CHAPTER I

INTRODUCTION
In 1826, Anthelme Brillat-Savarin wrote which is popularly translated into English as “tell me what you eat and I will tell you what you are”. Nutritionist Victor Lindlahr strongly believed in the idea that food controls health. This idea was popularized in the 1920s and 1930s. In the 1960s organic food was called the “food of the champions”. The idea of “you are what you eat” was again revived by the British Board casting company in a dieting programme aired between 2004 and 2007.

The concept of diet being the source of health and well being is still popular today. Amazon.Com has more than 63,000 books on diet on sale. In the last 20 years food preferences have taken a major change in focus. Foods are looked up on providers of health benefits in addition to meeting the basic nutritional needs. Thus diets to fight the four major global problems have emerged, namely diets to fight obesity, cardiovascular diets, diabetes and cancer.

In 1946, World Health Organization defined Health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. In the list of healthy lifestyle, diet is on the top of the list. Hence diet and lifestyle appear to be the basic for a healthy and disease free living. They are the cause of major diseases, particularly the cardiovascular diseases.

**Cardiovascular diseases (CVD)**

Cardiovascular diseases are a group of diseases which involve the heart and/or the blood vessels. Cardiovascular diseases can be classified in four types. They are as follows:

1. **Heart Failure**: In adequate supply of blood to the heart and blockage in the arteries will cause the heart to overwork this will eventually slow down the heart and it will stop.
2. **Arythmia**: This is a problem associated with improper beating of the heart.
3. **Heart value diseases**: Heart has four values. When they don’t function, the blood does not get pumped properly. This can lead to thrombus formation and stroke.
4. **Heart attack**: When the blood flow to a section of the heart muscle will begin to die leading to heart failure.
Cardiovascular diseases are collectively called as CVD or CHD (Coronary Heart Diseases). In the list of heart diseases the following diseases of the heart and blood vessels is included as shown in Table 1:

**Table 1**  
**List of Cardiovascular Diseases**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>Pain in the chest due to lack of blood supply to the heart.</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Narrowing of blood vessels due to build up of plaque.</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Heart muscle becomes inflamed</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Weakening of heart muscle due to lack of blood flow.</td>
</tr>
<tr>
<td>Coronary artery diseases</td>
<td>Refers to atherosclerosis.</td>
</tr>
<tr>
<td>Endocordites</td>
<td>Infection of hearts’ inner linking (endocordium) and valves.</td>
</tr>
<tr>
<td>Coronary thrombosis</td>
<td>When heart muscle stops functioning</td>
</tr>
<tr>
<td>Hypertension</td>
<td>High systolic/diastolic blood pressure</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>High blood lipids</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Myocardium stops functioning</td>
</tr>
<tr>
<td>Peripheral artery diseases</td>
<td>Blockage of arteries due to atherosclerosis</td>
</tr>
<tr>
<td>Stroke</td>
<td>Affect arteries in brain</td>
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</table>

A brief look through historical milestones in the discoveries related to heart diseases is as follows:

- **2698–2598 BC China**: Huang Ti, the Yellow Emperor, was thousands of years ahead of his time in writing in Nei Ching (Canon of Medicine): “The blood current flows continuously in a circle without a beginning or end and never stops” and “all the blood is under control of the heart”.
- **310–250 BC Egypt**: Erasistratus described the heart, veins, arteries and valves.
- **980–1037 Persia**: Avicenna (Ibn Sina) stated that the heart is located centrally to all organs of the body.
- **1210–1288 Syria**: Ibn al-Nafis described the pulmonary and coronary circulation
• 1509–1553 Spain: Michael Servetus described the pulmonary circulation in his book *Christianismi Restitutio*.

• 1525–1603 Rome, Italy: Andrea Cesalpino noted that the circulation system is a closed system, and was the first in modern times to coin the term “blood circulation”.

• 1559 Italy: Riva di Trento discovered that there are two coronary arteries, each supplying blood to half of the heart.

• 1628 England: William Harvey (1578–1657), a physician, published his thesis that the heart pumped blood around the body, in *De Motu Cordis*.

• 1677–1761 England: Stephen Hales, an English clergyman and scientist, first measured blood pressure by inserting a brass tube into the artery of a horse. This was a scientific experiment, published in 1733, demonstrating that the heart exerts pressure in order to pump blood (The horse died).

• 1749–1832 England: Edward Jenner, better known for smallpox vaccine, made the essential link between angina pectoris and disease of the coronary arteries.

• 1772 England: William Heberden (1710–1801) He was also the first to write about hyperlipidaemia as a risk factor when he noticed that the serum of an obese patient who suddenly died was “thick like cream”.

• 1815 England: London surgeon Joseph Hodgson claimed inflammation was the underlying cause of atherosclerosis and it was not a natural degenerative part of the ageing process.

• 1838 France: Louis René Lecanu showed that cholesterol was present in human blood.

• 1843 J. Vogel showed that cholesterol was present in atherosclerotic plaques.

• 1852 England: Fatty material in the coronary arteries described by Sir Richard Quain, which he attributed to nutrition.

**Global Burden of Cardiovascular Disease (CVD)**

At the beginning of the 20th century, cardiovascular disease (CVD) was responsible for less than 10% of all deaths worldwide. Today, that figure is about 30% and CVD is the leading cause of death worldwide with about 80% of the burden...
nowadays happening in developing countries. The global map of incidence of cardiovascular diseases is shown in Fig 1.

![Global Map of Heart Diseases](https://www.olinmontalvo.com)

**Fig . Global Map of Heart Diseases (Google Images. www.olinmontalvo.com)**

By 2020 it is expected that CVD will overtake infectious disease as the world’s leading cause of death and disability (Levenson et al., 2002). By this time, it is estimated that the variation in cardiovascular disease burden between higher income and lower income countries will have prolonged still more. At this time it is predictable that there will be about 6 million deaths and 35 million disability-adjusted life years (DALYs) annually from cardiovascular causes in higher income countries and about 19 million deaths and 170 million DALYs annually from cardiovascular causes in lower income countries (Neal et al., 2002).

Studies from Canada, United Kingdom, Singapore, South Africa and Mauritius have every time confirmed very high rates of coronary heart disease among individuals of South Asian origin (Öunpuu et al., 2000).

**CVD statistics in Indian**

The Indian subcontinent (including India, Pakistan, Bangladesh, Sri Lanka, and Nepal) is habitat to 20 per cent of the world’s population and perhaps one of the regions with the highest burden of CVD in the world. Although studies have
recognized that immigrants from the Indian subcontinent (South Asians) living in Western countries have a higher burden of cardiovascular disease than other ethnicities (Goyal et al., 2006).

Cardiovascular diseases in India, especially coronary heart disease, are most important contributors to the higher death rates, because Indians are more possible to extend coronary heart disease and have an earlier age of disease-beginning than are people in high-income countries (Patel et al., 2011).

Current studies from India and abroad demonstrate that Coronary Heart Disease (CHD) rates in India have doubled in both rural and urban India. So, the prevalence of CHD is now fourfold higher in urban India than in United States. When compared with Americans, Europeans and other Asians, CHD rates among Indians are five to ten folds higher under the age of forty (Sharma et al., 2002). The estimated prevalence of CHD is almost 3-4\% in rural areas and 8-11\% in urban areas among adults older than 20 years, representing a two fold increase in rural areas and a six-fold rise in urban areas over the past four decades. About 29.8 million people were estimated to have CHD in India in 2003; 14.1 million in urban areas and 15.7 million in rural areas (Shivaramakrishna et al., 2011).

In a study conducted in 45 rural villages in India, 32 per cent of all deaths were appropriate to CVD, outranking infectious diseases, which were dependable for 13 per cent giving clear data that the epidemic has reached its advanced stage even in rural India (Jeemon et al., 2010). World Health Organization (WHO) has predicted that from years 2000 to 2020 DALYs lost from CHD in India will be two fold in both men and women from the current 7.7 and 5.5 million respectively (Gupta et al., 2011). Area differences have also been reported, with the CAD prevalence being higher in southern than in northern India (Kamath et al., 1999).

**CVD statistics in Iranian**

The occurrence of cardiovascular disease (CVD) in Iran population is not only high but also the major causes of death in Iran (Aghasadeghi et al., 2008, Pahlavan and Frobert, 2004). Large numbers of Iranians have one or more major risk factors for
CVD. Coronary artery disease, the most common form of CVD, is the major cause of death in Iran today (Aghaeishahsavari et al., 2006).

The Islamic Republic of Iran is an example of countries in the Eastern Mediterranean Region of the World Health Organization (WHO) which impress a nutritional transition. Preliminary reports show that CVD is the most important reason of death in those over the age of 35 years (Nabipour et al., 2008).

Death registration in the Islamic Republic of Iran was initiated by the National Organization for Civil Registration in 1918, and has evolved over the past few decades into a new comprehensive death registration system operated by the Ministry of Health and Medical Education (MOH&ME). A checking of principal causes of death from registration data (Table 2) raises significant concerns about their value, with five being nonspecific cause categories such as “senility without mention of psychosis”, “unknown”, “other cardiac diseases”, “other unspecified disorders of the circulatory system” and “other respiratory diseases”. Further, although “heart failure” and “hypertensive diseases” are recognized causes of death, the number of deaths classified to these two categories appears disproportionately large in comparison with other countries with good-quality data (Khosravi et al., 2008).

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>%</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>19.5</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>9.2</td>
<td>3</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>3.2</td>
<td>7</td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>1.3</td>
<td>11</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.9</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2
Leading causes of death in the Islamic Republic of Iran as registered by MOH&ME in 2004–2005

MOH&ME, Iranian Ministry of Health and Medical Education.
**Cardiovascular Disease and Risk Factors**

The major risk factors for CVD are classified to two types:

1. Those cannot be changed (unmodifiable): Example Age, Gender, Heredity.
2. Those can be changed (modifiable): Example High blood pressure, High cholesterol, Smoking, Being overweight, Being inactive, Stress and tension, Diabetes. (Cannon,2007; Carty et al.,2002)

1) **Age**

The effect of age on CVD risk factor control is changeable (Subramanian et al., 2009). That means the occurrence of CVD is highest among older age groups (Cardi et al., 2009). Age is a major risk factor for CVD and appears to use its pathological effect primarily by way of age related harmful effects on arteries. Thus human aging is associated with arterial dysfunction and an increased risk of clinical vascular disease (Seals et al., 2008; Lakatta and Levy, 2003).

2) **Gender**

The occurrence cardiovascular disease is elevated in men than in women until menopause(Cartier et al.,2009; Price and Fowkes, 1997). Middle-aged women have a lower occurrence and rate of cardiovascular events compared with men of the same. The mechanisms responsible for this gender-specific difference are unclear (Hoetzer et al., 2006).

