Introduction

Chronic non-communicable diseases are one of the most important threats to the global economy. Among the most common non-communicable diseases that afflict humans worldwide are coronary artery disease (CAD) and diabetes, as reported by Anderson et al. (2010) and Bajaj (2010). CAD refers to any one of the conditions that affect the coronary arteries and reduce the flow of blood and nutrients to the heart. CAD is an epidemic of the recent times and has been considered by Gazino (2005) as the single most important disease in the world until 2020 in terms of morbidity, mortality, disability and economic loss. Epidemic of diabetes is also one of the main threats to human health in the 21st century.

Diabetes and cardiovascular diseases (CVD) often appear as two sides of a coin: diabetes mellitus has been rated as an equivalent of CAD, and conversely, many patients with established CAD suffer from diabetes or its pre-states. Among the cardiovascular conditions, CAD is the most prevalent in the diabetic patients and accounts for the large part of the increased mortality in these patients, as reported by Shirani and Dilsizian (2010). Patients with diabetes have a higher risk of CAD as compared to the non-diabetics, as reported by Berman et al. (2009).

India is experiencing an epidemiological transition, with a large and rising burden of non-communicable diseases, which have been estimated to account for 53% of all deaths and 44% of disability adjusted life years (DALYs) lost in 2005, as reported by Planning Commission (2007). According to World Diabetes Foundation (2010), India has the world's largest diabetes population, with an estimated 50.8 million people living with diabetes. Gupta and Phatak (2003) have reported that India has got the highest number of patients suffering from CAD and the number of CAD patients in India will reach 40 million in 2020. World Health Organization (WHO) has predicted net losses in national income from diabetes and cardiovascular disease to be International Dollar (ID) 336.6 billion in India between 2005 and 2015. Since Indians appear to have an increased predilection for both diabetes and CAD, identification of diabetic patients at risk for CAD
at an early stage when risk factor modification might delay or prevent the clinical onset
CAD in these patients, represents a major challenge.

1.1 Coronary artery disease

CAD is the condition which results due to accumulation of atheromatous plaques
within the walls of the coronary arteries that supply the myocardium with oxygen and
nutrients. CAD is characterized by the presence of atherosclerosis in the epicardial
coronary arteries. Atherosclerosis is a disease of large and medium-sized arteries
characterised by thickening and hardening of the vascular wall. The term atherosclerosis
is derived from the Greek word *athero*, meaning gruel or porridge, and *sclerosis*,
meaning hardening. Atherosclerotic plaque interferes with capability of arteries for
providing sufficient oxygen and nutrients to the heart muscles. Due to a reduction in
oxygen supply, ischemia (cell starvation secondary to a lack of oxygen) of the myocardial
cells can occur. With further progression, any increased demand on cardiac muscles may
produce angina pectoris or chest pain which is the cardinal symptom of CAD. In patients
with occlusive CAD, severe atherosclerosis eventually completely occludes the coronary
artery, causing the heart muscles supplied by the artery to die. This clinical event is
known as myocardial infarction and is accompanied by prolonged chest pain, nausea,
sweating, shortness of breath and weakness. Over time, CAD can weaken the heart
muscle and lead to heart failure (inability of heart to pump enough blood throughout the
body) and arrhythmias (problems with the speed or rhythm of the heartbeat). CAD is
usually diagnosed by using electrocardiography and/or angiography.

According to Anand *et al.* (2000), CAD prevalence is 10.7% among South Asians
and 4.6% in Europeans. According to American Heart Association (2006), CAD has an
estimated prevalence of 6.9% in men and 6% among women in USA. Levy and Kannel
(2001) have reported that CAD rates vary more than 10-fold among different populations.
According to Vital and Health Statistics (2005), the prevalence of CAD among various
ethnic groups in USA is: 5.9% among whites, 5.3% in Black African Americans, 4.5%
among Hispanics or Latinos and 3.8% among Asians. According to Mackay and Mensah
(2004), CAD and stroke are globally the second and third largest causes of disease burden
in men aged 15 years and older in 2002 with 6.8% and 5.0% of DALYs lost. Even in women, CAD and stroke are the third and fourth main causes of DALYs lost worldwide.

