CHAPTER TWO

REVIEW OF LITERATURE
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NORMAL STRUCTURE OF HEART

The heart is composed of cardiac muscle tissue that continuously contracts and relaxes. It must receive a constant supply of oxygen and nutrients. The coronary arteries are the network of blood vessels that carry oxygen and nutrient rich blood to the cardiac muscle tissue.

The blood leaving the left ventricle exits through the aorta, referred to as the left and right coronary arteries, emerge from the beginning of the aorta, near the top of the heart.

The heart is a muscular pump that ejects blood in to the vascular tree with sufficient pressure to maintain optimal circulation. The average weight of heart in an adult male is 300-350 gm while that of an adult female is 250-300gm. (Fig-1)

The initial segment of the coronary artery is called the left main coronary. This blood vessel is approximately the width of a soda straw and is less than an inch long. It branches in to two slightly smaller arteries: the left anterior descending coronary artery and the left circumflex coronary artery. The left anterior descending coronary artery is embedded in the surface of the front side of the heart. The left circumflex coronary artery circles around the left side of the heart and is embedded in the surface of the back of the heart.

Just like branches of a tree, the coronary arteries branch into progressively smaller vessels. The larger vessels travel along the surface of the heart; however, the smaller branches penetrate the heart muscle. The smallest branches, called capillaries, are so narrow that the red blood cells must travel in single file. In the capillaries, the red blood cells provide oxygen and nutrients to the cardiac muscle tissue and bond with carbon dioxide and other metabolic waste products, taking them away from the heart for disposal through the lungs, kidneys and liver (25).
The blood in the heart chambers moves in a systematic pathway.

Blood (low oxygen, high carbon dioxide) → venae cavae → right atrium → right atrium contraction → blood passes through tricuspid valve → blood enters right ventricle → right ventricle contracts and tricuspid closes → blood moves through pulmonary semilunar valve → blood moves into pulmonary trunk → pulmonary arteries transport blood to the lungs → blood is oxygenated → oxygenated blood transported back to heart (left atrium) via pulmonary veins → left atrium contracts, blood moves through the bicuspid valve into left ventricle → left ventricle wall contracts, bicuspid valve closes → blood passes through the aortic semilunar valve into the aorta → blood sent to tissue/cells → blood becomes deoxygenated (low oxygen, high carbon dioxide) (26) (fig-2).
Fig. 1: (A and B) Normal Structure of Heart

**A**
1. Right Coronary
2. Left Anterior Descending
3. Left Circumflex
4. Superior Vena Cava
5. Inferior Vena Cava
6. Aorta
7. Pulmonary Artery
8. Pulmonary Vein

**B**
9. Right Atrium
10. Right Ventricle
11. Left Atrium
12. Left Ventricle
13. Papillary Muscles
14. Chordae Tendineae
15. Tricuspid Valve
16. Mitral Valve
17. Pulmonary Valve
Aortic Valve (Not pictured)
The heart pumps blood into two closed circuits - the systemic circulation and the pulmonary circulation with each beat. The two circuits are arranged in series: the output of one becomes the input of the other, as would happen if you attach two garden hoses. The left side of the heart is the pump for the systematic circulation; it receives bright red, oxygen-rich blood from the lungs. The left ventricle ejects blood into the aorta. From the aorta, the blood divides into separate streams, entering progressively smaller systemic arteries that carry it to all organs throughout the body - except for the air sacs (alveoli) of the lungs, which are supplied by the pulmonary circulation. In systemic tissues, arteries give rise to smaller diameter arterioles, which finally lead into extensive beds of systemic capillaries. Exchange of nutrients and gases occurs across the thin capillary walls. Blood unloads $O_2$ and picks up $CO_2$.

In most cases, blood flows through only one capillary and then enters a systemic venule. Venules carry deoxygenated (oxygen-poor) blood away from tissues and merge to form larger systemic veins. Ultimately the blood flows back to the right atrium.

The right side of the heart is the pump for the pulmonary circulation; it receives all the dark red, deoxygenated blood returning from the systemic circulation. Blood ejected from the right ventricle flows into the pulmonary trunk, which branches into pulmonary arteries that carry blood to the right and left lungs. In pulmonary capillaries, blood unloads $CO_2$, which is exhaled, and picks up inhaled $O_2$. The freshly oxygenated blood then flows into pulmonary veins and returns to the left atrium (27).
Fig-2 Blood Flow in Heart

<table>
<thead>
<tr>
<th>Chamber of the Heart</th>
<th>Receives Blood From</th>
<th>Sends Blood To</th>
<th>Valves Through Which Blood Flows</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium</td>
<td>Superior vena cava, inferior vena cava, coronary sinus</td>
<td>Right ventricle</td>
<td>Right AV valve</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>Right atrium</td>
<td>Pulmonary trunk (blood enters pulmonary circuit of vessels)</td>
<td>Pulmonary semilunar valve</td>
</tr>
<tr>
<td>Left atrium</td>
<td>Pulmonary veins</td>
<td>Left ventricle</td>
<td>Left AV valve</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>Left atrium</td>
<td>Aorta (blood enters systemic circuit of vessels)</td>
<td>Aortic semilunar valve</td>
</tr>
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Coronary Circulation (Fig. 3)

Nutrients are not able to diffuse quickly enough from blood in the chambers of the heart to supply all the layers of cells that make up the heart wall.

For this reason, the myocardium has its own network of blood vessels, the coronary or cardiac circulation. The coronary arteries branch from the ascending aorta and encircle the heart like a crown encircles the head. While the heart is contracting, little blood flows in the coronary arteries because they are squeezed shut. When the heart relaxes, however, the high pressure of blood in the aorta propels blood through the coronary arteries, into capillaries, and then into coronary veins (27).

Coronary Arteries

Two coronary arteries, the right and the left coronary arteries, branch from the ascending aorta and supply oxygenated blood to the myocardium. The left coronary artery passes inferior to the left auricle and divides into the anterior interventricular and circumflex branches. The anterior interventricular branch or left anterior descending (LAD) artery is in the anterior interventricular sulcus and supplies oxygenated blood to the walls of both ventricles. The circumflex branch lies in the coronary sulcus and distributes oxygenated blood to the walls of the left ventricle and left atrium.

The right coronary artery supplies small branches to the right atrium. It continues inferior to the right auricle and ultimately divides into the posterior interventricular and marginal branches. The posterior interventricular branch follows the posterior interventricular sulcus and supplies the walls of the two ventricles with oxygenated blood. The marginal branch in the coronary sulcus transports oxygenated blood to the myocardium of the right ventricle (27).

Most parts of the body receive blood from branches of more than one artery, and where two or more arteries supply the same region, they usually connect. These connections called anastomoses provide alternate routes for blood to reach a particular organ or tissue. The myocardium contains many anastomoses.
that connect branches of a given coronary artery or extend between branches of different coronary arteries. They provide detours for arterial blood if a main route becomes obstructed. Thus, heart muscle may receive sufficient oxygen even if one of its coronary arteries is partially blocked (27).

**Coronary veins**

After blood passes through the arteries of the coronary circulation, it flows into capillaries, where it delivers oxygen and nutrients to the heart muscle and collects carbon dioxide and waste, then moves into coronary veins. Most of the deoxygenated blood from the myocardium drains into a large vascular sinus in the coronary sulcus on the posterior surface of the heart, called the coronary sinus. The deoxygenated blood in the coronary sinus empties into the right atrium. The principal tributaries carrying blood into the coronary sinus are the following -

- **Great cardiac vein** in the anterior interventricular sulcus, which drains the areas of the heart supplied by the left coronary artery.

- **Middle cardiac vein** in the posterior interventricular sulcus, which drains the areas supplied by the posterior interventricular branch of the right coronary artery.

- **Small cardiac vein** in the coronary sulcus, which drains the right atrium and right ventricle.

- **Anterior cardiac veins**, which drain the right ventricle and open directly into the right atrium.

**Layers of the Heart wall**

The transport of blood is regulated by cardiac valves, two loose flap like arteriovascular valves, tricuspid on the right and mitral (bicuspid) on the left, and two semilunar valves with three leaflet each, the pulmonary and aortic valves, guarding the outflow tracts. The normal circumference of the valvular openings
measures about 12 cm in tricuspid, 8.5 cm in pulmonary, 10 cm in mitral and 7.5 cm in aortic valve.

The wall of the heart consists of three layers, the epicardium (external layer), the myocardium (middle layer), and the endocardium (inner layer).

The outermost epicardium, the thin, transparent outer layer of the heart wall, is also called the visceral layer of the serous pericardium. It is composed of mesothelium and delicate connective tissue that imparts a smooth, slippery texture to the outermost surface of the heart.

The middle myocardium, which is cardiac muscle tissue, makes up the bulk of heart and is responsible for its pumping action. Although it is striated like skeletal muscle, cardiac muscle is involuntary like smooth muscle.

The innermost endocardium is a thin layer of endothelium overlying a thin layer of connective tissue. It provides a smooth lining for the chambers of the heart and covers the valves of the heart. The endocardium is continuous with the endothelial lining of the large blood vessels attached to the heart (27).
Fig- 3: Coronary Circulation

Coronary Circulation:

- Right Subclavian Artery
- Brachiocephalic Artery
- Right Pulmonary Artery
- Aorta
- Superior Vena Cava
- Right Coronary Artery
- Right Atrium
- Tricuspid Valve
- Interior Vena Cava
- Right Ventricle
- Right Common Carotid Artery
- Left Common Carotid Artery
- Left Subclavian Artery
- Aortic Arch
- Left Pulmonary Artery
- Pulmonary Trunk
- Left Atrium
- Left Pulmonary Veins
- Left Coronary Artery
- Anterior Interventricular Branch
- Circumflex Branch
- Mitral Valve
- Left Ventricle
Endothelial Cells

Endothelial cells form a monolayer that lines the entire vascular system (the endothelium). Their structural and functional integrity is fundamental to the maintenance of vessel wall homeostasis and circulatory function. Endothelial cells are polygonal, elongated cells that have many pinocytotic vesicles and form junctional complexes with their neighbours.

Vascular endothelium is a versatile multifunctional tissue having many synthetic and metabolic properties. Endothelial cells i) serve as a semipermeable membrane, controlling the transfer of small and large molecules into the arterial wall and through the walls of capillaries and venules; ii) Maintain the normothombogenic blood-tissue interface, by regulating thrombosis, thrombolysis, and platelet adherence; iii) Modulate vascular tone and blood flow; iv) Metabolize hormones; v) Regulate immune and inflammatory reactions, largely by controlling leukocyte interaction with the vessel wall; vi) Modify lipoproteins in the arterial wall and; vii) regulate the growth of other cell types, particularly smooth muscle cells.

Thus, the endothelial cell is an active participant in the interaction between blood and tissue. Moreover, besides contributing to the formation of thrombi, endothelial injury is critical to the initiation of atherosclerosis and the vascular effects of hypertension and other disorders (28).
Coronary Artery Disease

Epidemiology

The contribution of cardiovascular disease to the total population mortality was less than 10% until the beginning of the 20th Century. The dramatic socio-economic transition including urbanisation, increased food supplies, less demand on physical activity for transportation and work combined with advances in the treatment of infectious diseases in young age groups, resulted in rapidly growing prevalence of degenerative diseases. Within half of the century coronary artery disease became the leading cause of morbidity and mortality. According to the WHO mortality database from the year 2002 the cardiovascular mortality varies across European countries from below 3 to 9 per 1000 inhabitant. Although progress in the diagnosis, treatment and prevention of cardiovascular disease have resulted in a substantial mortality reduction, the total number of affected individuals is still increasing due to improved survival and an increasing overall longevity in the population (29).

The prevalence of coronary artery disease (CAD) has progressively increased in India during the last half of the twentieth century particularly among the urban population. This is expected to become most important cause of morbidity and mortality over the next two decades (30). Of all the ethnic groups people of Indian origin have one of the highest incidence of CAD (31,32).

The disease has been shown to affect Indians at younger age with severe diffuse form of involvement and unrelenting course (30). The prevalence of premature CAD in Indians is up to three times higher as compared to people of similar age group in the western world (33).

The prevalence of coronary artery disease is known to be very high both among migrant Asian Indians and also among people within the Indian subcontinent. Moreover, CAD in Asian Indians occurs prematurely as compared to Europeans. A host of new risk factors related to the metabolic syndrome have been
described in Asian Indians. Including an excess of non – insulin dependent diabetes mellitus (NIDDM), increased upper body obesity with an increase in waist – hip ratio (WHR), elevated plasma insulin levels (hyperinsulinemia) and increased insulin resistance.

The precise etiology leading to development of CAD, however remains incompletely understood although an increasing number of risk factors have been identified over the past several decades. These include abnormal levels of serum cholesterol with elevated levels of LDL and reduced levels of HDL cholesterol, serum triglycerides, hypertension, cigarette smoking, diabetes, male gender, postmenopausal state, advancing age, sedentary lifestyle and family history of heart disease. Increasing recognition that many patients with established CAD lack these traditional risk factors has led to search for additional new risk factors that may predispose individuals to CAD (34).