3) **Family History (Heredity)**

Family history is main risk factor of cardiovascular disease (CVD) (McCusker et al., 2004). Many of studies have proven that a family history of CVD is an independent risk factor for CVD. Compared with persons with no family history, those with a family history of CVD are 1.5 to 9.0 times more prone to development of CVD (Friedlander et al., 2010; Friedlander et al., 1985; Scheuner et al., 2006).

4) **Diabetes**

Cardiovascular disease is the main factor of morbidity and mortality in diabetes (Garcia et al., 1974). In 1999, the American Heart Association, in
collaboration with the National Institutes of Health, the American Diabetes Association, and the Juvenile Diabetes Foundation International, included diabetes as a main risk factor for CVD (Leandris et al., 2005). The common features of diabetes mellitus and cardiovascular disease (CVD) are obesity, high blood glucose/impaired glucose tolerance, dyslipidemia, and high blood pressure (Barlovic et al., 2011).

5) Blood pressure

Many of studies have shown a strong, linear, and independent positive association between blood pressure (BP) levels and risk of CVD occurrence and mortality among the general population (Wang et al., 2010; Chobanian et al., 2003; Gu et al., 2008). Therefore BP control has been proven that can be useful for reducing CVD and mortality (Oscar et al., 2005). Moreover the systolic BP is a stronger independent predictor of CVD than diastolic BP in all age groups (Thomas et al., 2006; Marijke et al., 2005).

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has introduced a new classification Blood Pressure (Veronica et al., 2004; Lloyd-Jones et al., 1999) (Table 3).

<table>
<thead>
<tr>
<th>JNC 6 Category</th>
<th>JNC 7 Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Optimal</td>
<td>120/80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129/80-84</td>
</tr>
<tr>
<td>Borderline</td>
<td>130-139/86-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>140/90</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159/90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160-179/100-109</td>
</tr>
<tr>
<td>Stage 3</td>
<td>180/110</td>
</tr>
</tbody>
</table>

**Table 3**

Changes in Blood Pressure Classification (JNC 6and 7)
6) High Cholesterol

Hypercholesterolemia is a risk factor for the development of cardiovascular disease (CVD) (Gabriel et al., 2010). The diagnostic for total cholesterol of CVD in individual contains of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (Robert et al., 2007).

High-density lipoprotein cholesterol transfers cholesterol to the liver therefore it can be cleaned from the body. High levels of HDL-C are connected with a reduced risk of stroke or cardiovascular events. Low-density lipoprotein cholesterol is a positive risk factor for CVD and Elevated Triglyceride levels increase cardiovascular risk when connected with high LDL-C levels (Vogenberg and Fendrick, 2010; Grundy et al., 2004). So, High blood concentrations of total cholesterol or LDL cholesterol increase the risk of CVD. Elevated concentrations of blood triglycerides have been measured an independent risk factors for CVD (Feldman, 1999; Criqui, 1991).

7 a) Diet

Dietary intake of fats, mainly the qualitative composition of fats in the diet, strongly effects the risk of CVD that can influence plasma lipids (total cholesterol, lipoprotein fractions (LDL, HDL) and triglycerides) (Reddy and Katan, 2004). Studies have shown that diets low in saturated fat and cholesterol and changing saturate fat with polyunsaturated fat may prevent CVD in many of initial experiments (Barbara et al., 2006; Kris-Etherton et al., 2003; Dayton et al., 1969; Turpeinen et al., 1979; Keys, 1983).

7 b) Obesity

Obesity is an independent risk factor for CVD (Poirier et al., 2006) as well as for other CVD risk factors, such as high blood pressure, elevated total cholesterol and LDL cholesterol (LDL-C), and low levels of HDL cholesterol (HDL-C) (Krauss et al., 1998). Overweight and obesity are measured by body mass index (BMI). BMI (weight in kilograms/height in meters\(^2\)) is often used as a main measure of fitness in children and adults. In adults, overweight is explained as a BMI of 25.0 to 29.9 kg/m\(^2\); obesity is defined as a BMI \(\geq 30\) kg/m\(^2\).
Increasing BMI is not the only cause of increase of risk of CVD (Poirier et al., 2006), But it is also possibly associated with insulin resistance Syndrome and elevated levels of inflammatory markers such as C-reactive protein and fibrinogen (Krauss et al., 1998).

8 a) Physically inactivity:

Physical inactivity related with an increased risk for cardiovascular disease (Brouwer et al., 2010; Eyre et al., 2004). Regular physical activity, fitness, and exercise are seriously the main key for the health of people of all age. Investigations have shown that the useful effects of exercise are associated with direct and indirect protective mechanisms. Improved fibrinolysis, enhanced endothelial function, reducing sympathetic tone, and other factors have not been known yet (Prasad and Das, 2009). On the other hand effects of physical inactivity are loss of glycemic control, decreased insulin sensitivity, low cellular expression of GLUT-4 in skeletal muscle that improve glucose metabolism in this organ and production of cytokines and adipokines like TNF-α, CRP, IL-6,IL-10 produced by adipose tissue. Physical activity can reduce plasma concentrations of inflammatory markers such as the markers of endothelial dysfunction (Brouwer et al., 2010; Boule et al., 2001; Duncan et al., 2003; Ren et al., 1994; Petersen and Pedersen, 2005; Oberbach, 2006; Goodyear and Kahn, 1998).

8 b) Stress and tension

Stress may be an independent predictor of both primary and secondary of CVD trials (Deepa et al., 1993; Anda et al., 1993). Psychologically stress may cause high blood pressure and higher pulse rate, decreased insulin sensitivity, elevated platelet aggregation and endothelial disorder. These effects, Individually may increase risk of CVD (Hiroyasu et al., 2002; Epel et al., 2006; Deepa et al., 2001; Anda et al., 1993).

Prevalence of risk among Indians and Iranians

Yet little is known about CAD and CAD risk factors in the Iranian population. A study of the prevalence of different CAD risk factors in an Iranian population showed that 6.3% of the study population were diabetic, 21.6% were smokers, and 15% had a positive family history of heart disease. 61% had total cholesterol
level > 200 mg/dl, 32% triglyceride > 200 mg/dl, 47.5% LDL-C > 130 mg/dl, 5.4% HDL-C < 35 mg/dl, 13.7% systolic blood pressure > 140 mmHg, 9.1% diastolic blood pressure > 90 mmHg and 87% of them were physically inactive. The study population contained patients who were admitted with confirmed CVD in Tabriz Heart Center, Tabriz, Iran, from February 2004 to May 2005 have showed a high occurrence of cardiovascular risk factors in confirmed CVD patients. The high prevalence of obesity, serum lipid disorders, low physical activity, hypertension, Diabetes, and cigarette smoking are indicative of the importance and significance of critical concentration to these risk factors (Hatmi et al., 2007). A new study in Tehran in Iran showed that the metabolic syndrome is highly prevalent in Tehranian adults, with an expected prevalence of about 30% in adults which is higher than that in mainly industrial countries such as the United States (Esmailzadeh et al., 2006).

Data from several cross-sectional studies prove the increased prevalence of risk factors of CHD such as smoking, type 2 diabetes, high blood pressure, dyslipidemia and obesity in urban Indians (Shivaramakrishna et al., 2010).

The study in Asian Indian subjects shows family history of coronary heart disease is a major determinant of multiple cardiovascular risk factors. Metabolic syndrome appears to be the main significant risk factor in individuals with family history of CHD (Gupta et al., 2000).

The study results of the prevalence of cardiovascular risk factors in two industrial units in Chennai in south India has showed increased prevalence of behavioral risk factors, central obesity, hypertension and diabetes in a select group of middle and high-income young urban males (Kaur et al., 2007). Lp(a), which is an important independent risk factor for CHD, is also involved. That has been indicated to be increased in Indian heart patients (Gambhir et al., 2000) and was an independent risk factor for CHD in NIDDM patients in South India (Mohan et al., 1998; Mahajan and Bermingham, 2004).

The studies indicate that coronary risk factors such as smoking and hypertension among uneducated and less educated people in rural India are more common. Also physical activity is greater among uneducated and less educated
groups. Lower weight and lower body mass index among these groups may be outstanding to overload of physical activity or to deficiency and under nutrition. Interestingly higher physical activity protects against coronary heart disease (Gupta et al., 1994).

**Dyslipidemia among India statistics**

Dyslipidemia is one of risk factors of major value in cardiovascular diseases. That contains abnormality in LDL-cholesterol, HDL-Cholesterol, and triglyceride level (Dalal et al., 2012).

Indian Council of Medical Research project reported the occurrence of dyslipidemia in 37.5% of adults 15 to 64 years of age, with a higher level of prevalence of dyslipidemia (62%) among young male industrial workers (Anthony and Maria, 2010). The prevalence of dyslipidemia was 50% higher (33% vs 21%) and obesity nearly doubles (24% vs. 13%) in South Indians vs. North Indians (Kinra et al., 2010).

Indians also have been exposed to have a unique lipid profile, characterized by low HDL cholesterol, hyper triglyceridemia, high total cholesterol by HDL ratio, and high triglyceride by HDL ratio (Gambhir et al., 2000).

Goel and colleagues recognized that in Indians the risk factors for CAD happen at much lower levels of total cholesterol and low-density lipoprotein cholesterol than other populations. High triglyceride and low high-density lipoprotein levels were observed in the Indian subjects. Younger patients had a more atherogenic lipid profile than the older subgroup with CAD. Younger patients had a more atherogenic lipid profile than the older subgroup with CAD (Goel et al., 2003; Setia et al., 2012). For example in Andhra Pradesh in India mean serum TC, LDL-C, and TG concentrations were increased. 52.7% of males and 42.9% of females having at least one abnormal lipid concentration. HDL-C was abnormally low in 7% of males and in 1.6% of females. The prevalence of hypercholesterolemia, hypertriglyceridemia and abnormally low HDL-C, especially the presence of insignificant hyper triglyceridemia, were higher in all the age groups. The increase was mainly important in the middle age group (40–59 years). Hyper cholesterolemia, hypertriglyceridemia
and abnormally low HDL-C have increased considerably over the past 10 years in urban adult populations in Warangal district, Andhra Pradesh in India (Estari et al., 2009).

**Dyslipidemia among Iranians**

In Iran, only few studies focusing on the resolve of lipid profile and the occurrence of dyslipidemia in children and adolescents have been conducted, which showed abnormal lipid profiles and a high prevalence of dyslipidemia (Klishadi et al., 2004; Azizi et al., 2001). The prevalence of dyslipidemia and detrimental lipid profiles in the schoolchildren of eastern regions of Iran are high (Fesharakinia et al., 2008). On the other hand, the study of Med-Line (1970–2012) shows a high occurrence of dyslipidemia in Iran. In a study of 2941 individuals, Sharifi et al. (2008) established that the mainly prevalent abnormality was a low serum HDL-C (< 50 mg/dl in females < 40 mg/dl in males; 73% overall, 63% for men, and 93.3% for women). Hyper triglyceridemia (> 150 mg/dl) was the second most common abnormality (40.6%) found. Furthermore, high total cholesterol (> 200 mg/dl) was observed in 35.4% of the subjects and the arrangement of hyper triglyceridemia and low HDL-C was observed in 9.9% of the subjects. Ebrahimi et al. (2009) also showed that low serum HDL-C concentration was one of the strongest factors independently associated with CAD in the Iranian population. Several reports have showed that dyslipidemia is significantly more common in Iranian patients (Estari et al., 2009).