CAD has assumed epidemic proportions in India, as urban Indians have CAD rates similar to overseas Indians, which is 4-fold higher than Americans. Enas and Senthilkumar (2002) have reported that during the past three decades there has been a substantial increase in CAD among developing countries particularly India, while during the same period there has been a significant decline in CAD mortality in developed countries. The data from the native Indian populations reported by Padmavati et al. (1959) had shown a low prevalence of CAD (1.05%) in 1950s. This has increased markedly, currently ranging from 5.0% - 17.9%, as reported in various studies from different regions of India. Mohan et al. (2001) have shown the crude prevalence of CAD to be 11% and the age-adjusted prevalence to be 9.0%. The disease is more prevalent in urban populations and there is a clear gradient in its prevalence from rural to semi-urban to urban populations.

According to Enas and Senthilkumar (2002), CAD among Asian Indians can be broadly categorized into 3 distinct forms: Type I or malignant type occurs in young individuals (<50 years) with marked prematurity and severity. This type is accompanied by the absence or low levels of traditional risk factors and the presence of high levels of newer risk factors. Type II occurs in older individuals (>65 years) with high levels of traditional risk factors and low levels of newer risk factors. Type III or mixed variety occurs between the ages of 50 and 65 and is accompanied by varying combinations of traditional and newer risk factors. Enas (2000) gave the cardinal features of CAD among Indians compared to other populations of the world:

- Higher rates: 2 to 4 fold higher prevalence, incidence, hospitalization, mortality.
- Greater prematurity: 5 to 10 years earlier onset of first myocardial infarction, 5 to 10 fold higher rate of myocardial infarction and death in young (<40 years of age).
- Greater severity: Three vessel disease common even among young premenopausal women, large myocardial infarction with greater muscle damage.
• Higher prevalence of glucose intolerance: Insulin resistance syndrome, diabetes, central obesity.

• Lower prevalence of traditional risk factors: Hypertension, obesity, cigarette smoking, cholesterol levels

• Higher prevalence of newer risk factors: High levels of lipoprotein A, homocysteine, fibrinogen and inflammatory markers.

• Higher rates of clinical events for a given degree of atherosclerosis: Double that of Whites, 4 fold higher than Chinese.

The CAD rates among first generation immigrants are usually intermediate between those of the country of origin and the country of immigration. Enas and Yusuf (1999) have reported that Asian Indians are singular exception in having higher rates of CAD than the native population of the adopted count. Asian Indians residing in different countries have higher rates of incidence, hospitalization, prevalence, morbidity, mortality and case fatality from CAD than people of other ethnicity. Several factors appear to have contributed to the acceleration of CAD epidemic in India:

• Demographic transition in Western countries was accompanied by a decrease in deaths due to infectious diseases and increased mortality due to non-communicable diseases. A similar demographic transition in India has also led to an increase in the number of older people (aged ≥60 years), from 19.61 million in 1950 to a projected 75.93 million in 2000, as reported by Sharma and Xenos (1992). According to Human Development Fact Sheet (2003) of India, the average life expectancy at birth in India is 63.7 years. This is much higher as compared with the national average of 41.2 years in 1951–1961 reported by World Bank (1993). The increase in life expectancy has brought a large section of the population to an age where CVD starts manifesting itself.

• Confluence of both traditional risk factors and newer risk factors in Indians. Conventional factors like hypercholesterolaemia, diabetes, hypertension, smoking owe their origin to growing urbanization and western acculturation amongst
Indians. Newer risk factors like hyperinsulinaemia, insulin resistance, lipoprotein A etc are determined by genes and their high prevalence amongst Indians explains the malignant nature of CAD that typically affects Indians.