Coronary artery disease is considered to be a multifactorial disease wherein hypertension (HTN), central obesity, non – insulin dependent diabetes mellitus (NIDDM), dyslipidaemia and smoking play a dominant role in its etiopathogenesis. It is also said that HTN, central obesity, NIDDM may be a part of cardiovascular dysmetabolic syndrome (CDS) also known as insulin resistance syndrome. Insulin resistance syndrome (IRS) may either be genetic and / or acquired. It is therefore interesting to go into the details of prevalence of important clinical components of IRS that is, HTN, obesity, NIDDM and dyslipidaemia, in several generations of a single family (35).

CAD most often results from a condition known as atherosclerosis which happens when a waxy substance forms inside the arteries that supply blood to heart. This substance called plaque,(fig-4) is made up of Cholesterol ,fatty compounds ,calcium and a blood clotting material called fibrin (36).
There are two kinds of plaque: Hard and soft. Most people know about hard plaque and how it can cause a heart attack. If hard plaque builds up in the arteries that supply blood to heart, the blood flow slows or stops. This decreases the amount of oxygen that gets to the heart, which can lead to heart attack (36).

When cholesterol plaque accumulates to the points of blocking the flow of blood through a coronary artery, the cardiac muscle tissue fed by the coronary artery beyond the point of the blockage is deprived of oxygen and nutrients. This area of cardiac muscle tissue ceases to function properly. The condition when a coronary artery becomes blocked, causing damage to the cardiac muscle tissue it serves, it is called a myocardial infarction or heart attack (25).
Coronary artery disease (CAD) (fig-5) is the most common cause of heart attacks. CAD is the end result of a complex process called atherosclerosis (commonly called "hardening of the arteries"). (fig-6) This causes blockage of arteries (ischemia) and prevents oxygen-rich blood from reaching the heart. A full-blown heart attack occurs when blood flow to the myocardium is blocked and tissue death occurs from loss of oxygen, severely damaging the heart. The medical term for heart attack is Myocardial infarction (37).

Fig No-5 Coronary artery disease (CAD): Heart disease. A condition in which sticky deposits (plaques) block the flow of blood to the heart, often causing chest pain (angina). Heart disease can lead to a heart attack. Untreated, high LDL cholesterol levels can lead to heart disease.
Fig No-6 Arteriosclerosis: A disease characterized by thickening and hardening of artery walls. The word "atherosclerosis" is often used to indicate any of the forms of arteriosclerosis.
Heart Attack

Heart attack (or myocardial infarction) is the most serious outcome of atherosclerosis. It can occur as a result of one or two effects of atherosclerosis: (fig-7)

1. If the artery becomes completely blocked and ischemia becomes so extensive that oxygen-bearing tissues around the heart die.

2. If the plaque itself develops fissures or tears. Blood platelets adhere to the site to seal off the plaque, and a blood clot (thrombus) forms. A heart attack can then occur if the formed blood clot completely blocks the passage of oxygen-rich blood to the heart.

Fig No-7 Heart attack: Also called a myocardial infarction. This is a complete blockage of blood flow to an area of the heart, causing heart cells to die. Untreated, high LDL cholesterol levels can lead to a heart attack.
**Angina**

Angina is the primary symptom of coronary artery disease and is typically experienced as chest pain. There are two kinds of angina (fig-8)

- **Stable Angina** is predictable chest pain that can usually be managed with lifestyle measures and medications, such as low-dose aspirin.
- **Unstable angina** is a much more serious situation than stable angina that is often an intermediate stage between stable angina and a heart attack. Unstable angina is part of a condition called *acute coronary syndrome*.

Fig No-8 **Angina**: A pain in the chest caused by inadequate blood flow through the blood vessels of the heart.
Acute Coronary Syndrome

Acute coronary syndrome (ACS) is a severe and sudden heart condition that requires aggressive treatment, but has not developed into a full blown heart attack.

Acute coronary syndrome includes:

- **Unstable angina.** Unstable angina is a much more serious situation than stable angina. It is often an intermediate stage between stable angina and a heart attack.
- **NSTEMI (non ST-segment elevation myocardial infarction).** This condition, also called non Q-wave myocardial infarction, is diagnosed when blood tests and ECGs suggest a developing heart attack. The injury in the arteries is less severe than with a full-blown heart attack (37).

Risk Factors For Coronary Artery Disease

The established risk factors for CAD are hypertension, hyperlipidemia, smoking, diabetes mellitus, age, male gender and family history of coronary artery disease. Each of these risk factors has been proven beyond doubt to increase the risk of cardiovascular disease and contributes to the development of atherosclerotic plaques.

Underlying lifestyle choices, like atherogenic diet, physical inactivity, obesity and smoking, all underpin the development of cardiovascular disease and can contribute to the onset of hypertension, diabetes and hyperlipidemia. A family history of CAD would suggest a genetic predisposition to developing atherosclerotic plaques. Lipid abnormalities that lead to CAD include elevated low-density lipoprotein (LDL), triglyceride (TG), lipoprotein(a), and reduced high-density lipoprotein (HDL). Diabetics, in addition to hyperglycemia, usually have other concomitant atherogenic risk factors as part of their metabolic milieu that place them at an increased risk (38).
The risk to developed coronary artery disease is influenced by multiple factors that can be classified in two groups (11):

1) Modifiable
2) Non-modifiable

1) Modifiable Risk Factors

a) Smoking

WHO has estimated that at present tobacco causes 2.5 million premature deaths per annum worldwide that increased more than ten-fold since 1950. It has been projected that at present rates of consumption, global annual mortality from tobacco will rise to 19 million in 2020’s. With consumption projected to rise still further, the actual figures may be greater (39).

Tobacco’s effect on CHD is overwhelming. It is not simply an independent risk factor, but rather an interactive one in that, smoking imparts the greatest risk for women already at high risk due to other prevalent coronary risk factors. It is not only atherogenic, but it also potentiates thrombotic process and induces coronary vasospasm (40).

b) Hypertension

Hypertension is defined as a systolic blood pressure of 140 mmHg or greater and/ or a diastolic blood pressure of 90 mmHg or greater in subjects who are not taking antihypertensive medication (41).

Hypertension has been established as a major modifiable risk factor for the development of coronary atherosclerosis that extends across racial, gender, and age categories. It frequently coexists with other risk factors, and the impact may be synergistic, especially between hypertension and hyperlipidaemia. The Framingham study found an association between hyperlipidemia and increased hypertension. Recent studies from Utah have identified families with “
dyslipidaemic hypertension”. This disorder may be related to “hyper- apoB”, increased triglycerides, decreased HDL, small dense LDL, hyperinsulinemia, and insulin resistance. Some antihypertensive agents, including diuretics and beta blockers, exacerbate dyslipidemia, although the clinical significance of these drug interactions is not known. Pharmacological lowering of blood pressure has been reported to cause an increased risk for a cardiac event, especially in men with established coronary atherosclerosis. This suggests that the relation between high blood pressure and CAD mortality follows a J- shaped curve, but the issue remains controversial (42).

c) Diabetes mellitus

In the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), diabetes is regarded as a CAD risk equivalent. Diabetes is a stronger risk factor for CAD in women than in men, with a 3 to 7 fold higher CAD incidence and mortality compared to a 2 to 3 fold higher risk in men. Diabetes increases the risk of heart failure by 8 fold in women compared to 4 fold in men (43).

d) Physical Activity

The role of physical activity in the prevention of CAD and in decreasing mortality after MI remains controversial. Recent epidemiological studies have shown an encouraging and beneficial trend in favour of this relatively low - cost and low-risk intervention. Long-term physical activity is known to be important in maintaining ideal body weight and muscle mass. Exercise also may play an important role in maintaining normal blood pressure and optimizing lipid values. Patients who exercise regularly have been reported to show a decreased incidence of sudden cardiac death. In contrast, some people who have been sedentary or at increased risk for malignant ventricular arrhythmia or acute MI when they begin to exercise.

Several epidemiological studies have shown a consistent inverse relationship between caloric intake per kilogram of body mass and CAD, probably
because of the protective effect of increased physical activity. Multivariate analyses have revealed that people with high levels of physical fitness have lower rates of CAD. Conversely, decreased levels of physical fitness are associated with increased risk of atherosclerosis (42).

e) Obesity

The prevalence of obesity is increasing and around 25% of women report no regular sustained physical activity. Obesity and upper body fat distribution are significant independent predictors of cardiovascular risk, especially in women. This is not surprising, in that the association of obesity include increased levels of LDL, triglycerides and lower levels of HDL. Further obesity is associated with insulin resistance, hyperuricemia, HT and importantly higher frequency of smoking. Again it remains uncertain whether the obesity pattern per se or the concomitant greater prevalence of other factors impart higher risk. Although the optimal approach to weight control in women has not been ascertained, weight control improves the cardiovascular risk profile. It is uncertain whether the results differ with diet, exercise, or with combination of these intervention used for weight control (40).

f) Dyslipidaemia

Patients with diabetes have high very-low density lipoprotein and total triglycerides, decreased high-density lipoprotein and elevated low-density lipoproteins. Furthermore, metabolic abnormalities exist in LDL-cholesterol particles and increased glycation of LDL-cholesterol, both of which increase atherogenicity (44).

g) Apoprotein

Studies indicate that low levels of apo-A and high levels of apo-B are also risk factors for CAD and are thought to be superior to traditional lipid measurement. Apolipoprotein A-1 is a major protein in HDL and is also seen in chylomicrons and has eleven variants (11).
h) Lipoprotein (a)-Lp (a)

Lp (a) is a genetically determined lipoprotein of human blood. It is a LDL like substance containing a unique lipoprotein apo (a) and stimulates plasminogen in structure. However, Lp (a) is 10 times more atherogenic than LDL (45). It has dual mechanism of action I) due to its LDL like action, it is atherogenic. II) due to its plasminogen like property, it is thrombogenic. Its adult levels are reached within one year of life and are not significantly influenced by age, sex, diet, environmental factors etc. Therefore, it starts its deleterious effects about 20 years earlier than most of the other risk factors. Presence of elevated Lp (a) levels during childhood predicts future premature CAD (46).

i) Hyperhomocysteinemia

One of the recently recognized risk factors for CAD is higher plasma homocysteine level (47). Plasma homocysteine level above 15 μM/L is known to increase the risk of CAD and stroke at a young age. Homocysteine causes vascular damage by the adverse effects on endothelial function by its prothrombotic, pro-oxidant and mitogenic effects. These effects can be largely neutralized by vitamin B6, B12 and folate intake.

j) Increased plasminogen activation inhibitor -1 (PAI-1)

High levels of PAI-1 is another emerging risk factor for CAD. PAI-1 has procoagulant effect and so elevated levels of PAI-1 in blood enhances thrombogenesis (11).

k) Coagulation factor VII

High plasma levels of coagulation factor VII has been found to be associated with enhanced risk for CAD. Dietary fat intake has also been found to influence factor VII level in blood (48,49).
I) Psychological factors

Depression enhances risk of myocardial infarction and repeat MI by three to four times in a past MI patient (50). Anger, hostility, social isolation and panic disorders are also associated with increased risk of CAD.

2) Non Modifiable Risk Factors

a) Age

Compared with the age group 34-44, CAD mortality among women increases 40-fold by the age of 80, when its incidence becomes identical in men and women. Women are about 10 years older than men at first manifestation of CAD, although they have a similar plaque burden. Women lose this 10-year advantage if they smoke, have diabetes, or had a premature menopause. The postmenopausal increase in the risk of CAD is related to a higher incidence of hypertension, diabetes, dyslipidaemia and obesity (43).

b) Gender

The dictum that women have a lower incidence of CAD than men is a function of the age group examined. CAD is much less common in premenopausal women than in age matched men, the difference most pronounced between ages. The purported protection of women from CAD becomes much less evident in their postmenopausal years, when the CAD rates for men and women begin to converge. The process of atherosclerosis does not appear to differ between men and women, and the risk factors correlated with the development of CAD appear to affect both sexes equally.

The presumption is that the differences in prevalence rates of coronary atherosclerosis between men and women are a function of the relative differences in estrogen and androgenic hormones. At puberty, circulating levels of testosterone increase in males and estrogen production increases in females (18).
c) Family History

A variety of studies, both case-control and prospective, point to familial aggregation of CAD. The aggregation of risk factors is well known and includes cholesterol, lipoproteins, blood pressure, diabetes, and obesity. Genetic and environmental influences on coronary risk may be difficult to distinguish. A population predisposition to hypertension or hypercholesterolemia may be determined by its intake of salt, saturated fat, or calories overall. The family at high risk for the development of CAD usually has at least one member who has hyperlipidaemia, Low HDL, hypertension, a positive family history of coronary disease, or positive family history of premature CAD. Familial aggregation studies, genetic studies, and the tracking of blood pressure have yielded evidence that children born to families with a high prevalence of these risk factors also are at risk for development of CAD (18).
Atherosclerosis And Coronary Artery Disease

Atherosclerosis is the leading cause of death worldwide. Coronary atherosclerosis accounted for 7.2 million deaths worldwide in 1996 representing one-third of total deaths in industrialized countries. During the same year, cerebrovascular atherosclerosis and disease accounted for an additional 4.6 million deaths.

