having Lp(a) levels >15mg/dl. There is a positive correlation of serum LP(a) levels with LDL and triglycerides level.

DISCUSSION

In Asian Indians, the coronary artery disease rate has been raised rapidly. The cause for its high prevalence of coronary artery disease in Asian Indians has been largely unexplained. It is due to the failure of traditional risk factors to explain which raises the possibility of a genetic susceptibility to coronary disease in Asian Indians.

So, studies on lipoprotein(a) levels are significant as lipoprotein(a) is known to be genetically determined. As Lp(a) values are different in various ethnic group populations, but in most of the studies revealed that south Asians have higher level of Lp(a) concentrations. It is proved by Enas et al study. Similar to this, the present study also showed that Lp(a) levels are increased in our population.

In diabetes mellitus, 67% of deaths are due to coronary artery disease. Framingham heart study showed that CAD, acute myocardial infarction and sudden death is 1-5 fold increased in diabetes patients. So, diabetic patients with coronary artery disease have worst prognosis when compared to non diabetic patient with CAD. Diabetes also predisposes to early thrombus, smooth muscle proliferation, endothelial and platelet dysfunction.

In the present study, hundred patients with acute coronary syndrome were taken, of which 50 patients are diabetic and 50 patients non diabetic. Serum Lp(a) was compared between these two groups, along with comparison of other parameters.

The two groups were selected from cases of acute coronary syndrome admitted at cardiology department of government Rajaji hospital, Madurai medical college, between July 2014 and September 2014. Both groups have equal number of cases and were age and sex matched for uniform comparison.

comparison of clinical profile in various studies

STUDY	NO	AGE	MALE/FEMALE	PROPORTION
Mohan et al	100	54 ± 8.1	72/28	1
Gazzarusso et	103	56.6± 2.3	62/13	1.1
Tseng et al	556	63. ± 10.4	43.6/56.4	1.0
Salehi et al	115	58.7± 13	31/10	1.2
Present study	100	50.82±13	50/50	1

The mean age of the cases studied in the present study is comparatively younger ($p>0.05$) than similar studies, except Mohan et al, with which the age is comparable. Ariyo et al in the suggest that elevated levels of lipoprotein (a) independently predict an increased risk of stroke, death from vascular disease, and death from all causes, in men but not in

women above the age of 60 years. Since the mean age in the present study is below 60, influence of increased age does not confound the results.

In the present study the mean age is in the early fifth decade, which is comparable to Mohan et al. This may be due to occurrence of acute coronary syndrome in an earlier age in the South Indian patients compared to western population.

The ratio between male and female patients in both controls and cases were proportionate in all the studies. Gender bias is also removed as both the groups are matched.

Post-menopausal state influences serum Lp(a) levels. Both the diabetic and non- diabetic group had comparable fraction of such patients. Females on Hormone replacement therapy were also excluded from the study as it alters athero thrombotic risk and Lp(a) levels.

Comparison of Lp(a) level in type -2 diabetics and non diabetics in various studies

Author	No. of cases	Lp(a) level in diabetes	Lp(a) level in non diabetes
Mohan et al	**100**	**15.1±3.3**	**12.1±4.6**
Tseng et al	**557**	**18.1±15.5**	**14.9±5.9**
Neki et al	**134**	**14.9±3.5**	**11.9±4.1**
Salehi et al	**115**	**16.8±4.4**	**13.3±5.1**
Present study	**100**	**27.62±12.8**	**12.5±5.42**

In the present study, Lp(a) values varied from 7 to 60mg/dl. Type-2 diabetic patients had higher Lp(a) level compared to non diabetic patients. The difference of means was statistically significant ($p<0.0001$). This was comparable with Mohan et al, Neki et al, and Salehi et al. This was because of similar patient sample and method used to measure serum Lp(a) level.

In the present study, considering the optimal cut off points at 15mg/dl, 80% of type-2 diabetic patients had Lp(a) > 15mg/dl, compared to 20% of non diabetic patients.