**Atherosclerosis**

Atherosclerosis is a word derived from the Greek languages; "arteria" meaning gruel and "sclerosis" meaning hardening. Atherosclerosis or hardening of gruel-like substance in the arteries results in reducing the diameter of the arteries, and was believed to be an inevitable consequence of aging. In 1815, Hodgson published a monograph when he claimed that inflammation was the underlying cause of atherosclerosis (Hodgson, 1815). In 1858, Virchow reported the presence of inflammatory cells in the atherosclerotic lesion and proposed that local injury to intima was the initiating stimulus for atherosclerosis (Meng, 2005). However, the inflammation hypothesis was ignored for over a century in favor of the cholesterol theory which was put forth much later (Ravnskov, 2002).
Several studies including Framingham study have shown that elevated serum cholesterol in an independent risk factor for heart diseases (Expert panel, 2001; Heart Protection Study Collaborative Group, 2001). However, for a given individual measurement of serum total cholesterol was useless in predicting the risk of heart diseases. Several studies showed that cholesterol did not correlate with degree of atherosclerosis (Oalmann et al., 1981; Sorlie et al., 1981; Stehbens, 2001). In 1963, Lande and Sperry observed that the degree of aortic atherosclerosis at autopsy of healthy individuals, who had died due to accidents or gunshot, was independent of their blood cholesterol concentration analyzed immediately of the death (Lande and Sperry, 1936). It was argued that the post mortem changes in blood cholesterol may have reduced this study useless. Paterson et al (1960)(Paterson et al., 1960) confirmed the observation of Lande and Sperry by taking the blood cholesterol of these subjects that were shown several times during their life time. Matheer et al (1961) (Matheer et al., 1961) showed that cholesterol concentration was almost constant up to 16 hours after death.

The discovery of lipoproteins in the blood carrying cholesterol and lipids gave a new lease to the cholesterol theory of heart diseases. High levels of low density lipoprotein (LDL) correlated with risk of cardiovascular diseases (CVD) better than high total cholesterol (Tomkins and Owens, 2012). Hence LDL became the target of therapy for prevention of heart diseases. (Steinberg et al., 1989). However, more than half of patients who had cardiac events were those whose LDL was in the optimal range.

In the early eighties the theory of oxidation as a cause of atherosclerosis was proposed (Parthasarathy 2010). According to this theory, LDL can undergo oxidation resulting in oxidized LDL which is no longer recognized by the LDL-receptor, but is recognized by the scavenger receptor of macrophages (Steinbrecher et al., 1984). It is now increasingly clear that oxidized LDL is not only a biomarker for atherosclerosis but also a cause for it. Atherosclerosis starts in childhood and progresses during adolescence and young adulthood to become clinically obvious coronary heart disease (CHD) in middle-aged and older individuals. The Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study showed
that the CHD risk factors (gender, age, serum lipoprotein concentrations, smoking, hypertension, obesity, and hyperglycemia) were related with both the early and highly developed lesions of atherosclerosis in adolescence and young adulthood, decades before the incidence of CHD (Mahan et al., 2006).

The ability of oxidized LDL to generate plaques has been investigated for over three decades. LDL has not only apo B but also other proteins including lipoprotein lipase (LPL). Although LPL is mostly involved in lipolysis of triglycerides from triglyceride-rich lipoproteins, it is also important in LDL metabolism (Wang and Eckel, 2009). Proteoglycans are important molecules in the attachment of LDL particles to the vascular wall and act as a docking mechanism for the LDL particles. Once the LDL particle has been attached to the endothelial surface further changes must occur before the cholesterol-rich particle becomes part of the atherosclerotic plaque. LDL aggregation seems very important in this process.

Phospholipase A2 (PLA2) is also associated with atherosclerosis. The LDL particle contains phospholipid. PLA2 action on phospholipids will release free fatty acids (FFA). Jayaraman et al., (2011) (Jayaraman et al., 2011) demonstrated that free fatty acids enhance LDL coalescence into lipid droplets. They suggest that lipid droplet formation contributes to the pro-atherogenic effects of FFA on LDL. Most of the lipids found in atherosclerotic plaques are from lipid droplets. LDL derived small lipid droplets are prominent in atherosclerotic lesions (Asplund et al., 2011). Modifications such as oxidation are required for droplet fusion. Lipoprotein associated PLA2 preferentially hydrolyses oxidised phosphotidyl cholines in LDL and may promote fusion of LDL particles and thus contribute to the enhanced atherogenicity of the oxidized LDL (Guyton and Klemp, 1994; Bancells et al., 2011). Hence Lipoprotein-associated PLA2 has emerged as a causative agent of atherosclerosis.

The major molecules of LDL that can get oxidized are apo B and the polyunsaturated fatty acids. However cholesterol and phospholipids can also be oxidized. There is one apo B molecule /particle and hence apo B is considered a strong risk marker for atherosclerosis. The amount of oxidised phospholipid on LDL appears to be a good marker of atherosclerotic progression (Ahmadi et al 2010). Apo
CIII is another molecule of relevance for cardiovascular disease. Apo CIII increases the binding of LDL to artery wall proteoglycans and increases accumulation of lipoproteins in the vascular wall (Davidsson et al., 2005; Olin et al., 2002; Huikka et al., 2009) found that diabetic LDL with high endogenous CIII content contained less unesterified cholesterol and more triglyceride. They further found that the high apo CIII content in diabetic LDL was associated with increased esterified cholesterol, sphingomyelin, ceramide and the ceramide containing ganglioside GM1. They suggest that these changes may be associated with higher membrane fluidity and higher freedom in lateral movement thus allowing Apo B to acquire a conformation which is more favorable for proteoglycan binding.

The initial lesion which ultimately leads to atherosclerosis is the fatty streak. Surprisingly, fatty streaks occur even in human fetal aortas. They are enhanced by maternal hypercholesterolaemia (Napoli et al 1997). Analysis of the streak shows deposition of cholesterol and lipid with disruption of the endothelial surface and infiltration of macrophages and also neutrophils, typical of an inflammatory reaction. Interestingly, these streaks appear to repair themselves and do not lead to any lasting damage.

Repair mechanism involves monocyte/ macrophage accumulation in an effort to clear cholesterol from the plaque. The macrophage does not have an LDL receptor and can only take up modified LDL. Modifications include oxidation, and glycation which can occur in the sub endothelial space. Once the macrophage takes up the LDL and becomes a foam cell it should be hypothetically be able to remove cholesterol to the reticulo-endothelial system for clearance but in the atherosclerotic process the macrophage gets trapped in the intima and is unable to escape due to the increase in size. When the LDL cannot be repaired it is removed by phagocytosis((Picard et al. 1992). Monocytes are unable to limit the level of oxidized LDL they engulf which results in an overload of lipids. The cells appear as “foam” filled and hence are called as foam cells. The foam cell is the ultimate marker of the atherosclerotic lesion. The development of the foam cell depends on uptake of cholesterol by macrophages. A novel mechanism has recently been described involving the immune pathway. The Toll-like receptor 4 (TR4) present on
macrophages recognizes minimally oxidized LDL (Miller et al., 2003; Miller et al., 2005). Complex signalling pathway induced by minimally oxidised LDL led to enhanced uptake of the minimally oxidised LDL, resulting in lipid accumulation. Choi et al., (2009) demonstrated that cholesterol ester hydroperoxides are natural ligands for TR4. Foam cells are biologically active and signal the endothelium to recruit more monocytes. The smooth muscle cells also are recruited. Thus the process results in pushing up of the endothelial cell layer resulting in narrowing of arteries (Miller et al., 2003; Miller et al., 2005). Since LDL-oxidation can result in the initiation of this process, elevated LDL had a higher risk of elevated oxidized LDL. It is apparent that the LDL particle depends for its atherogenicity to a large extent on its ability to be modified. The modification that has drawn a lot of attention is oxidation. Essentially the release of free radicals is enhanced from conditions such as hyperglycaemia, ischaemia, and infection. The free radicals would be available to oxidise the LDL particle (Steinberg and Witztum, 2010). The major sites of oxidation on the LDL particle include apo B and the polyunsaturated fatty acids but cholesterol and phospholipids can also be oxidised. There is one apo B molecule per particle and hence apo B is considered a strong risk marker for atherosclerosis. The amount of oxidised phospholipid on LDL apo B100 appears to be a good marker of atherosclerotic progression (Ahmadi et al., 2010).

The formation of atherosclerotic plaque requires that the LDL be attached to the endothelial surface. Once the LDL particle has been attached to the endothelial surface further changes must occur before the cholesterol-rich particle becomes part of the atherosclerotic plaque. LDL aggregation seems very important in this process. The mechanism whereby LDL particles fuse and coalesce into lipid droplets and thereby increase LDL in the artery wall is complex (Oorni et al., 2000). Jayaraman et al., (2011) (Jayaraman, 2011) demonstrated that free fatty acids enhance LDL coalescence into lipid droplets. They suggest that lipid droplet formation contributes to the pro-atherogenic effects of FFA on LDL. Most of the lipids found in atherosclerotic plaques are present in lipid droplets and LDL derived small lipid droplets are prominent in atherosclerotic lesions (Asplund et al., 2011). Modifications such as oxidation, lipolysis and proteolysis are prerequisites for droplet fusion. Enzymes from the Phospholipase A2 (PLA2) family hydrolyse phosphatidyl choline.
Lipoprotein associated PLA2 preferentially hydrolyses oxidised phosphotidyl cholines in LDL and may promote fusion of LDL particles and thus contribute to its enhanced atherogenicity (Guyton and Klemp, 1994). Thus lipoprotein associated Phospholipase A2 has emerged as a causative agent of atherosclerosis and as a new therapeutic target.