In addition, it has been projected that there will be a 28% increase in cardiovascular deaths over the next 5 years in developing countries. Based on global trends, the World Health Organization projects that, by 2020, approximately half of all deaths in developed countries and one-third in developing countries will be due to cardiovascular disease (51).

Atherosclerosis is a form of arteriosclerosis in which soft deposits of intraarterial fat and fibrin on the vessel walls harden over time. Atherosclerosis is not a single disease entity. It can take several forms, depending on the anatomic location, age, genetic and physiologic status, and risk factors to which the individual is exposed. It is the leading contributor to coronary artery and cerebrovascular disease (52).

According to American Heart Association (2002), atherosclerosis is a disease of large and medium-sized arteries characterised by thickening and hardening of the vascular wall. It involves a substance called plaque in the inner lining of the arteries. Over time, this buildup grows large enough to narrow the artery and significantly decrease the blood flow through it. When atherosclerosis affects the arteries that supply blood to the heart, it ultimately restricts blood flow to the heart muscle, causing heart pain (angina), irregular heartbeat (arrhythmia) and other problems. The plaques may also become fragile and rupture. Rupturing plaques form blood clots (thrombus) that may block the blood flow through an artery or break off and travel to another part of the body (embolus). If either happens and occludes a blood vessel that feeds the heart (coronary artery), MI
ensues. When atherosclerosis affects the arteries that supply blood to the brain, the person may suffer stroke. And if blood supply to the arms or legs is reduced, it may cause difficulty in walking and eventually gangrene (53).

Morphological Features of Atherosclerosis

The Normal Artery (fig- 9)

The arteries of the body have 3 layers in their walls: the tunica intima, the tunica media, the tunica adventitia.

1. Tunica intima – This is the inner coat of the artery. It is composed of the lining endothelium, subendothelial connective tissue and bounded externally by internal elastic lamina

   ♦ The endothelium is a layer of flattened cells adjacent to the flowing blood. Narrow junctions exist between the adjoining endothelial cells through which certain materials pass. The integrity of the endothelial layer is of paramount importance in the maintenance of vascular functions since damage to it is the most important event in the initiation of thrombus formation at the site.

   ♦ The subendothelial tissue consists of loose meshwork of connective tissue that includes myointimal cells, collagen, proteoglycans, elastin and matrix glycoproteins.

   ♦ The internal elastic lamina is a layer of elastic fibers having minute fenestrations.

2. Tunica media – Tunica media is the middle coat of the arterial wall, bounded internally by internal elastic lamina, externally by external elastic lamina. The layer is the thickest and consists mainly of smooth muscle cells and elastic fibers. The external elastic lamina consisting of condensed elastic tissue is less well defined than the internal elastic lamina.

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3. Tunica adventitia – The outer coat of arteries is the tunica adventitia. It consists of loose mesh of connective tissue and some elastic fibers that merge with the adjacent tissues. This layer is rich in lymphatics and autonomic nerve fibers.

The layers of arterial wall receive nutrition and oxygen from 2 sources:

1. The tunica intima and inner third of the media and nourished by direct diffusion from the blood present in the lumen.

2. The outer two third of the media and the adventitia are supplied by vasa vasora, the nutrient vessels arising from the parent artery (54).
Figure 9 The transition from the normal artery wall to the nascent atherosclerotic lesion. The normal muscular artery has a trilaminar structure. A monolayer of endothelial cells overlies the intimal layer and abuts a basement membrane. In human arteries, the intima normally contains a few resident smooth muscle cells and a layer of extracellular matrix. The internal elastic lamina constitutes the boundary between the intimal layer and the tunica media, normally filled with quiescent smooth muscle cells embedded in an elastin-rich extracellular matrix. When molecules associated with risk factors stimulate oxidative or inflammatory stress, they induce the expression of adhesion molecules for leukocytes and chemoattractants that draw the bound leukocytes into the intimal layer. This diagram does not depict the adventitia, the outermost layer of the blood vessel.
Gross Morphology of atherosclerotic lesions

Early lesions in the form of diffuse intimal thickening, fatty streaks and gelatinous lesions are often the forerunners in the evolution of atherosclerotic lesions (fig 10-A). However, the clinical disease states due to luminal narrowing in atherosclerosis are caused by fully developed atheromatous plaques and complicated plaques (fig 10-B and C).

1. Fatty Streaks And Dots

Grossly, The lesions may appear as flat or slightly elevated and yellow. They may be either in the form of small, multiple dots, about 1mm in size, or in the form of elongated, beaded streaks.

Microscopically, fatty streaks lying under the endothelium are composed of closely- packed foam cells, lipid- containing elongated smooth muscle cells and a few lymphoid cells. Small amount of extracellular lipid, collagen and proteoglycans are also present.

2. Gelatinous Lesions

Gelatinous lesions develop in the intima of the aorta and other major arteries in the first few months of life. Like fatty streaks, they may also be precursors of plaques. They are round or oval, circumscribed grey elevations, about 1 cm in diameter.

3. Atheromatous Plaques

A fully developed atherosclerotic lesion is called atheromatous plaque, also called fibrous plaque, fibrofatty plaque or atheroma. Unlike fatty streaks, atheromatous plaques are selective in different geographic locations and races and are seen in advanced age. These lesions may develop from progression of early lesions of the atherosclerosis described above.
Fig No 10: Histological types of atheromatous plaques.

A, EARLY Lesion

B, FULLY-DEVELOPED Atheromatous Plaque

C, Complicated Plaque
4. Complications in Plaques

Various pathologic changes that occur in fully-developed atheromatous plaques are called the complicated lesions. These account for the most serious harmful effects of atherosclerosis and even death. These changes include calcification, thrombosis, haemorrhage and aneurysmal dilatation. It is not uncommon to see more than one form of complication in a plaque.

i) Calcification - Calcification occurs more commonly in advanced atheromatous plaques, especially in the aorta and coronaries. The diseased intima cracks like an egg-shell when the vessel is incised and opened.

ii) Ulceration - The layers covering the soft pultaceous material of an atheroma may ulcerate as a result of haemodynamic forces or mechanical trauma. This results in discharge of emboli composed of lipid material and debris into the blood stream, leaving a shallow, ragged ulcer with yellow lipid debris in the base of the ulcer. Occasionally, atheromatous plaque in a coronary artery may suddenly rupture into the arterial lumen forcibly and cause thromboembolic occlusion.

iii) Thrombosis - The ulcerated plaque and the areas of endothelial damage are vulnerable site for formation of superimposed thrombi. These thrombi may get dislodged to become emboli and lodge elsewhere in the circulation, or may get organized and incorporated into the arterial wall as mural thrombi. Mural thrombi may become occlusive thrombi which may subsequently recanalise.

iv) Haemorrhage - Intimal haemorrhage may occur in an atheromatous plaque either from the blood in the vascular lumen through an ulcerated plaque, or from rupture of thin-walled capillaries that vascularise the atheroma from adventitial vasa vasorum. Haemorrhage is particularly a common complication in coronary arteries. The haematoma formed at the site contains numerous haemosiderin-laden macrophages.

v) Aneurysm formation - Though atherosclerosis is primarily an intimal disease, advanced lesions are associated with secondary changes in the media and adventitia. The changes in media include atrophy and thinning of the media and
fragmentation of internal elastic lamina. The adventitia undergoes fibrosis and some inflammatory changes. These changes cause weakening in the arterial wall resulting in aneurismal dilation (54).

Based on progressive pathological changes and clinical correlation, American Heart Association (1995) has classified human atherosclerosis into 6 sequential types in ascending order of grades of lesions (55) as shown in (fig.11).
Fig No 11. Varying stages of Atherosclerosis

Coronary artery at lesion-prone location

Type II lesion

- Adaptive thickening (smooth muscle)
- Intima
- Media
- Macrophage foam cells

Type III (preatheroma)

- Small pools of extracellular lipid

Type IV (atheroma)

- Core of extracellular lipid

Type V (fibroatheroma)

- Fibrous thickening

Type VI (complicated lesion)

- Thrombus
- Fissure and hematoma
Atherosclerosis is an inflammatory disease

Although atherosclerosis was believed to be exclusively a cholesterol storage disease for over a century, we rather understand atherogenesis today as a chronic inflammatory response driven by, and probably initiated by, hypercholesterolemia (56,57). The most persuasive and clear-cut evidence that atherosclerosis is an inflammatory disease comes from the identification of immune activity involving T cells, macrophages, antibodies, and complement in the developing plaque, even in the very earliest fatty streak lesions. Monocytes and T cells, through immune responses and complex interactions with vascular elements, modulate the development of the lesion and its stability (58-60). Inflammation probably occurs as a response to hypercholesterolemia and accumulation of oxidized lipids in the arterial intima, leading to endothelial dysfunction and monocyte penetration into the subendothelial space. These initial events are followed by a broad array of complex inflammatory and immune reactions that lead to atherosclerotic plaque development (Figure 12). It is now widely accepted that inflammation links dyslipidemia to atheroma formation and plays a key role in all phases of the atherosclerotic disease process, from lesion initiation to progression and, ultimately to plaque rupture and the ensuing thrombotic complications of cardiovascular disease (CVD).
Figure 12. The oxidative modification hypothesis of atherosclerosis. According to this hypothesis, increased LDL levels and subsequent oxidation of these particles in the vessel wall represent the initial injury that accounts for endothelial activation and dysfunction, monocyte adhesion and recruitment, and foam cell formation. There follows a broad array of inflammatory and immune responses induced by oxLDL and/or its component oxidized lipids. Abbreviations: LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein–1; oxLDL, oxidized low-density lipoprotein; SMC, smooth muscle cell.
Hypothesis of Atherogenesis

Atherosclerotic disease arises as a consequence of the formation of fatty plaques in the arterial wall that, in the advanced stage, can obstruct the lumen of a vessel, resulting in acute ischemic syndromes, which include coronary artery, cerebrovascular, and peripheral vascular disease (61).

Considerable evidence suggests that the process of atherosclerotic plaque formation starts in infancy, progressing slowly until adult life when, after a long asymptomatic period, clinical manifestations of the disease can be verified (61,62).

As stated above, atherosclerosis is not caused by a single etiologic factor but is a multifactorial disease whose exact pathogenesis is still not known. A number of theories have been proposed since the times of Virchow (54).

♦ Insudation hypothesis – the concept hypothesized by Virchow in 1856 that atherosclerosis is a form of cellular proliferation of the intimal cells resulting from increased imbibing of lipids from the blood came to be called the ‘lipid theory’, currently known as ‘response to injury hypothesis’ and now a days the most widely accepted theory.

♦ Encrustation hypothesis – The proposal put forth by Rokitasky in 1852 that atheroma represented a form of encrustation on the arterial wall from the components in the blood forming thrombi composed of platelets, fibrin and leucocytes, was named as ‘encrustation theory’ or ‘thrombogenic theory’. Since currently it is believed that encrustation or thrombosis is not the sole factor in atherogenesis but the components of thrombus (platelets, fibrin and leucocytes) have a role in atheromatous lesions, this theory has now been incorporated into the foregoing recent theory of response to injury.

Thus, there is no consensus regarding the origin and progression of lesion of atherosclerosis. The role of four key factors- arterial smooth muscle cells, endothelial cells, blood monocytes and hyperlipidaemia, is accepted by all.
However, the areas of disagreement exist in the mechanism and sequence of events involving these factors in initiation, progression and complications of disease. Currently, pathogenesis of atherosclerosis is explained on the basis of the following two theories.


1. Reaction-To-Injury Hypothesis

This theory is most widely accepted and incorporates aspects of two older historical theories of atherosclerosis— the lipid theory of Virchow and thrombogenic theory of Rokitansky.

♦ The original response to injury theory was first described in 1973 according to which the initial event in atherogenesis was considered to be endothelial injury followed by smooth muscle cell proliferation so that the early lesion, according to this theory, consist of smooth muscle cells mainly.

♦ The modified response-to-injury hypothesis described subsequently in 1993 implicates lipoprotein entry into the intima as the initial event followed by lipid accumulation in the macrophages which according to modified theory, are believed to be the dominant cells in early lesions (54).

Both of these theories – original and modified, have attracted support and criticism. However, following is the generally accepted role of key components involved in atherogenesis, diagrammatically illustrated in (Fig-13).

Endothelial injury – Endothelial injury constitutes the initial event of the process of formation of the atherosclerotic plaque, and atherogenesis may be considered a protective inflammatory response to endothelial aggression (63).
As a result of endothelial injury, blood monocytes are chemotactically attracted to the arterial wall, entering the subendothelial space where, by means of complex processing, they are changed into macrophages. These cells incorporate large quantities of oxidized LDL particles, transforming them into foam cells, which constitute the first chemically and microscopically detectable lesion by lipid deposits in the artery intima. Subsequently, monocytes continue to migrate to the intima; smooth muscle cells also start to migrate from the middle layer; also to accumulate lipid droplets, acquiring the appearance of foam cells. Following side-by-side localization on the intima’s surface, these cells become macroscopically visible as yellowish fatty streaks (63,66).