Type-2diabetic patients, have nearly 2 fold risk of higher serum lipoprotein(a) compared to non diabetic group, during acute coronary syndromes.

This phenomenon may be explained by 2 hypotheses:

A) Diabetic group had a pre existing high base line serum Lp(a) which contributed to the pre mature acute coronary syndromes.

B) Diabetic group underwent an accelerated acute phase reaction to acute coronary syndrome and may be prognostic marker in such situations.

Lp(a) level and lipid profile

In the present study, serum total cholesterol, LDL level, triglycerides and Lp(a) level were significantly higher($p<0.0001$) in the diabetic group when compared to non diabetic groups.

HDL are significantly lower in diabetic group when compared to non diabetic groups. In the present study, there was moderate positive correlation between serum Lp(a) levels and serum total cholesterol and LDL. This was consistent with Mohan et al. Raised Lp(a) can increase the coronary artery disease risk along with raised LDL in type-2 diabetes.

This suggests the basis for a genetic pre disposition to coronary artery disease among populations with elevated Lp(a) levels and concomitantly raised LDL levels.

MORBIDITY AND MORTALITY:

Diabetic patients with acute myocardial infarction have a higher mortality. Since the present study had a small sample and is a cross sectional study, this result cannot be concluded.

In the present study, cardiac arrest occurred in two diabetic patients because of fatal secondary ventricular fibrillation. Cardiac arrest occurred in one non-diabetic patient, who survived a sustained pulseless ventricular tachycardia.According to McGuire et al, during acute coronary syndrome, type 2 diabetes independently predicted mortality (relative risk [RR], 1.57), as well as cardiovascular death, new myocardial infarction, stroke, and new congestive heart failure. Moreover, compared with their non-diabetic counterparts, women had a significantly higher risk than men (RR, 1.98 and RR, 1.28). Interestingly, diabetic patients without prior cardiovascular disease had the same event rates for all outcomes as non-diabetic patients with previous vascular disease.

CONCLUSION

Type-2 diabetic patients have higher level of Lp(a) level during acute coronary syndrome when compared to non diabetic group. So, the type-2 diabetic patients have nearly 2 fold risk of having high Lp(a) level than non diabetic group.

Elevated Lp(a) in type -2 diabetic patients contribute to the accelerated atherogenic / prothrombotic state, causing major adverse cardiac events.

SUMMARY

- Serum Lp(a) level is high in type -2 diabetic patients with acute coronary syndrome when compared to non diabetic patients.
- Mean serum Lp(a) in present study was 27.62±12.8mg/dl. The value of Lp(a) varies from 7mg/dl to 60mg/dl.
- Triglycerides, total cholesterol and LDL were significantly higher in patients with type -2 diabetics and acute coronary syndrome compared to non diabetic patients.
- HDL cholesterol levels were significantly lower in patients with type -2 diabetic patients when compared to non diabetic group with acute coronary syndrome.

MASTER CHART

DIABETIC PATIENTS:

S.NO	NAME	AGE	SEX	LDL	TC	TG	HDL	Lp(a)
1	VIJAYA	48	F	124	217	270	14	60
2	SANKAR	45	M	112	190	192	35	40
3	KARUPAYEE	51	F	125	214	214	20	55
4	ALAGU	63	M	96	162	145	44	10
5	RAJENDRAN	37	M	119	182	194	35	42
6	RASATHY	56	F	120	172	198	35	35
7	INDIRANI	49	F	124	174	207	15	38
8	ALAGUMATHY	60	F	121	185	209	18	35
9	VEERAN	58	M	106	182	191	20	28
10	ABDULLA	38	M	62	172	146	40	10
11	RAJASEKARAN	54	M	119	174	188	30	25
12	RAJALAKSHMI	68	F	115	185	187	35	25
13	PALANIAPPAN	66	M	118	182	192	44	28
14	VIJAYAKUMAR	35	M	109	173	201	40	18
15	SURESH	31	M	107	172	200	38	15
16	POTHUMPONNU	66	F	121	206	218	20	35
17	NATARAJAN	61	M	101	191	198	30	20
18	BALAJI	28	M	123	172	228	14	40
19	GANESH	39	M	121	207	229	15	40
20	IRULLAYEE	55	F	124	203	225	18	38
21	KARUPPASAMY	55	M	129	205	226	18	32
22	ANNAMALAI	52	M	125	204	221	17	50
23	LAKSHMI	56	F	91	161	144	42	12
24	SELVI	54	F	105	164	167	32	15
25	RAJANGAM	81	M	109	172	175	35	12