These overall picture of atherosclerotic plaques shows that atherosclerosis is a complex process, and many components of the vascular, metabolic, and immune systems are involved in this process. Although low-density lipoprotein (LDL) remains the most important risk factor for atherosclerosis, immune and inflammatory mechanisms of atherosclerosis have gained tremendous interest in the past 20 years (Galkina and Ley, 2009). It is recognized that local inflammation occurs in the formation the plaques, as macrophages and other immune-competent cells are present in the lesions from an early stage. It is also known that inflammation acts as a main key in the weakening of the fibrous cap of the plaque, finally leading to plaque rupture (Lind, 2003). The development of an atherosclerotic plaque, a process that can be divided into three phases: initiation, progression and completion. The initial phase of vascular disease consists of the usually slow increase of an atherosclerotic plaque in large- and medium sized arteries. Thrombosis may not initiate this process; however, in later phases thrombosis frequently causes vascular occlusion, with its clinical consequences. Thrombi forming near or on plaque may develop into included into the plaque, where thrombin generation and the release of mediators by platelets may increase the rate of cell proliferation and extracellular matrix production, resulting in further growth of the plaque. Other factors, such as levels of the various lipoproteins, may also be important contributors to the development of plaque (Libby, 1998). However, Plaques enlarge as a result of the accumulation of low-density lipoproteins (LDL) in the sub endothelial space, followed by the diapedesis of Leukocytes and formation of foam cells, proliferation of smooth muscle cells, and production of connective tissue is recognized by the increase of lipid particles and cells of the immune system in sub endothelial regions, causing to narrowing of the arterial lumen and, following plaque rupture, to thrombosis. Many mechanism of the immune system are contained in the pathologic processes underlying the development of atherosclerosis: macrophages that develop into foam cells; T cells; autoantibodies;
autoantigens that are components of vessel walls and cholesterol particles; and
cytokines that are secreted by cells within atherosclerotic plaques, including
interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor-necrosis factor, interferon-
and platelet-derived growth factor. These factors subsequently lead to the
proliferation of vascular-smooth-muscle cells and the development of plaques. T cells,
predominantly type 1 T helper cells, are also recruited to the sub endothelial space
where they produce cytokines that can support a systemic inflammatory response
(Sherer and Shoenfeld, 2006). A summary of the process is given in Fig 2.

Figure 2: Early in the development of atherosclerosis, low-density-lipoprotein
cholesterol becomes oxidized, which results in endothelial cell
dysfunction and the expression of vascular cell adhesion molecules
and chemokines.

Role of Low Lipoprotein Density (LDL)

Lipoproteins are water-soluble globular particles that transport nonpolar lipids.
In humans, LDLs are the main Cholesterol transporters and consist of a hydrophobic
core containing Cholesteryl ester molecules, Triacylglycerols; and a surface
monolayer of polar lipids (primarily Phospholipids) and ApoB (Apolipoprotein-B) (Catapano et al., 2000). LDL is the main cholesterol carrier in the blood (Andreasen et al., 2001). That creates in the plasma from VLDL (very-Low Density Lipoprotein) created by the liver. VLDL is changed to LDL by the action of LPL (Lipoprotein Lipase), an enzyme that hydrolyzes triglycerides in VLDL, removing them from the VLDL particle and releasing free fatty acids. The removal of triglycerides from VLDL by LPL removes a greater proportion of Cholesterol, increasing the density of the particle and change it to LDL (Perrin-Cocon et al., 2001). The study of LDL has showed that an increased plasma level of LDL is related with an elevated risk of atherosclerosis and the study showed LDL does not from atherosclerosis plaque in a native form of that but oxidative of LDL is present accepted as a main cause in the pathogenesis of atherosclerosis (Mette et al., 2001).

**Oxidative stress and LDL Oxidation**

For the past several years, oxidative stress as a precipitating cause of atherosclerosis is extensively investigated both in humans and in animal models (Young and Mc Enency, 2001).

ROS contains oxygen ions/O₂⁻, free radicals (superoxide/O₂⁻ and hydroxyl radicals) and peroxides (hydrogen peroxide/H₂O₂) and they are produced of normal oxygen consuming metabolic process in the body that can modify other oxygen species, lipids, or proteins and acts as oxidative modification of LDL in artery wall in atherosclerosis (Morrell, 2009; Vogitzi, 2009). The LDL particle contains about 1600 molecules of cholesterol ester and about 170 molecules of triglycerides, which form a hydrophobic core of the particle. This is surrounded by about 700 molecules of phospholipids consisting mainly of Phosphatidylcholine and a small amount of sphingomyelin and lyso PC, and about 600 molecules of free cholesterol. This particle contain one molecule of the protein Apo B with 4536 amino acid residues. The LDL particle has about 2700 fatty acid molecules esterified with various molecules of the particle. (Jialal and Devaraj, 1996) About half of these fatty acids are polyunsaturated. Since the composition of the PUFA in the LDL particle is variable and since the particle contains varying amounts of anti oxidants like α-Tocopherol, LDL oxidation proceeds by multiple mechanisms, particularly when the oxidation is induced by
different oxidants (Steinberg and Witztum, 2010). Thus it is difficult to define what is actually oxidized LDL since there can be a variety of lipid and protein oxidation products as well as changes in the physical structure and properties (Chehin, 2001). Which of these is actually atherogenic is impossible to identify currently.

The process of oxidation of LDL begins with the oxidation of lipids of the LDL particle. The oxidative modification in vitro is generally followed by measuring absorption of UV light at 234 nm. The plot of OD vs time shows a biphasic curve with distinct phases. Initially, oxidation of LDL does not produce any measurable change in the OD at 234 nm. This phase is called the lag phase (Steinbraeche et al., 1984). During this phase the antioxidants are consumed by initiating free radical species this processing of this lag very slowly and depending on concentration of lipophilic antioxidants in LDL especially α-tocopherol, γ-tocopherol and carotenoid (Lipotakova, 1999) and LDL is not oxidized. When the endogenous antioxidants are completely consumed, the LDL shows a rapid increase in the OD at 234 nm. This phase is called the progression phase where the lipids and the proteins begin to be oxidatively modified. The speed of the processing of this phase increases and polyunsaturated fatty acids in LDL are rapidly oxidized to conjugated dienes and convert to the peroxyl radicals after this phase absorbance at 234 nm slowly falls. This phase is called the decomposition phase that can be appeared as a lipid hydroperoxide. The hydroperoxides will then breakdown to their aldehydes and ketones (Burkitt et al., 2001; Esterbauer et al., 1991). That some of them are used as biological markers, like 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) (Viigimmaa et al., 2010). These will react with lysine residues of ApoB forming Schiff's base. The LDL, so modified is no longer recognizes by LDL-receptor and is now recognized as oxidatively modified LDL. The oxidized LDL is no longer recognize by the LDL-receptor of the liver but is recognized by the scavenger receptor on phagocyte cells like macrophages. The macrophages in the arterial wall engulf the oxidized LDL and become filled with lipid. The cells appear as “foam” and are called foam cells. The foam cells are the progenitors of the atherosclerotic plaque.
Mechanism of in vitro oxidation

In vitro oxidation of LDL has been a convenient model to understand the in vivo process. Several studies have used Cu$^{++}$ or Fe$^{++}$ to initiate LDL oxidation in vitro (Quehenberger 1988). The oxidation of LDL has been shown to proceed through well defined phases. Once the oxidation has been initiated the lipid of the LDL particle undergo oxidation by free radical catalyzed mechanism (Young and McEneny, 2001). The conjugated double bond of polyunsaturated fatty acids of the lipid molecules in the primary target of the oxidant. The reactive methylene group between the two double bonds loses a proton. This is the key step in the initiation of lipid oxidation. The unstable radical then rearranges the double bond to give a conjugated diene. This conjugated dienes absorbs UV light maximally at 234nm and provides a convenient method for monitoring the progression of oxidation. (Lynch and Frei, 1993).

LDL-subtypes and LDL-oxidation

Based on its density LDL has been sub classified into at least three classes. The large LDL, medium LDL and small dense LDL have been separated and classified (Austin and Krause, 1995; Kraus and Burke, 1982). The size of the LDL particle is about the same as the space between two adjacent endothelial cells, which is about 26nm. Particles of diameter less than 20.5nm are called as small dense LDL (Koba et al., 2008). These particles can easily pass through the gaps between endothelial cells and enter the intimal space where they can get oxidized. (Phillips et al., 2005). Although there is no clinically relevant method to measure the amount of small dense LDL, it has been shown that individuals with high density lipoprotein (HDL-C) less than 35mg/dl and Triglycerides more than 250mg/dl have small dense LDL. LDL particle when it has moved out of the blood into the intima, it is out of reach of antioxidants present in the blood. Hence it is susceptible to oxidative modification. An atherosclerotic plaque is an ideal location for the oxidation of LDL.

Oxidation of LDL in vivo

There is adequate evidence to suggest that the process of LDL oxidation seen in vitro studies is also taking place in vivo. Several cell types produce powerful oxidants as anti microbial defense. Mitochondrial oxidation can also produce oxygen
free radicals. When pro oxidants are more than the anti oxidants, they can cause LDL oxidation. Thus pro inflammatory stimuli can initiate oxidative steps resulting in LDL oxidation.

**Plaque formation**

The major lesion characteristic of CVD is the arteriosclerotic plaque. The plaque contains of cellular essentials [primarily smooth muscle cells (SMC) but also some macrophages] and produced elements (including lipid deposits, collagen, elastin, and glycosaminoglycans). Important to the improvement of plaques is the proliferation of SMC within the initial area between the inner and outer layers of the artery wall (Penn, 1989; Colpo, 2005). Proliferation of plaques may happen not because of simple elevations in blood cholesterol, but because of critical physiological conditions that injure or weaken the structure of the arterial wall. These factors contain nutrient deficiencies, poor glycemic control, cigarette smoking, homocysteine, psychological stress, nitric oxide reduction, elevated iron levels, microbial infection, dietary trans fatty acids, excessive refined carbohydrate intake, and excessive omega-6 fatty acid intake and/or deficient omega-3 fat intake. All of these factors have been exposed to use an atherogenic effect isolated to serum cholesterol high (Colpo, 2005). The study shows that the formation of macrophage-derived foam cells are precursors of atherosclerotic plaques the Oxidative processes lead to the maturation of these plaques (Yusoff, 2002).

**Plaque Rupture**

Plaque rupture is the major event of luminal thrombosis in acute coronary syndromes occurring in 75% of patients disappearing of an acute myocardial infarction (Virmani et al., 2005). In most patients myocardial infarctions happen rupture of the fibrous cap, often at the areas of the lesion where macrophages enter, collect, and are activated and where apoptosis may create. Degradation of the fibrous cap may result from amplification metallo proteinases such as collagenases, elastases, and stromelysins. Metalloproteinase may be produced from activated T cells metalloproteinase of macrophages in the lesions, which promotes plaque instability and additional implicates an immune response (Ross, 1999).
The Table 4 in the below shows the factors of elevated of plaque rupture (Liao, 1998).