As the process evolves, not all modified LDL particles are taken up by macrophages. Some remain partly deposited in the extracellular matrix as groups of fat droplets (66,67). This leads to a dense accumulation of lipids in the extracellular space, constituting the so-called lipid nuclei formed by the increase and confluence of small groups of extracellular lipids. This lesion, called an atheroma, leads to intensive disorganization of the intima and thickening of the arterial wall that can be seen with the naked eye undergoing fissures (68).

As the process evolves, formation of fibrous connective tissue sets in. When associated with a lipid nucleus, it constitutes a fibroatheroma, containing a lipid nucleus, a fibrous plaque covering and giving rise to a haematoma, haemorrhage, and thrombosis. This situation constitutes the major cause of morbidity and mortality secondary to atherosclerosis (68).
Fig No- 13 Reaction -To-Injury Hypothesis

A. ENDOTHELIAL INJURY

Blood vessel wall
Denuded endothelial lining
Subendothelial connective tissue

Media

Endothelial injury

B. PLATELET ADHESION AND MONOCYTE MIGRATION

Blood macrophage
Foam cell
Intimal smooth muscle cells
Platelets

Lipid droplets
Cholesterol clefts

Proliferated intimal smooth muscle cells

C. INTIMAL SMOOTH MUSCLE CELL PROLIFERATION

Foam cell
Diabetes Mellitus

Diabetes is a disease that affects the body's ability to control and utilize its supply of fuel. When glucose, the body's main fuel source, is not properly regulated, blood glucose levels rise. If high blood glucose levels are sustained over time, abnormalities in the structure of blood vessels and nerves can result. This leads to organ and tissue damage and can have serious consequences affecting the eyes, kidneys and nerves. Other pathological processes and additional risk factors are strongly related to the development of cardiovascular disease, which is the leading cause of death in people with diabetes.

Normal Glucose Metabolism

Glucose is made available to the body in two ways: (69) from food that has been ingested and (70) through the body's own production of glucose by the liver. Although some tissues and organs can derive energy from other sources, the brain and central nervous system rely almost entirely upon glucose. Because the brain cannot store or synthesize glucose, it depends on a continuous supply of glucose from the circulation and extracts its energy supply on a minute-by-minute basis.

Three organ systems are involved in the regulation and utilization of glucose by the body. They are the liver, the pancreas and the skeletal muscle tissue. The liver plays two roles in the regulation of blood glucose. One is the storage and release of glucose that has been ingested from the diet; the other is the synthesis of its own glucose supply (The process of glucose production by the liver is called gluconeogenesis). Normally, when blood glucose levels are low, the liver releases some of its stored or synthesized glucose and blood levels rise. Conversely, when blood glucose levels are high, the liver stops producing and releasing glucose and blood levels fall.

The pancreas supplies two hormones: insulin and glucagon. Both are necessary for glucose metabolism. Insulin allows glucose to enter the cells where it can be utilized for energy. Glucagon has an action opposite that of insulin. Its role is to maintain blood glucose levels between meals and during the fasting state.
When blood glucose levels are high, such as after eating, the secretion of glucagon by the pancreas is inhibited.

Muscle tissue is the third organ system involved in glucose metabolism. As the primary target organ for the action of insulin, the skeletal muscle tissue contains the majority of insulin receptor sites. When insulin binds with receptor sites on the skeletal muscle, the "doors are open" for the entry of glucose into the cell. When muscle tissue has fewer available receptor sites than are needed by the cells for glucose entry, a condition called insulin resistance occurs. Insulin resistance plays a major role in the development of type 2 diabetes.

**Classification of Diabetes**

In recent years, the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus adopted some changes in the way that diabetes is classified. Previously, the two major types of diabetes had been known as insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The Expert Committee has eliminated these terms and replaced them with "type 1" and "type 2" diabetes, respectively. This change was made because it was felt that the newer system reflects the disease state based upon its cause rather than its treatment. Furthermore, Arabic numerals are now used to differentiate the two major types of diabetes (1 & 2), replacing the use of Roman numerals (I & II). The rationale for this is to avoid confusion between the Roman numeral II and the Arabic number 11.

Another change in the classification of diabetes is related to the use of the terms "adult onset" and "juvenile onset." Specifying the disease by age of onset is no longer accurate, since we are now finding that children can develop what was once known as "adult onset" diabetes. While the exact prevalence of type 2 diabetes in children is unknown, several studies have indicated that there has been a significant increase in recent years (71).
Pre-Diabetes

Blood glucose levels higher than normal, but not high enough to be diagnosed as type 2 diabetes, are generally defined as pre-diabetes. Pre-diabetes patients are diagnosed based on impaired fasting glucose (100-125 mg/dl) and/or impaired glucose tolerance (140-199 mg/dl), both of which are risk factors for developing diabetes and cardiovascular disease. According to the ADA, 41 million people in the United States between 40 and 75 years of age have pre-diabetes. Identifying patients with pre-diabetes is vital to delaying or preventing the onset of type 2 diabetes. The ADA recommends screening for pre-diabetes every three years in individuals more than 45 years of age, especially in those whose body mass index is greater than 24. Additionally, screening is recommended for any overweight individuals if they have risk factors for developing diabetes (72).

Type 1 Diabetes

Formerly known as "juvenile onset" diabetes, this type usually has its onset in people under the age of thirty. It is most often seen in people with a lean body type, although it can occur in people who are overweight. Type 1 diabetes results when the person's pancreas cannot produce any of its own insulin for use by the body. If the person with type 1 diabetes does not receive insulin from an outside source (such as injections), he or she is likely to develop a life-threatening condition known as ketoacidosis. In type 1 diabetes, the person will always require insulin from an outside source to stay alive.

Type 2 Diabetes

This type of diabetes has also been called "adult onset" or "maturity onset" diabetes. It is by far the most common type of diabetes, accounting for 90% to 95% of cases (73). Type 2 diabetes usually begins in people over the age of 30 and most commonly occurs in people over the age of 55. It is more likely to occur in those who are overweight. In the person with type 2 diabetes, the pancreas is able to produce at least some of its own insulin for use by the body. However, the insulin that is produced is either insufficient for the needs of the body or poorly utilized by the tissues. The need for an outside insulin source is variable in people with type 2
diabetes. Individual cases of type 2 diabetes may be treated with diet therapy, oral medications, insulin or any combination of these. The person with type 2 diabetes usually has a pancreas that is able to produce enough of its own insulin so that ketoacidosis is not likely to occur. However, they may require insulin injections to keep blood glucose levels under control for the prevention of other acute and chronic complications.

**Gestational Diabetes**

Gestational diabetes refers to the disease that develops during pregnancy and complicates about 7% of pregnancies. It is detected between 24 and 28 weeks gestation, usually following a glucose tolerance test. Women with gestational diabetes are at higher risk for hypertensive disorders and cesarean delivery. Neonatal complications of gestational diabetes may include large body size (macrosomia), hypoglycemia, hypocalcemia, polycythemia and hyperbilirubinemia (74). Although most women with gestational diabetes will have normal glucose levels within six weeks postpartum, more than half will have developed type 2 diabetes fifteen years after the pregnancy. Therefore, regular blood glucose testing is recommended for these women. Maintenance of a healthy body weight and regular physical activity may help prevent the onset of type 2 diabetes in this population (75). It is recommended that all pregnant women who have at least one risk factor for gestational diabetes be screened between the 24th and 28th weeks of pregnancy. Risk factors include age over 25 years, overweight before pregnancy, family history of diabetes, history of abnormal glucose tolerance, history of obstetrical complications and membership of a high-prevalence ethnic group (74).

Treatment of gestational diabetes includes close surveillance of mother and fetus due to the increased risks inherent in this type of pregnancy. Maternal fasting and postprandial blood glucose levels are usually checked several times a day. Nutritional management is considered the first-line therapy. If dietary management alone does not achieve fasting plasma glucose levels of 105 mg/dl or below, insulin therapy is usually indicated. Oral diabetic agents are not recommended in
pregnancy. There are no contraindications to breastfeeding in women who have had gestational diabetes.

Secondary Diabetes

Secondary diabetes occurs in some people due to a variety of medical conditions. These include diseases and tumours that affect the liver or pancreas. Secondary diabetes may also occur in susceptible people who take medications that can impair glucose metabolism. Commonly used medications that can induce diabetes in some people include corticosteroids (Prednisone), thyroid preparations, thiazide diuretics (HCTZ, Dyazide) and phenytoin (Dilantin), among others. Secondary diabetes usually resolves when the underlying cause is eliminated.

The patient with secondary diabetes should receive education in the treatment of the primary condition as well as the diabetes. Focus upon the primary condition by the patient and healthcare providers may fragment diabetes education. Although secondary diabetes is generally expected to resolve, the patient will always be at risk for recurrence (76).

Diabetes mellitus is far more powerful risk factor for women than for men. In women, the condition triples the incidence of CHD and multiplies ten-fold the incidence of myocardial infarctions. Mortality rates for CHD in diabetic women are three-to-seven folds higher than nondiabetic women. This is in comparison to two-to-four fold increase in male diabetics over male non-diabetics (77).

Diabetes mellitus is associated with a more adverse prognosis both during the hospitalization and on long-term following myocardial infarction (MI) for women than for men. In women with MI, DM doubles the risk of recurrent MI and quadruples the risk of heart failure. Furthermore, the higher prevalence of diabetes in women both at coronary artery bypass grafting surgery and at percutaneous transluminal coronary angioplasty may be an important contributor to the excess mortality associated with myocardial revascularization procedures in women. Although the mechanisms remain uncertain, the greater prevalence of hypertension, lipid abnormalities, and possibly fibrinogen abnormalities may be operative. It not only exacerbates the effects of other risk factors but also impairs
estrogen binding, thus negating the protective effects of estrogen on pre­
menopausal women (78). Non insulin dependent DM is associated with obesity,
abdominal and upper body fat distribution and insulin resistance, all of which have
been associated with higher CHD risk. More so than in men, obesity and upper
body fat distribution appear to be independent CHD risk factors in women.
Coronary Artery Disease And Diabetes

Cardiovascular complications are known to be the leading cause of death and morbidity in diabetic patients.

A direct association between diabetes and heart failure was first demonstrated in the Framingham Study, which showed that the risk of developing symptomatic heart failure was increased 2.4-fold in diabetic men and five-fold in diabetic women when compared with matched controls, independent of coexisting hypertension or ischemic heart disease (79). Diabetes mellitus was particularly prevalent among younger heart failure patients, with a four fold and eight fold increased risk of developing heart failure in diabetic men and women under 65 years old, respectively (80).

Diabetes has been well established as an independent risk factor for the development of coronary artery disease. Even in its asymptomatic form, coronary artery disease is still believed to be more common and often more extensive in diabetic patients. In the 7-year follow-up of the san Antonio Heart study, patients with diabetes with no history of coronary artery diseases were found to have as high a risk of acute myocardial infarction as those with a prior history of myocardial infarction (20.2 %versus 18.8%, respectively) (81). It is also well recognized that diabetic patients are more prone to silent myocardial infarctions (up to 30% of cases) presumably caused by alterations in pain perception from autonomic neuropathy. These observations have led to a casual association between myocardial ischemia and diabetic heart failure, with complications of ischemic heart disease being the primary reason for the increased risks in morbidity and mortality seen in diabetic heart failure (82). In the Framingham study, when only those patients who survived prior myocardial infarction were examined, diabetic women had a relative risk for heart failure three times greater than that of nondiabetic women (83). In the setting of an acute myocardial infarction, a clinical history of heart failure as well as the development of new-onset heart failure are more prevalent in the diabetic than in the nondiabetic population (84,85). Heart failure may occur in up to 50% of all diabetic patients.
who suffer myocardial infarction (86). These observations have been validated in large-scale clinical trials such as the Global Utilization of streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO - 1) trial, in which postinfarction heart failure was found to develop almost twice as frequently in the diabetic population (27% in the diabetic group requiring insulin therapy versus 20% in the diabetic group with no insulin versus 15% in the nondiabetic group) (87). The GUSTO - 2b trial also showed diabetics to be at increased risk of developing heart failure following an acute coronary syndrome (7.2% versus 3.8% in diabetic and nondiabetic patients, respectively) (88).

Although coronary artery disease may contribute to the development of heart failure in a proportion of diabetic patients, some patients do not have obvious ischemic insults that lead to progressive heart failure. In the clinical setting, every 1% increase in the baseline glycosylated haemoglobin level translates into a 15% increase in risk of developing heart failure (84).

Algorithm for management of diabetes in presence of coronary heart disease has not changed much. Diet, exercise, oral hypoglycaemia agents and insulin have remained the cornerstone of therapy. However, the paradigm has shifted from mere control of hyperglycemia to correction of a host of associated metabolic and haematologic abnormalities. (Table. 3 and 4). This approach only could mitigate the devastating consequences of the lethal combination of diabetes and coronary artery disease. Appreciating its importance, American Heart Association, in its scientific statement has pronounced diabetes a cardiovascular disease (89).

Over the last couple of decades we have understood better the natural history of type-1 and type-2 diabetes, as well as the pathogenetic mechanism involved in development of both macrovascular and microvascular complications. This has given us insight into developing therapeutic strategies which target key issues in the pathogenesis of diabetes and its complications.