- Relationship between low birth-weight (which is highly prevalent amongst Indian newborns) and enhanced susceptibility to risk factors also provide a plausible explanation for the excess burden of CAD among Indians.

### 1.2 Diabetes mellitus

The name diabetes mellitus has Greek and Latin roots. Diabetes comes from the Greek verb ‘to siphon’ and mellitus is Latin for ‘sweet’ like honey. Diabetes mellitus has been originally described as a disorder of excessive, sweet urine. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine and called the ailment ‘sweet urine disease’ (Madhumeha). According to WHO (1999), diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Diabetes, without qualification, usually refers to diabetes mellitus, but there are several rarer conditions also named diabetes. The most common of these is diabetes insipidus (insipidus meaning "without taste" in Latin) in which the urine is not sweet; it can be caused by either kidney or pituitary gland damage.

The earliest description of diabetes are found in ancient Indian, Chinese and Greek texts, as reported by Harris and Zimmet (1997), Keen and Alberti (1997) and Ammini (2010). WHO (1985) classified diabetes mellitus into insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). This system represents a compromise between clinical and aetiological classification and allows classification of individual subjects and patients in a clinically useful manner even when the specific cause is unknown. The latest classification by WHO (1999) encompasses
both clinical stages and etiological types of diabetes mellitus and other categories of hyperglycemia. The term IDDM and NIDDM are no longer used. The recent classification includes three main forms of diabetes: type 1 diabetes mellitus, type 2 diabetes mellitus (T2DM) and gestational diabetes; which have similar signs, symptoms and consequences, but different causes and population distribution.

T2DM (previously known as adult-onset diabetes, maturity-onset diabetes or NIDDM) is the most common form of diabetes. It is characterized by disorders of insulin resistance and insulin secretion, either of which may be the predominant feature. T2DM is the main driver of the diabetes epidemic and represents more than 90% of all diabetes cases. Type 1 diabetes mellitus describes the process of β-cell destruction that may ultimately lead to diabetes mellitus, with absolute insulin deficiency, in which ‘insulin is required for survival’ to prevent the development of ketoacidosis, coma and death. Gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. Other than the above forms, there are other specific types of diabetes also. Diabetes caused by genetic defects of the β-cell includes the forms of diabetes that are associated with monogenetic defects in β-cell function and are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Diseases of the exocrine pancreas (including pancreatitis, trauma, infection, pancreatectomy and pancreatic carcinoma) and various endocrinopathies can also cause diabetes. Certain drugs and infections (coxsackievirus B, cytomegalovirus, adenovirus, and mumps) may also induce diabetes.

According to WHO (1999), diabetes is diagnosed by demonstrating any one of the following:

- fasting blood glucose level $\geq 110$ mg/dl or fasting plasma glucose level $\geq 126$ mg/dl.
• plasma glucose at or above 200 mg/dl after a 75 g oral glucose load in a glucose tolerance test.

• random plasma glucose at or above 200 mg/dl.

Spellman (2010) reviewed the factors and mechanisms that cause T2DM. It is caused by two major factors: insulin resistance and impaired insulin secretion. Increased tissue resistance to insulin generally occurs first and is eventually followed by impaired insulin secretion. Insulin resistance prevents the proper use of insulin at the cellular level. As a result, glucose cannot enter target cells and accumulates in the bloodstream, resulting in hyperglycemia. There are numerous theories as to the exact cause and mechanism for this resistance, but central obesity (fat concentrated around the waist in relation to abdominal organs) predisposes for insulin resistance, possibly due to its secretion of adipokines that impair glucose tolerance. The high blood glucose levels in T2DM patients often stimulate an increase in insulin production by the pancreas. As a result, these patients often have excessive insulin production i.e. hyperinsulinemia. But over the years, β cell dysfunction develops and leads to impaired insulin secretion. The exact mechanism for β cell dysfunction is still not clear. Increased hepatic glucose production and decreased insulin mediated glucose transport in muscle and adipose tissues are the other contributing factors for T2DM.