**Table 4**

**Factors involved in Plaque Rupture**

<table>
<thead>
<tr>
<th>Mechanical factors</th>
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<tbody>
<tr>
<td>Increased circumferential stress</td>
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<tr>
<td>Vasospasm</td>
</tr>
<tr>
<td>High turbulent flow</td>
</tr>
<tr>
<td>Increased liquidity of lipid core</td>
</tr>
<tr>
<td>Thin fibrous cap</td>
</tr>
<tr>
<td>Plaque constituents</td>
</tr>
<tr>
<td>Increased esterified cholesterol</td>
</tr>
<tr>
<td>Decreased extracellular matrix</td>
</tr>
<tr>
<td>Increased metalloproteinases</td>
</tr>
<tr>
<td>Presence of T cells and macrophages</td>
</tr>
<tr>
<td>Fibrous cap</td>
</tr>
<tr>
<td>Decreased synthesis of collagen</td>
</tr>
<tr>
<td>Degradation of collagen</td>
</tr>
<tr>
<td>Loss of smooth muscle cells</td>
</tr>
<tr>
<td>Increased presence of cytokines</td>
</tr>
</tbody>
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**Prevention of CVD by Drugs**

Exploring all classes of risk factors allows for a clinical synthesis of risk. A high-risk condition will be clear when a patient has multiple categorical risk factors. The National Cholesterol Education Program (NCEP) and the National High Blood Pressure Education Program's Joint National Commission (JNC) suggested the counting of categorical risk factors as the primary step in clinical risk measurement (Grundy, 1999).

Thus based on cumulative wisdom, certain therapeutically relevant strategies have emerged over the last few decades.
**Statins**

Statins are as Hydroxymethylglutaryl CoA reductase inhibitors (Ridker, 2003; Maron et al., 2000), reduce the risk of myocardial infarction, stroke, and other cardiovascular events among individuals with established coronary disease and overt hyperlipidemia (Ridker, 2003; Maron et al., 2000; Brugts et al., 2009). Statins reduce plasma levels of LDL cholesterol, that high LDL is a primary risk factor in coronary artery disease (Shishehbor et al, 2003; Ritu, 2006).

A numerous of studies has also shown effects of statins in addition to cholesterol-lowering. These include reduced expression of tissue factors, decreased platelet activation, and improved fibrinolytic activity through protection of endothelial function (Palinski and Napoli, 2002). One of the key effects of the statins appears to be inhibition of leukocyte–endothelium interaction, an essential anti-inflammatory action. Other significant effects of the statins can be classified as follows: (a) Antioxidant following angioplasty (b) Anti-thrombotic (c) Vasculoprotective (d) Angiogenic (e) Membrane transport (Lefera et al., 2001).

**Fibrates**

The Veterans Affairs High Density Lipoprotein Intervention Trial has indicated that fibrates can decrease cardiovascular events and they can benefit the individuals with obesity and features of the metabolic syndrome (Robins, 2003).

Fibrates are commonly effective in lowering high plasma triglycerides and cholesterol in coronary heart disease. The prominent effects of fibrates are to decrease plasma triglyceride-rich lipoproteins (TRLs). Levels of LDL cholesterol (LDL-C) usually decrease in individuals with increased baseline plasma concentrations, and HDL cholesterol (HDL-C) levels are frequently elevated when baseline plasma concentrations are low.

Mechanisms of Action of Fibrates in human are as follows:

1. Stimulation of lipoprotein lipolysis by LPL owing to a reduction of TRL apoC-III content.
2. Induction of hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production by induction of β-oxidation and inhibition of hormone-sensitive lipase in adipose tissue.

3. Increased reduction of LDL particles by prevention of LDL receptor catabolism.

4. Decrease in neutral lipid (cholesteryl ester and triglyceride) exchange between VLDL and HDL probably from reduction plasma levels of TRL.

5. Increase in HDL production and stimulation of reverse cholesterol transport by enhancing the production of apoA-I and apoA-II in liver(Stales et al., 1998; Genets et al., 2009; Shepherd et al., 1994; Tonelli et al., 2004).

The ability of fibrates to prevent atherosclerosis is not related only to their hypolipidaemic effects but also to other 'pleiotropic effects', such as their anti-inflammatory, antioxidant and antithrombotic effects, as well as their ability to improve endothelial function. These drugs can decrease plasma fibrinogen levels and inhibit tissue factor expression and activity in human monocytes and macrophages (Elisaf, 2002).

**Niacin**

Niacin has been generally used as a pharmacologic agent to control abnormalities in plasma lipid and lipoprotein metabolism and in the treatment of atherosclerotic cardiovascular disease. This drug was used as early as 1955 but only in recent times cellular and molecular mechanism of action has been understood.

The effects of niacin include:

1) Reduction in triglycerides and apolipoprotein-B of Lipoproteins by decreasing fatty acid recruitment from adipose tissue triglyceride stores and inhibiting hepatocyte diacylglycerol acyltransferase and triglyceride synthesis leading to elevated intracellular apo B degradation. This results in reduced secretion of VLDL and LDL particles.

2) Increase in HDL is by decreasing the limited catabolic rate of HDL-apo AI without affecting the synthetic rates. The other beneficial effects of niacin include antioxidant and anti-inflammatory activities, and activation of nuclear
transcription factors such peroxisome proliferator’s activator receptor $\gamma$, probably via prostaglandin metabolism(Daniela et al., 2004).

**Role of HDL**

An inverse relationship between the concentration of high density lipoprotein (HDL) cholesterol and the development of coronary heart disease (CHD) is well recognized (Barter and Raye, 1996).

In 1951, Lindgren et al., first recognized two HDL subspecies by analytic ultracentrifugation. HDL$_2$, which has a density range of 1.063–1.125 g/ml, comprises the larger, cholesterol-rich particles and HDL$_3$, which represents the range 1.125–1.210 g/mL, comprises small, lipid-poor particles.

HDL can also be divided into two main subgroups due to their major apolipoprotein composition, those including only apoA-I (LpA-I) and those containing both apoA-I and apoA-II (LpA-I:A-II). In a large number of people, LpA-I is around one-third and LpA-I:A-II approximately two-thirds of the total HDL. LpA-I results more in HDL$_2$, whereas LpA-I:A-II is found more in HDL$_3$. Other apolipoproteins that are well recognized to be related to HDL contain apoA-IV; apoC-I, C-II, and C-III; and apoE. Most of these apolipoproteins are extremely transferable and can also be associated with apoB-containing lipoproteins (Berglund et al., 1999; Movva and Rader, 2008).
The structural heterogeneity in HDL particle structure is represented in Fig 3 (Rye et al., 2009).

Fig 3. HDL heterogeneity. The HDL in human plasma consist of several subpopulations of particles that vary widely in shape (A), density (B), size (C), composition (D), and surface charge (E).

Cardio protective function of HDL

The cardio protective function of high-density lipoprotein (HDL) and apoA-I is mainly refer to its ability to facilitate transport of cholesterol from peripheral tissues particularly macrophages to the liver (Rader, 2003). The relationship of RCT to atherosclerosis was first suggested by Ross and Glomset (Cuchel and Rader, 2006). HDL might carry a variety of proteins. These proteins can indicate roles of HDL.
Forty-eight proteins were recognized in HDL isolated by ultracentrifugation from healthy controls and/or CAD subjects. Twenty-two proteins with well-characterized roles in lipid metabolism and the antioxidant properties of HDL were detected. Another role of HDL identified from its proteins is in the prevention of plaque rupture (Vaisar, 2007).

**Reverse Cholesterol Transport (RCT)**

Reverse cholesterol transport is a multi-step process resulting in the net movement of cholesterol from peripheral tissues back to the liver. This cholesterol can be reused in newly synthesized plasma lipoproteins, and a part appears in the bile as free cholesterol or (after degradation) as bile acids. The cholesterol is also used for vitamin D, and steroid hormone synthesis.

About 50 years ago HDL-driven reverse cholesterol transport was described by Glomset (Glomset, 1963; Golmset and Norum, 1973). This process describes the role of HDL in returning the peripheral trine cholesterol to the liver for excretion into bile and subsequent elimination in feces. This process could have evolved to protect the extra hepatic tissues from accumulating excess cholesterol. If this model is true then the plasma HDL-C levels should be able to predict how much of cholesterol would be excreted in the bile and feces. However there are several reports where this is not true (Groen et al., 2001; Jolley et al., 1998, Xie et al., 2009).

The enzyme, 1ecithin: cholesterol acyltransferase (LCAT), appears in all recent accounts of RCT. LCAT, as fraction of plasma high density lipoprotein (HDL), elevates cholesteryl ester in this lipoprotein fraction. Two lipid transfer proteins supply to extra HDL remodeling. These are not like enzyme, these proteins are energy-independent, and they are for creating of concentration gradients. A phospholipid transfer protein (PLTP) stores lecithin to HDL and may be a cause in other remodeling reactions. A cholesteryl ester transfer protein (CETP) can transport cholesteryl ester completed by LCAT to other lipoproteins, principally triglyceride rich lipoproteins and LDL. HDL triglyceride can then be catabolized by the extracellular hepatic triglyceride lipase.
Even before Glomset, Spreey in 1927 had demonstrated that dogs that had undergo chronic biliary fistula surgery, fecal neutral stroll loss was increased compared with normal control dogs (Sperry, 1927). However Sperry’s work was ignores since the current operation at that time was that bile was the only source of fecal lipids. However Sperry’s work was confirmed by Pertsemilidis (Pertsemilidis et al., 1973; Dietschy and Siperstein, 1965; Dietschy, 1986).

In the classical RCT pathway liver plays a central role in removing cholesterol out of the body (Dewis and Eader, 2005; Wang and Rader, 2007; Lewos, 2006), liver also pays a central role in the non-biliary pathway by repacking peripheral cholesterol into lipoproteins synthesized in the liver and targeted to the intestine for excretions. However which lipoproteins are involved in this process is not known at present.

The molecular mechanisms investigation has been showed in the ATP-binding cassette transporter A1 (ABCA1) transporter promotes cholesterol efflux from macrophages to lipid-poor apoA-I, or pre-β-HDL, as an acceptor. More newly, another member of the ABC gene family, ABCG1, was recognized as a promoter of macrophage cholesterol efflux to mature HDL particles. Although SR-BI has been exposed to facilitate in vitro cholesterol efflux from macrophages to mature HDL, its role in mediating macrophage RCT in vivo is possibly not quantitatively essential.
Reverse Cholesterol Transport is depicted in Fig 4.

![Fig 4. Summary of Reverse Cholesterol Transport](Cho K-Y, 2009)

It has been shown that HDLs are directly antiatherogenic. The mechanism of the protection is unclear but possibly well relate both to an association of HDLs in plasma cholesterol transport and to a range of non-lipid transport functions of HDLs.