While type-1 diabetes is the result of absolute deficiency of insulin secretion from Pancreatic B cell, type-2 diabetes can be viewed as the end product of years of metabolic stress accompanying a state of insulin resistance. Insulin
resistance develops on a substrate of genetic susceptibility and is augmented by obesity and physical inactivity. Consequent B cell exhaustion leads to defective and diminished insulin secretion heralding the clinical onset of hyperglycaemia. (90,91)

Table 3: Metabolic abnormalities associated with diabetes mellitus
- Hypertension
- Increased LDL (small dense)
- Increased TG and VLDL
- Decreased HDL
- Increased FFA
- Increased Uric acid
- Microalbuminuria

Table 4: Haematologic abnormalities associated with diabetes mellitus
- Increased Platelet aggregability
- Increased Fibrinogen
- Increased PAI-1

Type 2 diabetes, an inflammatory cardiovascular disorder

In the last 50 years, health care systems throughout the world have faced a new epidemic dual disease: CVD-diabetes mellitus, which results in a large economic burden and a devastating toll of human suffering. CVD is the leading cause of death in diabetic patients and is responsible for much of morbidity-related to diabetes. As the number of adults with diabetes is increasing dramatically worldwide, development of new strategies for preventing diabetic cardiovascular complications undoubtedly represents a major challenge. The striking association between CVD and diabetes since the publication of the first large-scale epidemiologic investigation in the 1970s, has forced physicians to investigate the pathophysiological connection among these clinical conditions. Recent and compelling evidence has shown the significant and independent role of inflammation and insulin resistance in the development of both CVD and type 2
diabetes (92-94). These observations and the recognition that both atherosclerosis and type 2 diabetes share a common inflammatory basis have fueled the speculation that these two conditions might result from a shared antecedent, the so-called “common soil” hypothesis, and that chronic inflammation may represent a candidate mechanism linking type 2 diabetes and CVD (Fig No-14).

Inflammation: the widening interface between atherosclerosis and diabetes

![Diagram of proposed connections between lifestyle/genetic factors, insulin resistance, type 2 diabetes, inflammation, and atherosclerosis. Abbreviations: AGE, advanced glycation end-product; oxLDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1.]

As discussed above, atherosclerosis is an immunemediated inflammatory disease in which the secretion of multiple factors by infiltrating mononuclear cells plays a key role. Major mediators of this inflammatory response include the T helper type 1 proinflammatory cytokines and the IκB/nuclear factor-κB (NF-κB) system. Perhaps one of the most compelling aspects of basic science research into the inflammatory mechanisms involved in atherogenesis has been its headfirst collision with evidence from epidemiological trials showing the predictive value of circulating inflammatory markers on the development of CVD (95,96).
While the idea that insulin resistance and impaired insulin secretion are central to the pathogenesis of type 2 diabetes is not new, the notion that inflammation might be an accomplice in the pathogenesis of type 2 diabetes has been developed only recently (93,97). Since this hypothesis was first proposed in 1997 and 1998 (98,99) at least 12 studies have shown that circulating markers of inflammation predict the development of type 2 diabetes and that an ongoing cytokine-induced acute phase response is present in patients with diabetes and in those at risk for developing diabetes. The evidence implicating inflammation as a contributor to both atherosclerosis and type 2 diabetes carries embedded within it the prospect that inflammation may represent the common antecedent of both type 2 diabetes and atherosclerosis and thus a therapeutic target for these diseases. Recent reports of reductions in the incidence of type 2 diabetes accompanying pharmacological interventions for coronary heart disease prevention and the realization that several drugs with anti-inflammatory properties lower both acute phase reactants and glycemia (100-102) and possibly decrease the risk of developing type 2 diabetes, (103) offer support for this possibility.
Lipids, Lipoproteins And CAD

Plasma lipids and lipoproteins have been reported to be closely related to the development of coronary atherosclerosis. Plasma lipids are carried in the lipoproteins, each of which has a different effect on atherosclerosis. Therefore, the levels of individual lipoproteins are better predictors of coronary artery disease than those of plasma lipids (104).

The plasma lipoproteins are molecular complexes of lipids and specific proteins called apolipoproteins. These dynamic particles are in a constant state of synthesis, degradation, and removal from the plasma. Plasma lipoproteins are usually divided into five classes. Chylomicrons, very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low density lipoprotein (LDL) and high-density lipoprotein (HDL). Recent studies emphasize that the concentrations of LDL correlate positively and HDL correlate negatively with CAD (104).

Lipoproteins function both to keep lipids soluble as they transport them in the plasma, and to provide an efficient mechanism for delivering their lipid contents to the tissues. In humans, the delivery system is less perfect than in other animals, and as a result, humans experience a gradual deposition of lipid—especially cholesterol in tissues. This is a potentially life-threatening occurrence when the lipid deposition contributes to plaque formation, causing the narrowing of blood vessels—a condition known as atherosclerosis.

The principal lipids carried by lipoprotein particles are triacylglycerols and cholesterol, obtained either from the diet or de novo synthesis. Lipoproteins are composed of a neutral lipid core (containing triacylglycerol or cholesteryl esters or both) surrounded by a shell of apolipoproteins, phospholipid, and nonesterified cholesterol all oriented so that their polar portions are exposed on the surface of the lipoprotein, thus making the particle soluble in aqueous solution. The composition of the plasma lipoproteins is depicted in (fig-15) (105).
A relation between the concentration of components of plasma lipoproteins and the risk of coronary heart disease is well established (106).

Various plasma lipoprotein variables have been correlated with prevalence and incidence of clinical coronary artery disease, as also with its severity. The presence of a plasma lipoprotein, migrating as a distinct pre-beta band has been reported to be associated with CAD (107).

Inderjit S. Thind et al. found a strong positive correlation of total triglycerides and HDL triglycerides with acute myocardial infarction (AMI). However they showed lack of association of HDL cholesterol with MI in their study, which casts doubt on the prognostic significance of such a determination in CAD. They further indicated that single HDL cholesterol determinations can have little meaningful influence on the management of CAD. However, the percentages of high-density components of total cholesterol or triglycerides have significant correlations with M.I. (108).

Hamsten A et al, (1986) investigated the relationship of serum lipoprotein and apolipoprotein concentrations in angiographically determined CAD patients. The levels of LDL cholesterol and apolipoprotein B showed strong relationships to the extent and severity of coronary atheromatosis but not to the number and severity of distinct coronary stenoses. HDL cholesterol concentration correlated inversely with the coronary (109) atheromatosis score, whereas other variables reflecting HDL concentration and composition or VLDL lipids were not independently related to any of the coronary scores. The LDL triglyceride level, and index of IDL accumulation, was significantly correlated to the coronary atheromatosis score. Non-lipid risk factors were correlated neither to coronary atheromatosis nor to severity of stenoses.

Matti Nikkila et al., (1990) observed that the ratio of HDL cholesterol to total cholesterol was significantly lower in persons with single, double, and triple vessel disease than in persons without disease. Similar proportion of patients with CAD and without had serum cholesterol concentrations of $\geq 6.5$ mmol/l, but total cholesterol was significantly higher in patients with CAD (110).
Fig No-15 Composition of the plasma lipoproteins

- **Chylomicron**
- **Very-Low-Density Lipoprotein (VLDL)**
- **Low-Density Lipoprotein (LDL)**
- **High-Density Lipoprotein (HDL)**

- Triacylglycerol
- Cholesterol & Cholesteryl esters.
- Phospholipids
- Protein
N.R. Philips et al., (1993) reported that increased levels of remnant VLDL and IDL particles and decreased levels of HDL promote lesion progression, which in turn, may lead to an untoward clinical event or to a critical disease in myocardial perfusion calling for a revascularization procedure (111).

V.K. Bahl et al., (1995) showed no significant correlation of the plasma levels of total cholesterol, HDL, LDL, and VLDL cholesterol and triglycerides with the extent of CAD in terms of vessels significantly diseased on angiography. However, they noted higher values of lipoprotein(a) in patients with more extensive CAD (107).

Joya Ghosh et al., (2006) in their study reported that the mean total and LDL, VLDL cholesterol levels in coronary artery disease patients were found to be significantly higher. The mean HDL cholesterol was significantly low in CAD cases as compared to control group. Ratio of total cholesterol to HDL cholesterol and LDL to HDL cholesterol was very significantly raised in CAD (112).
Lipoprotein (a)

Chemical Structure-

Lipoprotein (a) was discovered in 1963 by Berg (113) and consists of two major components; an LDL particle containing the apoprotein B-100 molecule and an apoprotein(a) (apo-a) molecule linked by a single disulfide bond (114). Apo(a) is a large protein with an amino acid sequence similar to that of plasminogen. Both the apo(a) and plasminogen genes consist of specific coding sequences for loop structures stabilized by intrachain disulfide bonds, referred to as kringle domains. Five different Kringle domains (K1 to K5) are found in the plasminogen gene, and only K4 and K5 are present in apo(a) gene. The K4 sequence is repeated many fold in apo(a) gene(114,115). The multiple copies are similar but not identical to each other (116) (Fig. 17). This variation of apo(a) gene size leads to the heterogeneity of apo(a) protein size that also impacts on plasma Lp(a) level (117,118). In general, it is widely believed that smaller apo(a) sizes leads to higher plasma Lp(a) levels, although the relationship is complex (119,120).

Lp(a) is synthesized in the liver, and its molecular weight varies from 400 to 700 KDa. Although the plasma LDL concentration is primarily determined by the rate of removal, the Lp(a) level is controlled by the rate of synthesis at the level of the gene that encodes apo(a) (121).

Lipoprotein (a) is a cholesterol ester rich lipoprotein that is composed of low density lipoprotein (LDL) and a highly polymorph glycoprotein, apolipoprotein (a), which has a close homology with plasminogen. Due to its LDL like properties, it accumulates in the atrial valve leading to atherosclerosis. It has been shown to stimulate the secretion of plasminogen activator inhibitor and interfere with fibrinolysis. Lp(a) has both atherogenic as well as thrombogenic properties (7).
Fig. No-16 Chemical Structure of Lipoprotein (a)

Lipoprotein (a)
Lipoprotein (a) and Atherosclerosis

When present at low levels, Lp(a) may serve a protective function by binding and possibly degrading oxidized phospholipids formed during normal homeostasis or in acutely stressful situations (122). Lp(a) has also been shown to be involved in wound healing (123), and elevated levels have been noted in centenarians (124). When levels are chronically elevated, Lp(a) may be proatherogenic particularly because it has enhanced binding to the extracellular matrix of the artery wall (125). The close homology between Lp(a) and plasminogen has raised the possibility that it may inhibit endogenous fibrinolysis by competing with plasminogen binding on the endothelium. Lp(a) may bind and inactivate tissue factor pathway inhibitor and may upregulate the expression of plasminogen activator inhibitor (126, 127).

Acute myocardial infarction is the most important consequence of coronary artery disease. Although traditional risk factors of MI are helpful in diagnosis, specific clinical markers would be valuable in identifying the persons who are at risk. In the past few decades, much attention has been focused on serum Lp(a) and other lipids mainly because of their strong association with coronary artery disease (128).

Lp(a) is a complex lipoprotein consisting of a central core of LDL, covalently linked by a single disulphide bond to a polypeptide chain of apolipoprotein (a). The structural gene for apo(a) is located on chromosome six (128). The study carried out by Califf et al. was designed to verify whether there is increase in the concentration of Lp(a) and other lipids in young South Indian MI patients, without having any traditional risk factors except for positive family history and to compare the results with that of age matched healthy controls (128).

Lp(a) has now been recognized as an independent risk factor for CAD in many retrospective case control studies, and in some prospective studies in the western population (7). Many studies have shown a direct relationship between Lp(a) and coronary heart disease (128). These studies have shown that Lp(a) levels above 30 mg/ dl form a threshold above which the risk of premature CAD
increases rapidly (7). Lipoprotein (a) is fully expressed in the first year of life and its high level has almost the same predictive value as a family history of premature CAD (7).

The Coronary Artery Disease in Indians (CADI) study first reported the existence of increased Lp(a) levels in Asian Indians (Asian Indians refers to ‘South Asians’ residing outside India). Studies among Indians have also shown significant higher Lp(a) levels in patients with CAD (7).

Most studies have been carried out in patients of all groups with concomitant risk factors. R.K.Khullar (7) carried out a study to assess the Lp(a), lipid levels and coronary angiographic profile in young Indians (less than 40 years of age) with myocardial infarction (MI). Their results suggested a strong association of high Lp(a), HDL cholesterol, high TG with premature CAD in Indians.

Numerous studies carried out in several countries over the past 25 years have suggested that Lp(a) could be an independent risk factor for premature coronary artery disease (CAD). Six prospective studies concluded that Lp(a) is a risk factor for CAD but three other case – control studies did not arrive at this conclusion (129).

Geethanjali et al noticed that the levels of Lp (a) have a wide scatter and a definite cut-off level could not be established. Hence they carried out study in a large number of patients and studied the relationship of serum Lp(a) levels with their phenotypes (129).