MASTER CHART FOR DIABETIC PATIENTS CONTINUES..

26	RAJATHI	61	F	122	216	219	30	7
27	RAGHURAM	53	F	99	164	146	40	10
28	KANNIYAMMAL	58	F	111	172	181	32	20
29	KAVITHA	35	F	113	171	186	34	25
30	SUNDARAM	49	M	119	178	190	30	14
31	RAJA	34	M	126	225	224	25	30
32	MEENAKSHI	52	F	120	189	260	18	26
33	VINOTHKUMAR	30	M	97	164	146	30	14
34	ASHARUDEEN	26	M	100	175	158	36	20
35	VIJAYAVEERAN	47	M	123	270	280	15	55
36	VEERAYEE	46	F	206	164	148	44	50
37	VANITHA	44	F	124	206	224	15	35
38	LAKSHMI	62	F	120	208	209	17	30
39	KANNABIRAN	48	M	130	165	146	40	20
40	ARAYEE	60	F	106	171	168	38	15
41	LAKSHMI	68	F	109	172	171	35	20
42	SURENDIRAN	36	M	128	270	250	20	20
43	SUNDARAMOORTHY	75	M	127	250	218	20	24
44	ANANTHI	40	F	96	163	150	44	25
45	BALASARASWATHI	57	F	60	164	154	20	22
46	SIVAKUMAR	28	M	108	184	171	35	33
47	MATHIYAZHAGAN	78	M	102	186	170	28	35
48	SUNDARI	38	F	118	193	181	25	28
49	MARIAMMAL	50	F	121	217	220	21	25
50	MARUTHAYEE	60	F	98	162	151	55	20

MASTER CHART :

NON DIABETC PATIENTS

S.NO	NAME	AGE	SEX	LDL	TC	TG	HDL	Lp(a)
1	CHELLAPPAN	74	M	94	141	119	60	10
2	SIVAKUMAR	40	M	95	144	120	62	11
3	SENNIYAMMAL	65	F	101	154	135	50	7
4	BALAMURUGAN	56	M	102	156	143	50	12
5	LAKSHMIYAMMAL	65	F	111	162	155	52	10
6	KALLIAYAMMAL	80	F	96	141	121	58	14
7	KALASALINGAM	58	M	97	150	128	48	15
8	KARUPPANNAN	60	M	114	161	155	46	10
9	IRULLAYEE	60	F	116	162	161	45	10
10	SHANMUGAM	81	M	118	160	180	19	10
1	SELVI	45	F	96	145	121	58	7
12	MARUTHAYEE	68	F	95	143	125	55	7
13	VIJAY	29	M	94	144	127	54	10
14	GOPAL	45	M	95	149	131	54	6
15	THANGALAKSHMI	66	F	99	151	138	50	12
16	SHAHUL HAMEED	28	M	96	151	134	60	15
17	INDRANI	72	F	102	158	144	48	14
18	MALAR	58	F	103	168	148	48	20
19	POOVAYEE	61	F	110	167	147	45	14
20	NACHIYAPPAN	78	M	111	161	150	25	14
21	PARAMESHWARAN	50	M	93	141	124	60	10
22	SELVAM	44	M	80	144	125	62	11
23	KUMARI	67	F	114	165	140	55	12
24	JOTHI	45	F	118	190	160	25	25
25	SRINIVASAN	62	M	116	174	155	30	18

MASTER CHART FOR NON DIABETIC PATIENT CONT..