HDL is not only the main transporter of cholesteryl ester hydroperoxides, but it also reduces the total amount of lipid peroxides generated on LDL during oxidation. Several enzymes are present on HDL: paraoxonase, lecithin:cholesterol acyl transferase, platelet activating factor acetylhydrolase, phospholipase D and protease. Apolipoproteins, such as apolipoprotein AI, could also have enzymic activity.
**Anti inflammatory activity**

The second best recognized function of HDL is its role as an anti-inflammatory regulator. This is accomplished through infracting vascular endothelium and circulating inflammatory cells (Goreton et al., 2011). Atherosclerosis has been definitely recognized as an inflammatory disease. An important event in the initiation of atherosclerosis is adhesion of circulating monocytes to activate endothelial cells and their subsequent Trans endothelial migration to the sub endothelium. This process is created by adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. The unfavorable expression of these adhesion proteins in response to the “injury” are induced by different inflammatory stimuli, containing cytokines and non cytokines such as interleukin-1, tumor necrosis factor-α (TNF), and oxidized or native LDL. The ability of HDL not only to inhibit the cytokines-induced adhesion protein expression has been well known. It has been reported that human HDL deeply inhibit the expression of VCAM-1, ICAM-1, and E-selectin in human umbilical vein endothelial cells (HUVEC) activated by TNF or interleukin-1 but also HDL profoundly inhibit the TNF-induced sphingosine kinase activity and sphingosine 1-phosphate production. Role of Sphingosine kinase contains in intermediary adhesion protein expression and endothelial cell activation after TNF stimulation and as a signaling pathway in mediating a variety of cellular functions such as cell growth, proliferation, and inflammatory reaction.

HDL can inhibit the production of chemo-attractant protein (MCP-1) (Toll et al., 2008). HDL can maculate vascular tone by affecting the production of Nitric Oxide, a mediator of vascular smooth muscle cell contraction. HDL can also interact with circulating WBCs to limit inflammation. For example ApoAI can inhibit the expression of monocyte surface protein CDIIb, which is an integrin molecule involved in vascular adhesion (Marphy et al., 2008).

**Antioxidant activity**

HDL can directly inhibit the oxidation of LDL and other targets that contain phospholipids. HDL serves as a sink for oxidized lipids by direct transfer of oxidized lipids from LDL (Bowry et al., 1992). The transfer of oxidized phospholipids from
LDL prevent the free radical catalyzed chain reaction (Navab et al 2000) also some of the advanced oxidation products of phospholipids serve as ligands for scavenger SR-BI to promote the uptake of modified lipoprotein. It has been proposed that when oxidized phospholipids are present on HDL, the receptors that recognize this Ox-HDL are different from those that recognize oxidized LDL (Valiyaveettil et al., 2008).

The oxidized phospholipids transferred to HDL can be detoxified by HDL-associated enzymes, of which paraoxonase is predominant.

**ApoAI:** ApoAI has been shown to be antioxidant in addition to its role in reverse cholesterol transport. ApoAI and transfer oxidized phospholipids from LDL to HDL and also from cells to HDL (Navab et al., 2000A, Navab et al., 2000B).

HDL bound ApoAI can directly reduce cholesterol ester hydro peroxides and phosphatidyl choline hydro peroxides via methionine residue 112 and 148 of ApoAI (Garner et al 1998). Introducing by the study that supports antioxidant role of ApoAI does not support the antioxidant function of either PON1, PAF-AH or LCAT in the prevention of LDL-oxidation by HDL (Zerrad-Saads et al., 2009).

The negative correlation of HDL with risk of cardiovascular diseases is therefore attributed to the presence of ApoAI rather than HDL-associated cholesterol. In fact very high levels of HDL-C or large sized HDL particles were actually associated with a twofold increased risk for CVD (Vanders Steeg et al., 2008).

**ApoAII:** ApoAII was also antioxidant and protected VLDL from oxidation more efficiently than control HDL (Boisfer et al., 2002). However, ApoAII was found to displace PON1 from HDL.

**Other Apo proteins:** ApoE2 has been shown to have antioxidant activity but ApoE4 was shown to be pro inflammatory. ApoAI was also antioxidant but it was associated with HDL particles contain PON1. ApoAII was also shown to be antioxidant (Saer et al., 2003; Ophir et al., 2005; Navab et al., 1997; Frougakos et al., 2005; Remaley et al., 2001; Ostos 2001).
The antioxidant effect of HDL is because of anti oxidant enzymes associated with HDL like paraoxonase (PON). Although the primary role of LCAT is the esterification of cholesterol in HDL, LCAT can also hydrolyze oxidized polar phospholipids generated during lipoprotein oxidation. The diversity of anti oxidative actions of HDL particles suggests that HDL supply efficient defense of LDL from oxidation in vivo.

**Paraoxonase (PON)**

**Structure of PON**

Serum paraoxonase (PON) (E.C. 3.1.8.1) is protein with molecular mass of 43KDa (355amino acids) and a calcium-dependent esterase, that is recognized to catalyze hydrolysis of organophosphates. That hydrolyzes organophosphates such as paraoxon, diazoxon, sarin, and soman, and also arylesters such as phenyl acetate, and is generally speared among tissues such as liver, kidney, intestine, and also serum, where it is related with HDL. Experiments show that PON1 can prevent LDL oxidation. In fact reduction of lipid hydroperoxide is believed to be due to PON1 (Macknen et al., 1991; Watson et al., 1995; Shih et al., 2000).

Studies in the early 1990s led to the purification of rabbit and human paraoxonases. Members of the PON family have been recognized not only in mammals and other vertebrates, but also in invertebrates. The human genome contains two *PON1*-like genes, chosen *PON2* and *PON3*. (Krisch, 1968; Geldmacher-von Mallinckrodt et al., 1969, 1979; Zech and Zurcher, 1974; Playfer et al., 1976; Carro-Ciampi et al., 1981; Eibergand Mohr, 1981; Eckerson et al., 1983a, 1983b; Muelleret al., 1983; Ortigoza-Ferado et al., 1984). Human PON1 and PON2 each have nine exons, and the exon/intron junctions occur at equivalent positions. PON1 and PON2 genes are both on chromosome 7 in human and on chromosome 6 in the mouse (Primo-Parmo et al, 1996; Gupta et al., 2009; Horke et al., 2007). The proteins PON1 and PON3 are circulating in serum residing on the high-density lipoprotein fraction, but PON2 is cell related (Horke et al., 2007).

The gene for human serum PON recognize two common polymorphisms: Q or R at position 191 (glutamine or arginine, respectively) and M or L at position 54 (methionine or leucine, respectively). PON Q and PON R qualitatively be at variation
in their abilities to hydrolyze different organophosphates. The Q allele is responsible for the protecting effect of PON against atherosclerosis and the R allele is to be associated to the risk for coronary heart disease (Aviram et al., 1998).

**Role of PON**

Low Serum PON activity was found in patients after myocardial infarction, in patients with familial hypercholesterolemia and in patients with diabetes mellitus in comparison with healthy subjects (Aviram et al., 1998). It is also known as an independent predictor of new CHD events (Mackness et al., 1998). PON1 mass and activity in the plasma considerably affect the risk of developing cardiovascular disease (Getz and Reardon, 2004).

In human serum, paraoxonase is in close substantial association with HDL, which thus acts as its carrier and site of action (Abbott et al., 1995).

On the other hand, the studies have been studied not only the antioxidant activity of high density lipoprotein (HDL) is widely distributed to the paraoxonase (PON) 1 located on but also that two other members of the PON gene family – PON2 PON3 – may also have important antioxidant properties (Mackness et al., 2004; Ng et al., 2005) and may show antiatherogenic capacities as well (Ng et al., 2005). PON1 antiatherogenic effects contain the breakdown of oxidized lipids in oxidized lipoproteins and macrophages, inhibition of oxidized LDL uptake by the Cells, reduce in macrophage cholesterol biosynthesis and stimulation of HDL-mediated cholesterol efflux from macrophages (Rock et al., 2008).

Studies show aryl esterase activity, one of the functions of PON enzyme, facilitates reverse cholesterol transport in HDL (Aksoy et al., 2007). PON also act as important guardians against cellular damage from toxic agents, such as organophosphates and against bacterial endotoxins (La Du et al., 1999).

In humans, higher PON1 activity is associated with lower incidence of cardiovascular events (Soran et al., 2009). As the function of HDL is beginning to be unraveled the cardio protective role of PON1 is being questioned as to whether it is correlational and not causal (Brijmohun et al., 2009). It was reported that the PON1
activity is a given population can vary up to 40 fold (Mueller et al., 1983; Devies, 1996; Richter and Furlong, 1999) and PON1 protein levels as much as 13 fold (Costa et al., 2003)

**Modulation of PON1 by Life Style Factors**

Smoking cigarette smoke extract was found to inhibit PON1 activity (Nishin and Watanabe, 1997) studies in human have confirmed that PON1 activity is reduced by cigarette smoking (James et al., 2000). However, when smoking is stopped, the PON1 activity is restored within 3-24 months.

Although alcohol was shown to inhibit PON1 activity in vitro, consumption of low levels of alcohol in human was actually shown to increase PON1 activity as well as PON1 protein levels, light drinkers had 39.5% higher PON1 activity whereas heavy drinkers had 45% lower PON1 activity in the serum.

**Fat Consumption**

A study was carried out on 12 health men where they were fed a meet rich in used cooking oil. The PON1 activity decreased by 27% up to 8 hr. But by 12 hr it returned to normal levels (Sutherlaned et al., 1999).

Replacement of dietary saturated fat by trans fats reduced serum PON1 activity by about 6% (de Roos et al., 2002). In another study on rat fed with triolein, tripalmitine or fish oil showed interesting results. The group that was fed, tripalmitine had no change in PON1 activity. The group that was fed triolein showed a 46% increase in PON1 activity. However, the group that was fed fish oil, had a 39% decrease in PON1 activity. The effect of olive oil on PON1 has been confirmed in human studies where the effect was maximum in women when compared with men (Wallece et al., 2001). Administration of w-3 PUFA to 14 patients with familial combined hyper lipidemia for 8 weeks resulted in a 10% increase in PON1 concentration.

**Antioxidants**

In vitro and in vivo studies in experimental animals have shown the protective effects of phyto chemicals who question and glatridin. Administration of pomegranate juice to 13 healthy man resulted in a 20% increase in serum PON1.
Role of diet in atherosclerosis

Dietary habits are usually developing in childhood and recognized by young adulthood. Diets elevated in fat, particularly saturated fat, are often correlated to obesity, hypertension and hypercholesterolemia. Data recommend that caloric intake is rising among all ethnicities, age and socioeconomic groups, and diets include more energy-dense, nutrient-poor foods. Given the strong relationship between diet and disease, it is essential to estimate and address dietary behaviours and readiness for modify at a young age for useful prevention of CVD and associated co-morbidities (Sharma et al., 2008).

Atherogenic Diet

Is cholesterol the Cause of atherosclerosis?

Atherosclerosis or hardening of gruel like substance in the arteries results in reducing the diameter of the arteries, and was believed to be an inevitable consequence of aging. In 1815, Hodgson published a monograph when he claimed that inflammation was the underlying cause of atherosclerosis (Hodgson, 1815). In 1858, Virchow reported the presence of inflammatory cells in the atherosclerotic lesion and proposed that local injury to intima was the initiating stimulus for atherosclerosis (Meng 2005). However, the inflammation hypothesis was ignored for over a century in favor of the cholesterol theory which was put forth much later (Ravnskov, 2002).