Lipoprotein (a) is a complex lipoprotein (Lp) macromolecule that contains apolipoprotein (a), which shares 80% to 90% homology with plasminogen. It acts as a competitive inhibitor of tissue type plasminogen activator and thereby helps in modulating the fibrinolytic system. Moreover Lp(a) is an important regulator of synthesis of plasminogen activator inhibitor (PAI – 1) by endothelium. All these lead to a prothombotic state (130).
Since the role of serum lipoprotein (a) [Lp(a)] levels in the pathogenesis of coronary artery disease (CAD) was first described in 1963(131), the plasma Lp(a) levels have been implicated as a major independent risk factor for premature CAD and restenosis of coronary lesions, in various ethnic populations. The Lp(a) levels are highly vary over a 1000 - fold range among individuals in a population (132) but remain remarkably constant in an individual over time. In Caucasians and Chinese, the distribution of Lp(a) is highly skewed towards lower levels (133) whereas in Africans and African Americans, the curve of Lp(a) levels has a more Gaussian distribution. (131 -135) African Americans have 2 – 3 fold higher Lp(a) levels than either Caucasians or Chinese. The apo(a) gene was implicated as a major determinant of Lp(a) levels when it was noted that the apo(a) glycoprotein varied in size over a wide range and that its size tended to be inversely related to plasma concentration of Lp(a) (136).

Since upto 90 percent of the variance in Lp(a) levels has been attributed to the apo(a) gene locus, there is hypothesis that polymorphism of the apo(a) gene other than size could contribute to the increase of Lp(a) level in CAD patients. Several types of polymorphisms, size as well as sequence changes in the apo(a) gene have been reported to influence the variability of plasma Lp(a) concentration(136).

Since most of the studies have been carried out in patients of all age groups with concomitant risk factors, the significance of elevated Lp(a) levels in young patients with premature CAD remains unaddressed. The present study was carried out to assess the Lp(a) levels and its role as a risk factor in patients of angiographically – proven CAD below 40 years of age (137).
**Fibrinogen**

**Chemical Structure**

Fibrinogen is a large (340-KDa) glycoprotein synthesized in the liver and is composed of two identical subunits linked through a disulfide bond. Each of the subunits consists of three polypeptide chains (Aα, Bβ, and γ) encoded by three separate genes on the long arm of chromosome 4 (138). The final step in the coagulation cascade, the conversion of soluble fibrinogen into insoluble fibrin polymer, is mediated by thrombin, which cleaves fibrinopeptide A from the Aα chain and fibrinopeptide B from the Bβ chain. The proteolytic fragments of fibrinogen have several other functions, including stimulating hematopoiesis, promoting smooth muscle proliferation, and having a possible role in controlling bacterial infection. Elevated fibrinogen concentrations occur as a consequence of increased hepatic production or reduced clearance from the circulation (139) (Fig 17)

Fig 17: Chemical Structure of Fibrinogen

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**Human fibrinogen**

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Fibrinogen And Atherosclerosis

Plasma fibrinogen regulates cell adhesion, chemotaxis, and proliferation, influence platelet aggregation and blood viscosity, interact with plasminogen binding, and, in combination with thrombin, mediates the final step in clot formation and the response to vascular injury (140-142). Recent data also suggest that the association of fibrinogen with CAD may relate to its role in inflammation(143).

Fibrinogen, also called Factor I, is a blood plasma protein produced by the liver that plays an important role in blood coagulation. Blood coagulation is a process in which several components of the blood form a clot. When blood escapes from a rupture in a blood vessel, coagulation is triggered. Several proteins, called coagulation factors, go into action to produce thrombin. The thrombin then converts fibrinogen to fibrin. Fibrin produced from fibrinogen is the main protein in a blood clot (144).

It surrounds the cells in the blood and plasma and helps form the clot. The resulting clot, which is stabilized by Factor XIII, remains intact from 10 to 14 days, the time required for healing to take place. When there is a problem with fibrinogen, i.e., either it is missing or it does not function properly, the clot has difficulty in forming. This can result in hemorrhaging or thrombosis (144).

The normal value of fibrinogen in the blood is from 2 to 4 g / l (grams / liter). The amount of fibrinogen in blood can be measured from a blood sample.

Acute coronary syndromes - unstable angina and acute myocardial infarction represent unstable phase in the spectrum of ischaemic heart disease. The occasional observation of red streaks along the course of main coronary trunks at the time of bypass surgery and the observation of inflammation contributed to the syndrome by stimulating or enhancing local haemostatic and vasoconstrictor responses (145-148).
A growing body of evidence indicates that plaque inflammation may play a key role in the pathogenesis of acute coronary syndromes (149,150). The assessment of the inflammatory response may improve the prognostic stratification of patients with acute coronary syndromes (151,154). In addition to fibrinogen and C-reactive protein (CRP), serum levels of amyloid A protein, tumour necrosis factor and interleukin have also been found to be raised in patients with unstable angina (154). The easily measurable systemic markers of inflammation such as blood levels of serum fibrinogen and CRP reflect the intensity of inflammatory cell activation in the culprit stenosis, resulting in thrombosis, plaque fissure and smooth muscle hyperreactivity. The levels of these markers therefore also predict the consequent clinical events and the prognosis (151-155).

Fibrinogen is a protein that plays a key role in blood clotting. Fibrinogen is a sticky, fibrous coagulant in the blood that appears to significantly increase the risk of experiencing one of the leading causes of death and disability - stroke. Analysis of the large-scale Eurostroke project (156) showed that "fibrinogen is a powerful predictor of stroke" - including fatal and nonfatal strokes, first time strokes, and hemorrhagic and ischemic strokes. Dividing the population into four groups (quartiles) based on their fibrinogen levels, researchers estimated that the risk of stroke increased by nearly 50% for each ascending quartile. Individuals whose fibrinogen levels were in the highest quartile were almost seven times more likely to suffer a hemorrhagic stroke, and more than twice as likely to die from a stroke.

Importantly, higher levels of fibrinogen raised the risk of stroke independently of cardiovascular risk factors such as smoking and hypertension. Still, high blood pressure and high fibrinogen levels appeared to be the most dangerous combination, elevating a person's risk of stroke even more. Each year, strokes account for about 1 of every 15 deaths in the United States. More than one-fourth of the people who suffer a stroke are under age 65.

A recent study measured baseline fibrinogen levels in over 2000 men and women being treated at a preventive cardiology unit of a large city hospital. About half of the patients had coronary artery disease (CAD). Acevedo M et al (157)
found that patients with CAD tended to have higher fibrinogen levels than those without the disease. Of the patients whose fibrinogen levels fell within the two highest quartiles (>331 mg/dl), about 75% of men and 50% of women were diagnosed with clinical CAD. A previous history of heart attack in the group with CAD was also associated with significantly higher average levels of fibrinogen.

These results show that patients with CAD, particularly those who have experienced a heart attack, often have higher fibrinogen levels. But are elevations of this marker merely an after-effect of the disease? To find out, investigators further tracked the health of the patients for an average of 24 months after their treatment at the cardiac care unit. They discovered fibrinogen was a strong and significant independent predictor of death from all causes in both men and women. The percent mortality rate jumped by over seven-fold in those with the highest fibrinogen levels, compared to those with the lowest levels.

Fibrinogen's association with increased mortality is probably directly related to its ability to promote thrombosis, or clots, by causing platelets to clump inside blood vessels. This is one of the main mechanisms underlying ischemia and heart attack. Exercise, quitting smoking, and certain medications have been shown to lower fibrinogen in the short term.

A number of studies show elevated fibrinogen to be a major risk factor for coronary heart disease (heart attacks) and cerebrovascular disease (strokes), which together account for about 60% of deaths in the elderly. In fact, fibrinogen may possibly be the major risk factor, exceeding the "contributions" of homocysteine, cholesterol and other lipids in the pathogenesis of these diseases. Elevated fibrinogen levels have also been associated with a number of other diseases, including cancer, diabetes and hypertension (158).

SG Thomson, et al prospectively studied over 3,000 patients with angina pectoris (chest pain due to coronary artery insufficiency) (159) and found if fibrinogen levels were low, even highly elevated levels of cholesterol and/or C-reactive protein presented little risk of heart attacks. However, high levels of
fibrinogen in combination with low-moderate levels of cholesterol presented a significant risk.

Fibrinogen levels have been shown by a number of research teams to rise about 25 mg/dl per decade of age (160). Even if they are described as being in good health. A team of scientists in China also recently compared fibrinogen levels in two families, one family with a history of long life in many of its members, compared to another family with traditionally shorter life expectancies. The scientists concluded that low plasma fibrinogen levels are correlated with longer life (161).

No drug (with the possible exception of estrogen) or lifestyle change is known to significantly alter fibrinogen levels, although quitting smoking does result in slight reductions in fibrinogen levels. However, for those of us who don't smoke, there has been little, if any, advice which could be given to lower fibrinogen from the conventional medical approach. Nutritional supplements can reduce fibrinogen levels and presumably the inherent risk of hyper-fibrinogenemia-related diseases.
Calcium

Hypertension is an asymptomatic and important disease of modern civilized life. The overall prevalence of hypertension has been reported to range from 6-32% (162).

Essential hypertension is associated with disturbed calcium metabolism. The calcium ion plays a major role as an intracellular second messenger in excitation contraction coupling in cardiac and smooth muscle cells. An increase in peripheral vascular resistance was a uniform finding in all types of established hypertension. The free intracellular calcium concentration determines the tension in vascular smooth muscle cells thereby resulting in peripheral vascular resistance. An increased calciuria could be a feature of the essential hypertensive patients (163).

Abnormalities of calcium metabolism have been described in patients with essential hypertension. Zidek et al. (164) found an increased intracellular calcium activity in normotensive subjects with a familial hypertensive disposition in comparison with normotensives without family history of hypertension. Touyz et al. (165) showed significantly increased intracellular calcium levels in essential hypertensives. Some authors (166,167) have reported lower concentrations of serum calcium in the hypertensives than in normotensive subjects. In these investigations, serum calcium levels were studied in essential hypertensive and their first-degree relatives.

Since their introduction, calcium antagonists have been widely used for various cardiovascular diseases, particularly angina pectoris, arrhythmias and hypertension. Their beneficial effects are related to systemic vasodilation, caused by inward flow of calcium ions through the different calcium channels.

At present, several trials have proven that calcium antagonists reduce the risk of strokes, coronary artery disease, dementia and major fatal and non-fatal cardiovascular events. In spite of the abundant evidence already available, several questions remain unanswered and are being addressed by ongoing or planned trials. Some studies are being conducted to know whether specific calcium
antagonists, over and above their blood pressure lowering effects, might exert a beneficial effect in specific subgroups of hypertensive patients (168).

Diabetic subjects experience a disproportionately large number of coronary heart disease events. Although microvascular complications adversely affect quality of life, macrovascular complications are responsible for most cases of death and disability associated with diabetes. In particular, myocardial infarction, stroke, and sudden coronary death are of great importance (162-171). Standard coronary risk factors appear to carry greater significance in those with diabetes (172,173) but risk stratification using other risk factors does not explain their excess risk.

Pathologic studies have demonstrated a strong correlation between the presence of coronary calcium and the amount of atheromatous plaque (174,175). Furthermore, computed tomography (CT) calcium scanning has been shown to predict subsequent coronary events (175-178). However, few studies have examined the predictive accuracy of calcium measurement in diabetes.

The South Bay Heart Watch (SBHW) is a prospective cohort study designed to determine the relation between radiographically detectable coronary calcium and coronary outcomes in high-risk adults. This is a report of data obtained from the SBHW cohort to determine whether CT coronary calcium assessment is useful for prospectively discriminating diabetic subjects destined to suffer a coronary event.

Calcification is closely associated with atheromatous plaque, and is a recognized marker for coronary artery disease (179). Until recently, it was believed that calcium present in the atheromatous plaques is in the form of calcium phosphate, precipitated in a passive manner. However, recent findings indicate that calcification is an active process and calcium is deposited as hydroxyapatite, similar to that in active bone formation (180). It is known that the amount of calcium in the coronary arteries is better correlated with the amount of atherosclerosis in different individuals and, to a lesser extent, with the segments of the coronary tree in the same individual. There are numerous articles on the
correlation of coronary calcium with angiographically proven coronary artery disease; however, there are no such large studies from India.

Significant associations between serum calcium and blood pressure have been demonstrated in several studies, and it has been hypothesized that serum calcium could play a major role in the development of hypertension. Associations have also been found between serum lipid levels and blood pressure. However, little is known about any possible association between serum lipids and serum calcium. In the report from the University of Ghent, Belgium, the researchers used data from a large nutrition survey to investigate the relationship between serum calcium and serum lipids in men and women.
C - Reactive Protein

Chemical Structure –

C – reactive protein (CRP) was first detected in 1930 by Tillet and Frances, who identified a substance in the sera of patients acutely infected with pneumococcal pneumonia that formed a precipitate when combined with polysaccharide C of Streptococcus Pneumoniae (181). It was found subsequently that this reaction was not unique to pneumococcal pneumonia but could be observed with a large variety of other acute infections and inflammatory states.