Obesity is the most important risk factor for T2DM, as reported by Bajaj (2010). The majority of patients with this form of diabetes are obese, and obesity itself causes or aggravates insulin resistance. Obesity is found in approximately 90% of developed world patients diagnosed with T2DM. Many of those who are not obese according to BMI may have an increased percentage of body fat distributed predominantly in the abdominal region. Abdominal fat is especially active hormonally.

Other factors for T2DM include ageing and family history. It is often associated with strong familial, likely genetic, predisposition. Individuals with first-degree relatives with T2DM have a much higher risk of developing it, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of diabetes. It occurs more frequently in
women with prior gestational diabetes mellitus and in individuals with hypertension or
dyslipidemia. Its frequency varies in different racial/ethnic subgroups. However, in the
last decade, T2DM has increasingly begun to affect children and adolescents, probably
due to greatly increased childhood obesity seen in recent decades in some places.

On the basis of data from population-based epidemiological studies, King et al.
(1998) have estimated the global burden of diabetes at 135 million in 1995, with the
number reaching 299 million by the year 2025. Wild et al. (2004) have estimated the
worldwide prevalence of diabetes to be 4.4% in 2030. On the basis of studies from 91
countries, Shaw et al. (2010) have estimated the world prevalence of diabetes among
adults (aged 20–79 years) to be 6.4% in 2010, affecting 285 million adults. It is estimated
to increase to 7.7%, and 439 million adults by 2030. There is substantial variation in
diabetes prevalence worldwide, with a prevalence of practically zero, in rural Third
World countries and 37-50% among the Asia-Pacific Islanders and American Indians.
Several ethnic groups: Hispanics, Blacks, Native American and Asians are particularly
susceptible to T2DM. Asia is one of the regions that have high prevalence of diabetes and
it is estimated that 20% of current global diabetic population resides in South east Asia
region. Table 1 shows the current prevalence estimates for diabetes mellitus in South east
Asia.

Table 1: Prevalence estimates of diabetes mellitus in South east Asia for 2010

<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>Percentage prevalence of Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>South east Asia</td>
<td>7.0</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>6.1</td>
</tr>
<tr>
<td>Bhutan</td>
<td>2.9</td>
</tr>
<tr>
<td>India</td>
<td>7.1</td>
</tr>
<tr>
<td>Maldives</td>
<td>6.5</td>
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<tr>
<td>Mauritius</td>
<td>17.0</td>
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<tr>
<td>Nepal</td>
<td>3.3</td>
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<tr>
<td>Sri Lanka</td>
<td>11.5</td>
</tr>
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</table>

Source: International Diabetes Federation (2010)
India has long passed the stage of a diabetes epidemic. The problem has now reached, in scientific language ‘pandemic proportions’. According to Bajaj (2010), India has 50.76 million people with diabetes. Sicree et al. (2006) have reported that according to International Diabetes Federation (IDF) estimates, the total number of diabetic subjects are around 40.9 million in India and this is expected to rise to 69.9 million by the year 2025. Wild et al. (2004), on the basis of WHO study, have reported the number of persons with diabetes in India in 2000 to be nearly 31.7 million and estimated that this number is likely to increase to 79.4 million in 2030. The age standardized prevalence rate for diabetes mellitus in India has been reported to be 4.3% using the WHO (1999) criteria and 3.6% using the ADA criteria (Sadikot et al. 2004a, Sadikot et al. 2004b). In a national non communicable disease risk factor surveillance conducted in six different geographical locations in India, Mohan et al. (2008) have reported that there is a geographical difference in the overall prevalence of self-reported diabetes, with the centres in southern states having a higher prevalence i.e. Trivandrum (9.2%); Chennai (6.4%) compared with Delhi (6.0%) and Ballabgarh (2.7%) in north, Dibrugarh (2.4%) in east and Nagpur (1.5%) in west/central India. The lowest prevalence of self-reported diabetes has been recorded in rural (3.1%) followed by peri-urban/slum (3.2%) and the highest prevalence in urban areas (7.3%).