Several studies including Framingham study have shown that elevated serum cholesterol in an independent risk factor for heart diseases (Expert panel, 2001, Heart Protection Study Collaborative Group, 2002). However, for a given individual measurement of serum total cholesterol was useless in predicting the risk of heart diseases. Several studies showed that cholesterol did not correlate with degree of atherosclerosis (Oalmann et al., 1981, Sorlie et al., 1981, Stehbens, 2001).

Diet as a modulator of diseases is a well known concept the idea that an imbalance of dietary fats and dietary cholesterol results in high serum cholesterol leading to atherosclerosis and CVD has dominated scientific studies for decades. The “Diet –Heart” hypothesis proposed by Ahrenes has the following syllogism.
1. Intake of saturated fats increases serum cholesterol.
2. High serum cholesterol leads to atherosclerosis
3. Atherosclerosis leads to heart diseases.

Although each of these statements have been individually proved in some experimental set up the "Diet –Heart" hypothesis has not been validated by clinical trials or epidemiological studies.

Over the years a new variation of the diet- heart hypothesis has emerged, this is characterized by the new syllogisms as follows:

1. Dietary intake of n-3 PUFA increases its concentration in cell membranes and in free fatty acids.
2. Higher n-3 PUFA leads favorably alters cardiac ion channel function.
3. Altered ion channel function modifies cardiac action potential.
4. Modified action potential reduces myocardial vulnerability to ventricular fibrillation.

These new paradigm has been validated by epidemiological studies and randomized clinical trials.

The lack of evidence for a causal role of dietary cholesterol and saturated fat and a protective role of PUFA leads to a dilemma. As there is no doubt that an excess of saturated fats may raise serum cholesterol and an excess of PUFA may reduce it at least in experimental animals, then why does it not reflect in clinical studies? The answer may be that high cholesterol may be a risk factor heart diseases, it may correlate with heart diseases but not a cause for it.

**Anti-atherogenic Diet**

Anti-atherogenic factors contain antioxidants, fish oils and other polyunsaturated (if protected from oxidation), fiber and trace minerals such as copper, manganese, selenium and zinc (Addis et al., 1995). One of antiatherogenic diet is unsaturated fatty acids that it has been recommended that an increasing the consumption unsaturated fatty acids is beneficial not only for reducing and
preventing of CVD and also beneficial for hypertension that may help to decrease of blood pressure (Martirosyan et al., 2007).

One of trace minerals of antiatherogenic diet is magnesium it has already been exposed that magnesium supplementation can reduce the cholesterol deposition in the vessel wall in rabbits as well as in mice fed a high cholesterol diet. The study of that also shows the effect of dietary magnesium on the atherogenic process has been increased in several animal experiments. Rabbits fed a high cholesterol diet supplemented with an increase in magnesium load were shown to have lower levels of cholesterol and triglycerides and less extensive atherosclerotic lesions. It has also been demonstrated that oral magnesium supplementation can also decrease platelet-dependent thrombosis in patients with coronary artery disease that a reduction in platelet reactivity would thus reduce plaque progression (Ravn et al., 2001).

**Mediterranean Diet**

The Mediterranean region compresis of land around the Mediterranean Sea and carrers three continents, namely Europe, Asia and Africa. There are 21 countries in the region.

The concept of the Mediterranean diet originated from the Seven Countries Study initiated by Ancel Keys in the 1950s. The traditional dietary patterns typical of Crete, much of the rest of Greece, and southern Italy in the early 1960s were considered to be largely responsible for the good health observed in these regions (Hu, 2003; Willett et al., 1995; Trichopoulou and Lagiou, 1997; Lasheras et al., 2000).

The relative protection noted in Southern Europeans was initially assumed to be because of the dietary practices of the Southerners. What was apparent from this study was that the diet of Southern Europe like Spain and Portugal was low in animal fat, high in areals, pubes and vegetables and the use of olive oil. A Mediterranean diet has many important health benefits, while not sparing on taste or making you feel like you are disappointed yourself.

In order to validate this hypothesis a single blind secondary prevention trial called the Lyon diet Heart study was taken up. In this study 50-70% reduction in the
risk of cardiovascular risk was reported (de Lorgeril et al., 1994, de Lorgeril et al., 1999 and de Lorgeril et al., 1997). The dyeno study showed the importance of fresh fruit and vegetables, bread and cereals, and fish in the diet (de Lorgeril and Salen, 2000) greeks and the population from Sothern Italy and Spain also had one more essential component in their diet, namely \( \alpha \)-Linolenic acid. The Greeks got it from leafy vegetables and eggs of chicken fed green leafy6 material. They also got it from walnuts. Studies among the old in Greece, Denmark, Australia, Spain and China have exposed that the largely Mediterranean dietary pattern was more significant for long life than single nutrients. These conclusions suggest that a Mediterranean diet is related with longer survival (Trichopoulou, 2001).

Interestingly the mortality rate from heat diseases in the Mediterranean Island of Malta were not similar to those of people of Greece or Southern Spain, but was higher and resembled that of people Malta was conquered by several different nations and each conqueror left behind their largely of food. The overall result is an unique dietary pattern quite different from that of the region.

The major properties of the Mediterranean diet (Figure 5) includes a large amount of plant food [fruits, vegetables, whole-grain cereals (including bread and potatoes), nuts, and legumes]; olive oil as the main source of fat; fish and poultry consumed in low-to-moderate amounts; partly low consumption of red meat; and moderate consumption of wine, normally with meals, low consumption of milk and dairy products (Michelli, 2003; Willett et al., 1995; Trichopoulou, 1997; Lasheras et al., 2000).
Recently, Singh et al. has tested an “Indo-Mediterranean diet” in 1000 patients in India with presented coronary disease or at high risk for coronary disease. As compared with the control diet, the intervention diet — characterized by increased intake of mustard or soybean oil, nuts, vegetables, fruits, and whole grains — decreased the rate of fatal myocardial infarction by one third and the rate of unexpected death from cardiac causes by two thirds (Hu, 2003). Considering all the evidence relating to diet and inflammation, the most excellent diet for protecting against the metabolic derangements related with obesity and metabolic syndrome would be elevated in fibre-rich cereals, fruit, vegetables, fish, virgin olive oil and nuts; moderate in wine; and low in meat, processed meat foods and no trans-fatty acids (Bulló et al., 2007).

**Beneficial of fruits**

Increased intake of fruits, vegetables, herbs and some of their component decrease risks and may prevent some diseases (Amagase et al., 2001).

In condition of health benefits, fruit high consumption in daily diets has demonstrated to mainly decrease the event and mortality rates of cancer,
cardiovascular disorders, and other diseases caused by oxidative stress (Knekt et al., 1997; Cox et al., 2000; Vattem et al., 2005; Riboli and Norat, 2003; National Academy Press, Washington, DC, 1989).

Fruits and Nuts are rich in phenols, flavonoids, isoflavonoids, phytosterols and phytic acid, and have been associated to decrease in plasma lipids and offer defense against cardiovascular disease (Serra et al., 2004; Ortega, 2006).

Appel et al., (1997) also reported that a diet rich in fruits has a positive effect on blood pressure in both normotensive and hypertensive adults. Fruits are main sources of diet potassium, and potassium (K) has itself been showed to apply a defensive function on bone and the Ca health. This effect, can play a role in hypertension. Because calcium balance involves calcium intake, calcium absorption, and calcium excretion, factors effecting each of these functions must be measured for their impact on bone health. Dietary factors which influence the quantity of Ca lost in urine are as important for the calcium health as dietary factors influencing in Ca intake and Ca absorption (Rafferty et al., 2005).

Fruits are not only high in fiber but also high in β-carotene, vitamins C and E, polyphenols and various important minerals. These main components have been recommended to be responsible for the beneficial effect of fruits on human health, and particularly cardiovascular disease (Panagiotakos and Polychronopoulos, 2005).

**Beneficial effects of Vegetables**

Properly planned vegetarian diets are beneficial for health and nutritional sufficiency (Craig, 2010). Vegetarian diets are related not only with lower body weight (Dwyer, 1988) and lower blood pressure (Beilin and Burke, 1995; Appleby et al., 2002; Fraser, 1999; Key et al., 1999; Kelly et al., 2006) but also associate with lower risks of MS and certain chronic diseases than are nonvegetarian diets (Fraser, 2009; Cragio, 2009; Key et al., 2009; Appleby et al., 2002; Fraser, 2003).

Lower blood pressure levels may also be associated the potassium, magnesium, antioxidants, dietary fat, and fiber found in vegetarian diets (Berkow and Barnard, 2005).
Williams et al.,(1999) demonstrated that regular consumption of vegetables during the year was inversely related with the risk of Type 2 diabetes(William et al.,1999). Bazzano et al.,(2002) showed in the first NHANES epidemiological follow-up study that incidence of vegetable consumption was inversely connected with stroke incidence, stroke mortality, ischemic heart disease mortality, CVD mortality, and all-cause mortality in the general U.S. population(Bazzano et al.,2002).

Epidemiologic studies in children have shown that there are beneficial relationships between asthma, atopic disease and dietary antioxidants, such as vitamin C, some carotenoids, selenium, and antioxidant-rich vegetables and fruits(Devereux and Seaton,2005).

**Beneficial effects of Oils**

Preclinical and clinical studies show a good association between dietary habits and the rate of disease. Diets elevated in some kinds of fat may enhance the risk of heart disease and some forms of cancer (Amagase et al.,2001). A number of components of the diet have been shown to influence plasma lipid and lipoprotein concentration. For example, replacing saturated fatty acids with polyunsaturated fatty acids (PUFA) is considered to lower low-density lipoprotein (LDL) concentration and may promote a modest lowering in HDL concentration(Richard et al.,1980; Wardlaw and Snook,1990).

Oils also contain secondary metabolites from the plant (Gershenzon and Croteau, 1991) which have an extensive range of effects on health, including positive effects on cardiovascular diseases, some tumors, and inflammatory processes. (Harborne and Williams,2000; Reddy et al., 2003; Trouillas et al., 2003). These properties depend on their capacity to scavenge free radicals, prevent peroxidation of membrane lipids, chelate metals, and stimulate the activity of antioxidant enzymes(Gutie´rrez et al., 2003; Lee et al., 2003).

Animal studies have postulated the non-hydrogenated Coconut oil decreased total cholesterol, (Cox C et al.,1955; Sundram et al.,1994) low density lipoprotein cholesterol (LDL-c) and triglyceride levels and raised high density lipoprotein cholesterol (HDL-c) values (Nevin,2004).
**Fatty acid profile of dietary fats**

The nutritional effects and biological properties of dietary fats are related to their fatty acid composition. They are classified mainly as saturated, mono saturated and poly saturated.