CRP is a calcium-binding pentameric protein consisting of five identical, noncovalently linked, 23-KDa subunits (182). It is present in trace amounts in humans and appears to have been highly conserved over hundreds of millions of years (183). CRP is synthesized primarily by hepatocytes in response to activation of several cytokines, such as interleukins 1 and 6, and tumor necrosis factor-α (TNF-α). Because the clearance rate of CRP remains constant, its serum level is determined only by its rate of production.
Fig – No 18: Potential mechanisms of C-reactive protein (CRP) involvement in the pathogenesis of atherosclerosis


C – Reactive Protein and Atherosclerosis (fig 18)

C-reactive protein is synthesized by the liver and its functions are uncertain, it seems to play a role in tissue inflammation and binds to complement Clq (184). It is a known acute phase marker of tissue injury, infection and inflammation.

The process of atherogenesis has traditionally been considered to consist of the accumulation of lipids within the artery wall However, recently it has been shown to be much more than simply fat accumulation.

Atherosclerosis is now considered to be an inflammatory disease. The lesions of atherosclerosis represent a series of highly specific inflammation (185).

Evidence accumulated over the past decade supports a central role for inflammation in all phases of the atherosclerotic process, from lesion initiation through progression and, ultimately, plaque rupture (186). Recruitment of mononuclear leukocytes to the intima is one of the earliest events in the formation of an atherosclerotic lesion and is followed shortly by their adhesion, transmigration into the subendothelial space and transformation into foam cells (187). T lymphocytes are also attracted to the site of early lesion development (188) and along with the endothelial cells secrete cytokines and growth factors, further amplifying the proinflammatory state and promoting migration and proliferation of smooth muscle cells (188). The cells of the atheromatous plaque produce TNF-α, which together with interferon-γ and interleukin-1, increase interleukin-6 and CRP production (188). CRP is expressed in atherosclerotic plaque (189) and may enhance expression of local adhesion molecules (190), increase expression of endothelial plasminogen activator inhibitor 1 (191), reduced endothelial nitric oxide bioactivity (192), and alter low-density lipoprotein (LDL) cholesterol uptake by macrophages (193). The expression of human CRP in CRP-transgenic mice directly enhances intravascular thrombosis (194) and accelerates atherogenesis (195). CRP has been found within thin cap atheromas and immunohistochemical deposition of CRP within plaques corroborates the concept that inflammation is an important component to plaque instability reflected by serum CRP (196). (Fig-19)
Fig-19 The role of C-reactive protein in atherogenesis

(A) Endothelial dysfunction. (B) Endothelial cell activation. (C) Plaque formation. (D) Plaque rupture. (E) Inhibition of EPC survival and function. AT1R, angiotensin type 1 receptor; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; ET-1, endothelin-1; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin 6; IL-8, interleukin 8; MCP, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotidase phosphate; NFkB, nuclear factor kB; NO, nitric oxide; PAI-1, plasminogen activator inhibitor type 1; ROS, reactive oxygen species; SMC, smooth-muscle cells; VCAM-1, vascular cell adhesion molecule-1; VSM, vascular smooth muscle.
The CRP response has no diagnostic specificity, but serial measurement can be helpful in clinical management. It is a powerful screening test for organic disease and is useful in monitoring known infections / inflammatory disease and their response to treatment (197).

CRP is a trace protein in healthy subjects with a median concentration of around 1 mg/L. Its values can reach up to 400mg/L (198) in acute phase response. Increased CRP values significantly predict coronary events in out patients with stable or unstable angina (199) and in hospital patients with severe unstable angina and predict outcome after coronary angioplasty (201). Even in healthy asymptomatic people in the general population individuals with baseline CRP value in the top third of the distribution (geometric mean 2-40 mg/L) have twice the future risk of a coronary event than in those with values in the bottom third (mean 10 mg/L) (202). Recent results from the US National Health and Nutrition Examination Survey (NHANES) have demonstrated similar findings (203).

Cigarette smoking, increased age, body mass index and systolic blood pressure in men, and body mass index and diabetes in women, are strongly associated with a greater likelihood of CRP levels of > 1.0 mg/dl (203). The association of CRP with body mass indeed reflects the importance of adipose tissue as a source of baseline escalating interleukin-6, the main cytokine mediator of increased CRP production (204). The timing of measurement of CRP levels appears to be important as well. In an elegantly designed study by Zebrack et al, it was shown that when measured during hospitalization for acute myocardial infarction, CRP was not predictive of longterm outcome (205). Pre-discharge CRP levels were higher after MI than after unstable angina or stable angina. Where as CRP is strongly predictive of long term death (MI) for patients presenting with stable or unstable angina, it is not predictive shortly after acute MI. Therefore, CRP measurements should be delayed until the acute phase reaction is over and levels have returned to baseline.

Tamakoshi K et al. have shown a statistically significant positive correlation between CRP and body mass index (BMI), total cholesterol,
triglycerides, LDL-C, fasting glucose, fasting insulin, uric acid, systolic blood pressure, and diastolic blood pressure and a significant negative correlation of CRP with HDL-C in a study of 3692 Japanese men aged 34–69 years of age. They conclude that there are a variety of components of the Metabolic Syndrome (ME), which are associated with elevated CRP levels in a systemic low-grade inflammatory state (206).

The association of carbohydrate intake and CRP levels has recently been evaluated (207). Dietary glycaemic load was significantly and positively associated with plasma CRP levels in healthy middle-aged women, independent of conventional risk factors for ischemic heart disease. Therefore it is possible that exacerbation of the pro-inflammatory process may be a mechanism whereby a high intake of rapidly digested and absorbed carbohydrates increases the risk of ischaemic heart disease, especially in overweight women prone to insulin resistance.

CRP predicts prognosis in several other subgroups of patients. For example, a 10 year follow up of patients with a past history of premature MI showed that the relative risk of cardiac death was doubled with increasing CRP quartiles and patients in the top quartile had six times as high risk of cardiac death as patients in the lowest quartile (208). Similarly, in patients with peripheral vascular disease, the high incidence of severe MI is strongly predicted by pre-procedural measurement of CRP, independent of previous CAD and traditional cardiovascular risk factors (209). Moreover, elevated CRP constitutes an independent predictor of advanced carotid plaques in dyslipidaemic subjects (210).

Despite overwhelming evidence that CRP is an independent predictor of coronary events, several issues remain unresolved so far. First, it is not known whether increased CRP production reflects arterial inflammation or inflammation elsewhere in the body (211). This can have important implications for therapy, for example systemic therapy for risk reduction (aimed at lowering CRP levels and/or reducing inflammation) versus local therapy (e.g., angioplasty and bypass). The
First approach may more effectively prevent acute coronary events than the second more invasive one (212).

Second equally important but yet unresolved issue is that whether CRP has a pathogenic role in CAD or its levels rise merely as a result of inflammation. CRP is known to selectively bind to LDL, particularly the partly degraded LDL found within atherosclerotic plaques and is generally present with it, and activated complement, within such plaques (213). Bound CRP activates complement, is pro-inflammatory and may thus contribute to atherogenesis. The third related issue is that of effect of lowering CRP levels on atherosclerosis process. Statins are known to lower CRP levels, suggesting that some of their beneficial effects may be mediated via suppression of inflammation. Recently, trimepirazine was shown to significantly lower plasma CRP levels in patients with acute MI (214). Despite these isolated findings, it will be possible to definitely know whether CRP has a pathogenetic role only when drugs are developed that selectively inhibit CRP production or binding. The efficacy of correcting CRP levels has also not yet been tested, it will need to be done, including in special populations such as the elderly (215).

The fifth issue is a purely practical one, that of measurement of CRP. Should it be done in all patients of CAD; only in symptomatic patients, or may be in all adult males and post-menopausal females. For this, sensitive and cheap assays need to be developed first.

It is likely that a sensitive CRP assay may in fact become a new risk assessment marker for cardiovascular disease and guidelines for its application are under discussion.

Currently, it is certain that in those patients who have CAD, raised CRP levels do indicate a high risk group, which may require intensive management.

The rupture of vulnerable plaque is the most important mechanism by which atherosclerosis leads to the acute ischaemic syndromes of unstable angina, acute myocardial infarction and sudden cardiac death (216). These vulnerable plaques are lipid rich atheromatous plaques that have a thin fibrous capsule (217).
However the specific mechanisms responsible for plaque weakening have not been clearly determined. There is substantial evidence implicating an inflammatory process in the pathogenesis of acute coronary syndromes. Local inflammatory cells can generate and release cytokines that have potential to activate the endothelium transforming its natural antiadhesive and anticoagulant properties. Furthermore, inflammatory cytokines may reduce matrix synthesis and increase its degradation, favouring plaque rupture. Finally cytokines may enhance endothelin synthesis in endothelial cells and macrophages resulting in increased smooth muscle reactivity to local vasoconstrictors. The evidence supporting this hypothesis that inflammation is critical in the pathogenesis of acute coronary syndromes comes from a variety of sources.

There is considerable progress in the search for inflammatory markers in acute coronary syndromes. Studies have reported that local release of thromboxane B2 in the coronary circulation was associated with recent episodes of ischaemic chest pain in unstable angina (218).

Increased concentration of C-reactive protein have been reported in unstable angina and in acute myocardial infarction (219). Moreover the concentration of C-reactive protein in unstable angina increase independently of myocardial cell injury, as shown by normal concentration of creatine kinase and troponin T(220).

Although the evidence is strong in support of CRP as an independent risk factor for ischemic heart disease, the mechanisms underlying the association are unclear. However, recent data suggest a direct pathogenic role for CRP in atherosclerosis (221). The rates of coronary events increase significantly with increased in the baseline levels of CRP. In a randomized trial lovastatin therapy reduced CRP level significantly by 14.8%, an effect not explained by lovastatin induced changes in lipid profile (222). Statin therapy thus may be effective in the primary prevention of coronary events among persons with relatively low lipid levels but with elevated levels of CRP (223).

UC Davis physicians have discovered that this protein is not just a marker for heart disease, but that it actually damages the blood vessel wall by blocking a
Uric Acid

Uric acid, generated from xanthine by the enzyme xanthine oxidase, is the final product of purine degradation in humans. The association between high serum uric acid and incidence of coronary artery disease was reported more than fifty years ago (225). Since then, numerous clinical and epidemiological studies have explored the association more precisely. Such studies confirmed that elevated uric acid was a predictor of cardiovascular disease. However, a great controversy arose as to whether elevated uric acid was an independent risk factor for CAD or it was merely a marker of co-existing conditions such as hypertension, abdominal obesity, diabetes mellitus, hyperlipidemia, inflammation, impaired renal function and diuretic treatment.

The contradictory data obtained in the studies have been analysed and reviewed by independent research groups. Although different potential mechanisms explaining the association between high serum uric acid and CAD have been proposed, a well-established pathophysiological link is still missing (226-229).

The concentration of uric acid, as well as other risk factors for the development of CAD, is strongly influenced by different genetic factors and lifestyle habits.

Traditionally, elevated serum uric acid (SUA) is linked to gout. Recent investigations have shown that there may be a relationship between hyperuricemia, ischemic heart disease and metabolic syndrome, which is characterized by obesity, dyslipidemia, diabetes and hypertension. Although a direct relationship between SUA and cardiovascular disease is difficult to prove due to confounding factors like hypertension and diabetes, Strasak et al have recently demonstrated that SUA is an independent predictor of mortality due to congestive heart failure and stroke (230).

Previously, Gerber et al (231) had also documented an increased incidence of cardiovascular mortality among hyperuricemic subjects. But interestingly, they
also found an association between low SUA levels and fatal stroke. In the Losartan Intervention For Endpoint reduction (LIFE) in hypertension study (232), the researchers observed that up to 29% of the reduction in the composite end point of death, myocardial infarction and stroke, is seen with the use of losartan, and this was attributable to a decrease in the SUA, implying a link between SUA and both stroke and coronary heart disease.

Madsen et al (233) have also concluded that in patients not using diuretics, with significant, angiographically defined CAD, the SUA predicted mortality, independent of traditional risk factors. Although the findings of Strasak et al (230) are contradictory in this regard, whether they hold true regardless of diuretic use is not known.

While the topicality of serum uric acid (SUA) being a risk factor is currently controversial (234,235) there is little controversy regarding its association as a risk marker associated with cardiovascular (CVD) and renal disease (especially in patients with hypertension, diabetes, and heart failure). SUA seems to be a graded marker of risk for the development of coronary heart disease (CHD) or cerebrovascular disease and stroke compared with patients with normal uric acid levels and especially those in the lower 1/3 of its normal physiological range (234,236-246).

LK Niskanen et al. have demonstrated new information regarding this subject. They were able to demonstrate that elevations of SUA levels were independent of variables commonly associated with gout or the metabolic syndrome in association with CVD mortality in middle aged men (236).

In 1951, Gertler MM and White PD et al. sat out to determine the clinical aspects of premature coronary heart disease in 100 male patients 40 years old and younger. Their findings were increased mesomorphic body build, shorter stature, increased anterior- posterior chest wall diameter, and increased cholesterol and uric acid as compared to the normal population (247).