26	PREMKUMAR	34	M	110	168	151	48	15
27	VEERALAKSHMI	48	F	94	141	119	58	12
28	RAJAN	88	M	74	144	121	54	10
29	ANAND	40	M	102	190	145	48	10
30	BHARATHI	50	F	114	158	154	46	11
31	KANNAN	48	M	110	155	179	35	6
32	ARUNACHALAM	40	M	94	145	120	55	13
33	INDIRA	54	F	99	148	132	55	14
34	KALAIVANI	40	F	99	156	145	44	14
35	GOVINDAMMAL	44	F	125	250	156	42	30
36	PARAMESHWARI	63	F	80	146	127	58	7
37	SEETHAPATHI	56	M	95	144	128	55	10
38	VALLI	58	F	101	160	147	35	10
39	NIRMALA	48	F	76	200	122	58	7
40	KANNIYAMMAL	62	F	104	166	135	45	6
41	JOTHILAKSHMI	49	F	96	190	120	62	10
42	RAJATHI	52	F	116	210	140	20	10
43	BALA SUBRAMANI	55	M	105	164	155	45	5
44	KAYALVIZHI	47	F	104	168	156	50	20
45	GANESAN	53	M	75	146	170	60	10
46	RAJKUMAR	29	M	98	148	128	54	25
47	SARAVANAN	29	M	94	151	124	54	20
48	KARUPPAYEE	60	F	108	175	135	50	11
49	NATARAJAN	55	M	104	166	156	40	10
50	ANJUGAM	62	F	117	200	162	25	25

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PROFORMA

Comparative study of lipoprotein (a) level in diabetics and non-diabetics with acute coronary syndrome

NAME: **CASE NO:**

AGE/SEX: **IP NO :**

OCCUPATION: **DOA :**

ADDRESS: **DOD :**

HISTORY OF PRESENTING COMPLAINTS:

1. H/O Chest pain

Duration:

Associated with sweating ,palpitation, dizziness: YES/NO

Aggravating factors:

Relived by rest: YES/NO

2. H/o dyspnoea:

NYHA Class:

H/o orthopnoea present or not:

3.H/o cough-

PAST HISTORY:

H/o diabetes mellitus: yes/no

If yes, duration:

Anti-diabetic drugs:

H/o hypertension:

H/o CVA:

H/o PTB:

H/o epilepsy:

PERSONAL HISTORY:

FAMILY HISTORY:

EXAMINATION:

GENERALEXAMINATION:

VITALS:

Pulse: **Blood pressure:** **RR:** **spo2:**

ANTHROPOMETRY:

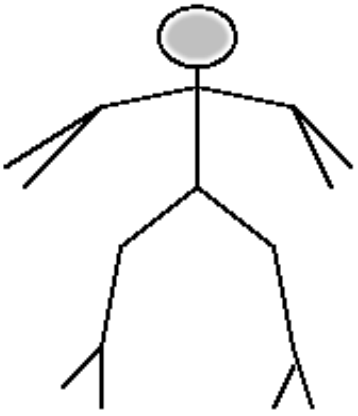
Height: **Weight:** **BMI:**

- **Pallor**
- **Cyanosis**
  Clubbing
- **Generalized lymphadenopathy**

Cardiovascular system:

Date						
Pulse						
Blood Pressure ⟺						
⇑						
Jugular Venous pulse:						
Apical Impulse:						
S_1						
S_2						
S_3						
S_4						
Murmurs:						
Rub:						
Carotid bruits:						
Epigastric bruits:						

Peripheral pulses



RESPIRATORY SYSTEM:

ABDOMEN EXAMINATION:

CNS EXAMINATION:

INVESTIGATIONS:

Blood sugar at the time of admission:

Fasting blood sugar: **2hr blood sugar:**

Blood urea: **serum creatinine:**

Hb: **urine analysis:**

LIPID PROFILE:

Total cholesterol:

TGL level :

HDL level :

LDL level :

VLDL level :

LIPOPROTEIN(a) level:

Echocardiogram:

THYROID PROFILE:

ELECTROCARDIOGRAM:

ECG	AT THE DAY OF ADMISSION	1ST DAY	2ND DAY	3RD DAY
RATE				
RHYTHM				
AXIS				
P WAVE				
PR INTERVAL				
Q WAVE				
QRS				
ST SEGMENT				
T WAVE				
QTC INTERVAL				

TREATMENT:

FOLLOW UP:

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.S.Akila Akilaprakash1@gmail.com	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai.	**Comparative study of Lipoprotein (a) Level in diabetics and non diabetics with acute coronary syndrome.**	**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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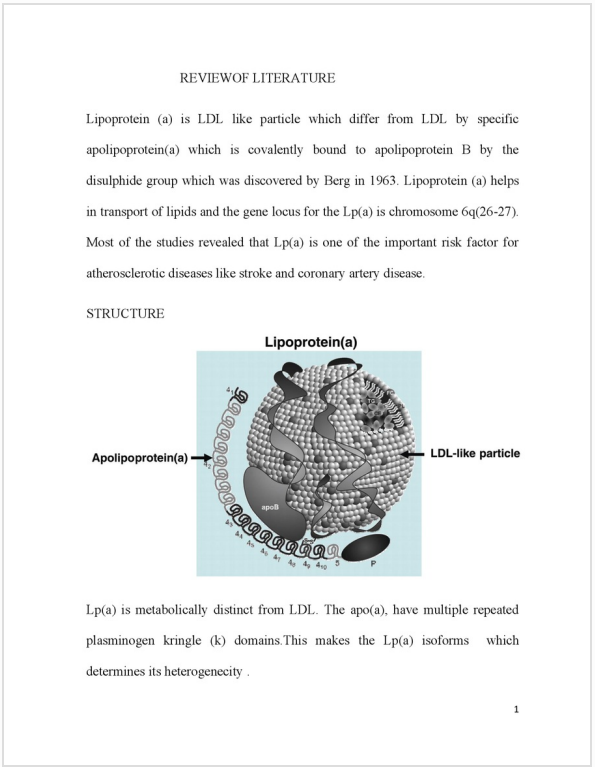

REVIEWOF LITERATURE

Lipoprotein (a) is LDL like particle which differ from LDL by specific apolipoprotein(a) which is covalently bound to apolipoprotein B by the disulphide group which was discovered by Berg in 1963. Lipoprotein (a) helps in transport of lipids and the gene locus for the Lp(a) is chromosome 6q(26-27). Most of the studies revealed that Lp(a) is one of the important risk factor for atherosclerotic diseases like stroke and coronary artery disease.

STRUCTURE

Lp(a) is metabolically distinct from LDL. The apo(a), have multiple repeated plasminogen kringle (k) domains.This makes the Lp(a) isoforms which determines its heterogenecity .

1

REVIEWOF LITERATURE

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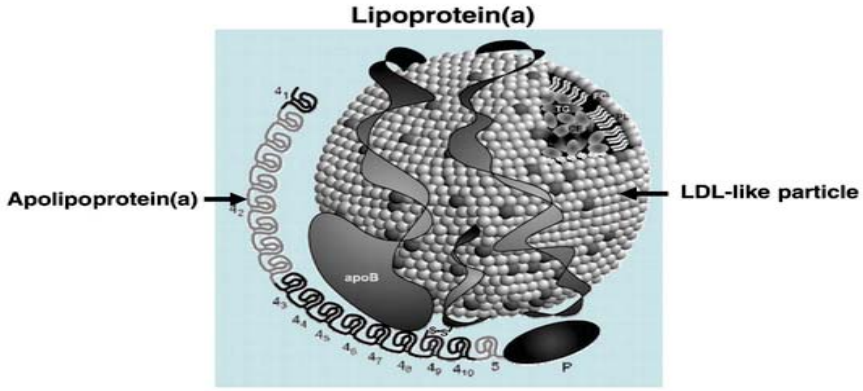
STRUCTURE



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