Among the poly unsaturated fatty acids two are nutritionally important. They are $\omega$-3 and $\omega$-6 families. The parent fatty acid of $\omega$-6 family is linoleic acid and that of $\omega$-3 family is linolenic acid. There are their additional fatty acids important for human health. They are archidonic acid which is a $\omega$-6 fatty acid, eicosapentanoic acid which is a $\omega$-3 fatty acid and docosa hexanoic acid which is also a $\omega$-3 fatty acid. Fish are the primary sources of the long chain $\omega$-3 fatty acids. Beneficial effects of eating fish have been established in experimental animals as well as in human studies.

**Fish oil**

The polyunsaturated fatty acids found in fish (eicosapentaenoic and docosahexaenoic acids) efficiently control haemostatic factors, and prevent cardiac arrhythmias, cancer and hypertension. They also play a major function in the protection of neural functions and the inhibition of specific psychiatric disorders.

**Healthy Lifestyle**

A healthy lifestyle started early in life and continued to older ages is mainly effective for the avoidance of diseases and disability(Kennedy and Offutt,2000). In general healthy lifestyle such as not smoking, intake a healthy diet, exercising, and obtaining optimal body weight may be additional useful in decreasing risk of cardiovascular disease, diabetes, and cancer than any other single factor (Stampfer et al.,2000; Chiuve et al.,2006; Hu et l.,2001;Platza et al.,2001; Knoops et al., 2004; Trichopoulou et al.,2003).

In agreement with the task force report of the European Society of Cardiology on “Prevention of Coronary Heart Disease in Clinical Practice,” (Wood et al.,1998;Krauss et al., 2000; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,2001) and the conclusions reached from international comparisons of mortality(Kesteloot ,1992).
The majority significant recommendations for lifestyle factors in relative to possible health gains are contained in the following three rules:

- Don’t smoke.
- If you use alcohol, do so in moderation.
- Be moderately to strongly physically active at least 30 minutes each day.

In large eventual cohort of actually healthy women, a healthy lifestyle consisting of moderation from smoking, low body mass index, moderate alcohol consumption, standard exercise, and healthy diet was related with a considerably decreased risk of total and ischemic stroke (Kurth and Moore, 2006).

**Unhealthy lifestyle**

Unhealthy lifestyle such as smoking, excessive alcohol use, an unhealthy diet and unsatisfactory physical exercise are also associated to an increased risk of cardiovascular conditions.

Unhealthy lifestyle behaviors, such as physical inactivity, insufficient fruit and vegetable intake, high alcohol use, and smoking, frequently occur together (Orleans, 2004; Pronk et al., 2004; Strecher et al., 2002; de Vries et al., 2008).

These are associated to chronic diseases like cardiovascular diseases and cancer (Pelle et al., 2009; Albert et al., 2009; Graham et al., 2007; Molenaar et al., 2000; Ezzati et al., 2007).

Studies have demonstrated that those who have a poorer income and educational level (ie, a low socioeconomic status) are commonly more disposed to have an unhealthy lifestyle (Tu and Cohen, 2008).

**Exercise**

Exercise is physical activity that is designed, controlled, cyclical, and having a goal in mind that enhancement of one or more mechanisms of physical fitness is an objective (Carl et al., 1985).
Types of exercise

Physical exercises are generally divided into three types (http://www.nhlbi.nih.gov/health/public/heart/obesity/phy_active.pdf). Due to the overall effect they have on the human body:

1) Flexibility exercises, such as stretching, improve the range of motion of muscles and joints.

2) Aerobic exercises, such as cycling, swimming, walking, skipping rope, rowing, running, hiking or playing tennis, focus on increasing cardiovascular endurance (O'Connor et al., 2005).

3) Anaerobic exercises, such as weight training, functional training, eccentric training or sprinting, increase short-term muscle strength (de Vos et al., 2006).

Beneficial effects of Exercise:

The benefits of exercise have been demonstrated since antiquity. Marcus Cicero, around 65 BC, stated: "It is exercise alone that supports the spirits, and keeps the mind in vigor." (http://www.inspirational-quotes-and-quotations.com/quotes-about-exercise.html). The link between physical health and exercise (or lack of it) was only created in 1949 and showed in 1953 by a team led by Jerry Morris, Kuper Simon (11 September 2009). "The man who invented exercise". Financial Times (http://www.ft.com/cms/s/2/e6ff90ea-9da2-11de-9f4a-00144feabdc0.html; Morris et al., 1953).

Exercise prevents cardiovascular disease, and its antiatherogenic effects have been explained in different animal models (Froelicher, 1972; Kramsch et al., 1981). Exercise can also completely control risk factors that are related with cardiovascular disease: hypertension, diabetes mellitus, obesity, elevated plasma lipids, and endothelial dysfunction (Shephard et al., 1999).

Exercise positively changes lipid and carbohydrate metabolism. The exercise-induced raise in high density lipoproteins is powerfully related with changes in body weight (Tran and Weltman, 1985).

Moreover, standard exercise in overweight women and men raises the beneficial effect on blood lipoprotein levels (Wood et al., 1991). A 2008 review of
cognitive enrichment therapies (strategies to slow or reverse cognitive decline) resulted that "physical activity and aerobic exercise in specific, increases older adults cognitive function" (Hertzog et al., 2008). There are several possibilities for why exercise is useful for the brain. Examples are shown:

1. Raising the blood and oxygen flow to the brain.
2. Elevating growth factors that help create new nerve cells and promote synaptic plasticity (van Praag et al., 1999; Hunsberger et al., 2007).
3. Enhancing chemicals in the brain that help cognition, such as dopamine, glutamate, nor epinephrine, and serotonin (Parker-Pope, 2006).

When a person exercises, levels of both circulating serotonin and endorphins are raised. (Andrea, 1999). These levels are expected to remain elevated even several days after exercise is discontinued, possibly contributing to improvement in mood, elevated self-esteem, and weight control (Dr. Kenneth R. Fox).

A 2010 review of published scientific research recommended that exercise mainly develops sleep for most people, and helps sleep disorders such as insomnia (Buman and King, 2010).

**Genetic Factor in CVD**

The health conditions and disease report of human societies have traditionally been associated with the level of their economic development and social organization. With industrialization, the main causes of death and disability, in the higher societies, have changed from a prevalence of nutritional deficiencies and infectious diseases, to those defined as degenerative [chronic diseases such as cardiovascular disease (CVD), cancer, and diabetes]. This change has been followed “the epidemiologic transition.” (Omran, 1971). At any specified time, different countries in the world or even different regions within a country are at different stages of the epidemiologic transition. This transition can happen not only between different disease categories (eg, deaths from childhood diarrhea and malnutrition giving way to adult chronic diseases), but also within a specific disease category (eg, rheumatic heart disease of the young giving way to chronic coronary artery diseases of middle age or valve calcification, degeneration, and heart failure of the elderly) (Pearson et al., 1993).
Several factors may supply to these practical interpopulation differences in the CVD profile. One of those genetic factors explain variance in the risk of event CVD within populations by providing the source for differences in individual inclination in a common and reasonably homogenous environment. They also link to interpopulation differences, due to changeable frequencies of one or more genetic determinants of risk in different ethnic groups. Genetic assistance to lipid disorders, obesity, salt sensitivity, insulin resistance, coagulation derangements, and endothelial dysfunction are being search (Goldbourt et al., 1994).

Variations in CVD rates between different parts of the world suggest relations between genetic susceptibility and obvious environmental changes usually derived to urbanization, rising wealth, and a range of other influences from early childhood to adulthood (Yusuf et al., 2001). Coronary heart disease has a tough hereditary factor. There also show to be genetic influences on some of the psychosocial factors that relate to cardiac risk, such as antagonistic dispositions (Manuck at al. 1999) and cardiovascular stress reactivity (Hewitt and Turner, 1995). In theory, it is possible that some of the social rise in cardiovascular disease might be due to growth of higher risk genes in lower status groups (Marmot et al., 1978).
Aim and Scope:

HDL particles are distinguished by their capacity to exert a wide spectrum of antiatherogenic biological activities, including 1) their capacity to mediate cellular cholesterol efflux by facilitating reverse cholesterol transport (RCT) from the arterial wall and peripheral tissues to the liver, 2) their ability to protect LDL against oxidation, 3) their potent anti-inflammatory actions on cells of the arterial wall, 4) antiapoptotic, 5) vasodilatory, 6) antithrombotic, and 7) antiinfectious activities. Since now CVD is beginning to be recognised as a consequence of inflammation, attention is focussed not only on oxidation but also on inflammation. Inflammation is a systemic body response aimed to decrease the toxicity of harmful agents and repair damaged tissue. Chronic inflammation, which may be measured as circulating levels of an acute-phase protein, such as C-reactive protein (CRP), represents a major CV risk factor. Both the plasma levels and apolipoprotein content of HDL can be significantly altered during the acute phase as well as during acute and chronic inflammation. SAA is able to replace apoA-I in small, dense HDL upon induction of the acute phase. In such SAA substituted HDL, 20 molecules of SAA have been estimated to replace all 3 molecules of apoA-I in each HDL particle. SAA may provide stability to the HDL particle but would not have the functionality of HDL. Also oxidative stress and inflammation can modify HDL associated proteins such as PON and LCAT. As a consequence of decreased LCAT activity, increased HDL concentrations of free cholesterol are frequently observed. This may be the reason why high HDL-C may not correspond to high protection from CVD.

Earlier studies from our lab have shown that South Indians have high HDL and high PON and yet they have a high risk of cardiovascular diseases. Several hypotheses have been put forth to explain this paradox. Although it is possible that Indians are genetically predisposed to the risk of CVD, chronic inflammation as an underlying cause cannot be ruled out. This chronic inflammation may be a part of the diet and lifestyle as well as environment in which Indians live.

To investigate this hypothesis, we wanted to choose a genetically distinct group but living in the same environment and having access to the same food materials as Indians. The Iranian community living in Mysore provided a convenient
model to test these hypotheses. Since the Iranians are genetically distinct from the Indian population but living in the same environment and exposed to the same risk factors as the other Indians, a comparison of the HDL and PON of the Iranians with that of the Indians would give a comparative picture of the susceptibility of the two to dietary and other modifications. This comparative study will give insights into the contribution of environmental factors and lifestyle on the risk of cardiovascular diseases.

**Objectives:**

The major objective of the study was to compare the HDL and PON of Iranians with that of the Indians with a special emphasis on their role in the risk for CVD.

The specific objectives are:

1. Comparison of serum lipid profile of Iranians and Indians.
2. Comparison of serum Lipoproteins from Iranians and Indians for their susceptibility of oxidative modification in vitro.
3. A comparison of the level of modification of the HDL and PON in the blood of Iranians and Indians.
4. Comparison of markers of oxidative stress like oxidized lipids, antioxidant enzymes, reduced glutathione, high sensitive C-Reactive Protein, and the levels of pro and antioxidants.
5. Comparison of diet, lifestyle and other risk factors of Iranians and Indians.