A much larger trial (1967) confirmed the initial interest in SUA and CVD with the publication of the early, large (5,127 participants), epidemiologic, seminal
Framingham study. This classical paper by Kannel et al. noted an elevated SUA was also associated with an increased risk of coronary heart disease for men aged 30–59 (248). In addition to the important finding of elevations in lipoproteins (specifically cholesterol levels greater than 250 mg/100 ml) being associated with CHD, there also appeared a definite association of elevated SUA, which was associated with an increase in the incidence rate of CHD. The above authors also noted that subjects in this study with evidence of impaired carbohydrate metabolism or disordered purine metabolism could be assumed to have accelerated atherogenesis (248).

Johnaon RJ et al nicely demonstrated that hyperuricemia predicts cardiovascular events in the general population, the hypertensive population, and patients with pre-existing CVD. Furthermore hyperuricemia predicts the development of future hypertension (244).

There are certain clinical clustering groups with increased cardiovascular risk, which have associated hyperuricemia. Non-diabetic patient groups with accelerated atherosclerosis, Type 2 DM patient groups with accelerated atherosclerosis (atheroscleropathy), congestive heart failure patient groups with ischemic cardiomyopathy, metabolic syndrome patient groups (with hyperinsulinemia, hypertension, dyslipidemia, impaired glucose tolerance, and obesity), renal disease patient groups, hypertensive patient groups, African American patient groups, patient groups taking diuretics, and patient groups with excessive alcohol usage. Each of these clustering groups has metabolic mechanisms that may help to explain why SUA may be elevated. In addition to the recurring finding of an elevated tension of oxidative-redox stress and ROS in many of the groups is the importance of the MS and insulin resistance.

Hyperuricemia and highly sensitive C-reactive protein (hsCRP) each play an important role in expanding the original Syndrome X described by Reaven in the atherosclerotic process. The above quartet does not stand alone but interacts in a synergistic manner resulting in the progression of accelerated atherosclerosis and arterial vessel wall remodeling along with the original players and the A-FLIGHT-88.
U toxicities. The MS of clinical clustering has been renamed multiple times over the past 16 years indicating its central importance to cardiovascular disease and was included in the recent National Cholesterol Educational Program – Adult Treatment Panel III (NCEP ATP III) clinical guidelines in order to assist the clinician in using this important tool to evaluate additional cardiovascular risk (249-252).

**Uric acid and inflammation**

Uric acid and highly sensitive C-reactive protein (hs CRP) each now share a respected inclusion as two of the novel risk markers – risk factors associated with the metabolic syndrome. It is not surprising that these two markers of risk track together within the MS. If there is increased apoptosis and necrosis of vascular cells and inflammatory cells in accelerated – vulnerable atherosclerotic plaques as noted in the above section then one would expect to see an increase in the metabolic breakdown products of RNA and DNA with adenine and guanine to its end product of uric acid. SUA elevation may indeed be a sensitive marker for underlying vascular inflammation and remodeling within the arterial vessel wall and capillary interstitium.

Is it possible that SUA levels could be as similarly predictive as hsCRP since it is a sensitive marker for underlying inflammation and remodeling within the arterial vessel wall and the myocardium (253).

Uric acid is known to induce the nuclear transcription factor (NF-kappaB) and monocyte chemoattractant protein-1 (MCP-1) (254). Regarding TNF alpha it has been shown that SUA levels significantly correlate with TNF alpha concentrations in congestive heart failure and as a result Olexa P et al. conclude that SUA may reflect the severity of systolic dysfunction and the activation of an inflammatory reaction in patients with congestive heart failure (59). Additionally, uric acid also stimulates human mononuclear cells to produce interleukin-1 beta, IL-6, and TNF alpha14 (244).
CRP and IL-6 are important confounders in the relationship between SUA and overall mortality in elderly persons, thus when evaluating this association the potential confounding effect of underlying inflammation and other risk factors should be considered (256).

It is a matter of controversy as to whether uric acid is an independent predictor of mortality in patients with coronary artery disease or whether it represents only an indirect marker of adverse outcome by reflecting the association between uric acid and other cardiovascular risk factors (257).
Microalbuminuria

Microalbuminuria is a well-known risk factor for coronary artery disease in diabetics and nondiabetics. It is associated with higher cardiovascular mortality, especially in diabetics. However there are few data linking angiographic severity of CAD to microalbuminuria.

Microalbuminuria is known to be an independent risk factor for cardiovascular death in type 2 diabetic patients but the mechanisms underlying this association have not been clarified. It could be that other cardiovascular risk factors that are frequently associated with microalbuminuria, such as hyperglycemia, hypertension and endothelial dysfunction, might also contribute to the increased cardiovascular mortality observed in these patients. In addition, dyslipidemia has also been described in type 2 diabetic patients with microalbuminuria. Although those studies did not specifically assess the effect of nutrient intake, the effect of dietary habits on the development of dyslipidemia in these microalbuminuric patients cannot be ruled out.

Dietary habits influence serum lipid levels and renal function in patients with diabetes. For example, higher intake of fish protein has been shown to be related to a lower risk for microalbuminuria in type 1 diabetic patients, and replacement of red meat with chicken reduces albumin excretion rate and serum cholesterol levels in microalbuminuric type-2 diabetic patients (258).

Early studies in patients with renal insufficiency clearly document that lower levels of blood pressure result in slower rates of decline in renal function. Proteinuria is the hallmark of renal disease in diabetes and is now recognized as an independent risk factor for cardiovascular disease. Microalbuminuria is clearly associated with increased CV risk in hypertension and predicts nephropathy progression in type 1 diabetes. Indeed, international abstracts demonstrate a strong, linear relationship between severity of angiographic coronary artery disease and albuminuria.
Microalbuminuria is an established marker of diabetic nephropathy. It begins insidiously and may precede the diagnosis of Type 2 Diabetes mellitus, occurring with the insulin resistance syndrome and its components, including obesity and hypertension. It is estimated that a duration of greater than 6 years of DM 2 may have existed before the diagnosis. Microalbuminuria is a persistent, increased urinary excretion of albumin. MAU refer to the excretion of albumin in urine at a rate that exceeds normal limits but is less than the detection level of traditional dipstick methods. Results are expressed as mg/24 hours urine specimen (259-262).

Data from the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) indicated that 8.8% of US adults had microalbuminuria (263). Older age, female gender, and non-Hispanic black ethnicity were associated with a higher prevalence (263). Population surveys also demonstrate an excess of microalbuminuria among individuals with diabetes and hypertension, the prevalence increasing with disease duration (263,264). In NHANES III (conducted 1988 to 1994), 28.8% of participants with diabetes and 16.0% with hypertension had microalbuminuria versus 5.1% of the subpopulation with no risk factors (264).

**Cardiac Disease and microalbuminuria**

Microalbuminuria seems to correlate with various cardiac abnormalities and diseases, including left ventricular (LV) dysfunction and hypertrophy, electrocardiographic abnormalities, and ischemic heart disease (IHD) (265). The Strong Heart Study demonstrated a significant association between microalbuminuria and echocardiographic parameters of LV systolic and diastolic function in a cohort of 1576 Native Americans with diabetes (266). Furthermore, a correlation has been noted between UAE and echocardiographic measures of LV mass index, LV hypertrophy, and concentric hypertrophy in untreated hypertensive patients (267). The larger Losartan Intervention For Endpoint reduction in hypertension (LIFE) study confirmed this finding.
A study that involved 64 asymptomatic patients with type 1 diabetes revealed a higher incidence of myocardial ischemia, detected by stress echocardiography and electrocardiography, in the presence of microalbuminuria (268). Electrocardiographic recordings from 7579 PREVEND participants without diabetes showed an independent association between microalbuminuria and infarct patterns, major ischemia, and minor ischemia (269). This group subsequently reported that, in patients with electrocardiographic ST-T segment changes, microalbuminuria could identify those who were at increased risk for all-cause and cardiovascular mortality (270).

Microalbuminuria was also associated with a 2.3-fold (95% CI 1.3 to 3.9) higher RR of IHD in a population-based study of 2085 individuals without previous IHD, renal disease, or diabetes (271). Survival free from IHD during follow-up was 97% among patients with normoalbuminuria versus 91% among those with microalbuminuria. It is interesting that the IHD risk that was associated with other conventional CVD factors more than doubled in the presence of microalbuminuria (271). Elevated UAE also correlates directly with angiographic evidence of CAD. A study of 308 patients who underwent elective coronary angiography revealed that patients with angiographic evidence of CAD had significantly higher urinary albumin levels than disease-free individuals and that UAE increased progressively with CAD severity (272).

The pathophysiologic processes that link microalbuminuria and CVD are unclear. Microalbuminuria could be a cause or a consequence of vascular disease. In the STENO hypothesis put forward by Deckert et al (273) albumin leakage into the urine is a reflection of widespread vascular damage. In a sense, the kidney is the window of the vasculature. In view of these considerations, endothelial function and chronic inflammation have been suggested as possible candidates to explain the association between microalbuminuria and CVD (274,275). However, there are many inconsistencies in the literature. It is true that low-grade inflammation can be both a cause and a consequence of endothelial dysfunction, and some studies used markers of inflammation such as C-reactive protein, IL-6, and TNF-α, which indicate that low-grade inflammation is associated with the occurrence and the
progression of microalbuminuria and with an associated increased risk for atherosclerotic disease (276-278).

Although many cross-sectional and a few prospective studies indicated that microalbuminuria is associated with several cardiovascular risk factors such as aging, male gender, hypertension, diabetes, smoking, obesity, and dyslipidemia, it is clear that these explain, at most, a very small part of the association between microalbuminuria and atherosclerotic events. As with measures of endothelial function and inflammation, it is possible that this is related to inadequate quantification of these exposures, or there could be confounding by other risk factors that might cause both the microalbuminuria and the associated CVD.

Another interesting theory is that some individuals are born with varying degrees of vascular function within a physiologic range and, therefore, excrete a variable amount of microalbumin (279). This inherent variability of the vascular state as determined by urine microalbumin excretion may be associated with susceptibility to subsequent organ damage (279). This could also explain why microalbuminuria is a predictor of not only CVD but also new-onset hypertension and diabetes (280). If this proves to be the case, then it may be desirable to identify these individuals to consider early interventional strategies to provide primary prevention. This hypothesis also raises the question about individualizing BP, cholesterol, and glucose goals in patients with microalbuminuria and associated increased susceptibility to organ damage. In a sense, the kidney may serve as a barometer of an appropriate BP goal; that is, the level of BP at which normalization of UAE occurs. Similarly, intensification of glycemic control and intensive reduction of LDL cholesterol if associated with normalization of UAE may represent a biomarker of therapeutic success. Future clinical trials will need to address these considerations given what is known and not known about the relationship between microalbuminuria and CVD.

Because microalbuminuria precedes the appearance of hypertension and diabetes and independently predicts CVD risk (279), screening for UAE, a relatively simple process, should facilitate early vascular disease detection.
Traditionally, a dipstick test has been used to measure protein in the urine. However, it is semiquantitative and insensitive, particularly when detecting albumin concentrations <300 mg/dL. A variety of antibody-based methods are available to measure urinary albumin. These include RIA, nephelometry, immunoturbidimetry, and ELISA. A more modern HPLC method that is more sensitive to detect microalbuminuria has been developed (281). Whether this method helps to identify patients who are at increased risk for CVD compared with the traditional antibody-based methods is unknown. However, because there is a continuous relationship between the amount of UAE and cardiovascular events, it is likely that more sensitive measures may assist in the higher dosage angiotensin receptor blocker or using both an ACE inhibitor and an angiotensin receptor blocker together in full dosage may facilitate even greater reduction in microalbuminuria (282,283). Thiazide diuretics also help to reduce proteinuria (284), and dietary salt restriction may also be helpful in reducing UAE (285).

Strict glycemic control also delays the onset of microalbuminuria, the progression of microalbuminuria to clinical proteinuria, and the development of nephropathy in patients with either type 1 or type 2 diabetes(262,286,287). Glycosaminoglycans have also been demonstrated to reduce albuminuria (288). Whether these specific therapeutic strategies will prevent progression of CVD because they reduce microalbuminuria is unknown. The Steno-2 trial demonstrated that intensified BP, cholesterol, and glycemic control in patients with type 2 diabetes was associated with decreased risk for cardiovascular events (289). However, this was not correlated with reduction in UAE. There is some debate in the literature as to whether statins reduce UAE (290-292). Both the National Kidney Foundation and the ADA recommend an LDL cholesterol goal of <100 mg/dL for patients with advanced renal disease or diabetes (262,287). For patients with diabetes and CVD, an LDL goal of < 70 mg/dL is appropriate. Disturbances in triglyceride, HDL, and non-HDL levels should also be addressed (262,287). Moreover, one needs to consider strategies to improve diet by reducing saturated and trans fats and dietary salt. In addition, efforts to assist in smoking avoidance, proper exercise, and weight control should be encouraged. Epidemiologic and clinical evidence has established a pathophysiologic link between...
microalbuminuria and CVD in patients with diabetes and hypertension and in the general population. This correlation is observed even at levels of albuminuria below the conventional threshold for microalbuminuria (293). Screening for UAE can help clinicians estimate a patient's CVD risk and, if positive, should prompt the early introduction of a multifactorial intervention strategy that aim to improve the overall CVD risk factor profile as well as prevent further loss of renal function.