According to Mohan et al. (2007b), the ‘Asian Indian Phenotype’ makes Asian Indians more prone to diabetes. This phenotype refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, higher waist circumference (WC) despite lower body mass index (BMI), low adiponectin and higher C-reactive protein (CRP) levels. The sudden increase in diabetes prevalence during the last few years is also due to urbanization and life style changes.

Chronic elevation of blood glucose level in diabetic patients leads to damage of blood vessels, leading to microvascular disease (due to damage to small blood vessels) and macrovascular disease (due to damage to the arteries). The microvascular complications include diabetic retinopathy, nephropathy and neuropathy. Diabetic retinopathy can be defined as damage to microvascular system in the retina due to prolonged hyperglycaemia. Retinopathy may begin to develop as early as 7 years before
the diagnosis of diabetes in patients with T2DM. Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. It is defined by proteinuria >500 mg in 24 hours in the setting of diabetes and is preceded by microalbuminuria (albumin excretion of 30-299 mg/24 hours). According to Gross et al. (2005), about 7% of patients with T2DM may already have microalbuminuria at the time they are diagnosed with diabetes. Diabetic neuropathy is recognized by the American Diabetes Association (2007) as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. It can be classified as peripheral, autonomic, proximal, and focal. Each affects different parts of the body in different ways.

Macrovascular complications of diabetes include various cardiovascular complication like CAD, cerebrovascular complications, peripheral vascular disease and diabetic myonecrosis (muscle wasting). Diabetes significantly increases the risk for developing cardiovascular disease and has been reported by Franco et al. (2007) to be the major reason for a nearly 8-year shorter life expectancy of the diabetic patients. Among the cardiovascular conditions, CAD is most prevalent in the diabetic patients and accounts for the large part of increased mortality in these patients. CAD leads to angina or myocardial infarction in diabetic patients. The most common cerebrovascular complication in diabetic patients is stroke. According to Turner et al. (1998), stroke occurs in 6% of diabetic patients within 10 years of diagnosis. Peripheral vascular disease contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot. The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system.

1.3 **Coronary artery disease in type 2 diabetes mellitus**

Diabetes acts an independent risk factor for CAD. According to Laakso (2001), more than 70% of patients with T2DM die of CVDs. Although a considerable decline in the incidence of CAD is reported among the general population in western countries,
there has been no decrease in CAD mortality among diabetic subjects (Haffner 1999, Ford et al. 2007). The long-term cardiovascular mortality is similar in diabetic patients without prior myocardial infarction and non-diabetic patients with pre-existing myocardial infarction (Haffner et al. 1998, Dagenais et al. 2009). Patients with diabetes but without other conventional risk factors for atherosclerosis have a risk of death from CAD 2–4 times that of age-matched controls (Stamler et al. 1993, Uusitupa et al. 1993). Insulin resistance is an independent risk factor for CAD, as reported by Wheatcroft et al. (2003).

The Framingham Heart Study reported by Kannel and McGee (1979) gave the first report on the increased prevalence of CAD in T2DM. The prevalence of CAD among diabetic patients (39.1% in males and 27.2% in females) in this study has been reported to be higher in diabetic patients as compared to non-diabetic subjects (19.1% in males and 10.2% in females). Ramachandran et al. (1998) have reported the prevalence of CAD as 14.2% in a population based study in Chennai (India). Mohan et al. (2001) have reported the prevalence of CAD to be 21.4% among diabetic subjects and 9.1% in subjects with normal glucose tolerance. The prevalence of CAD among diabetic patients in various studies from India has been reported to range from 4.5% to 33.5%. Several clinic based studies from India (Verma et al. 1979, Garg et al. 1994, Patel et al. 1996, Das et al. 1999) have found CAD as the leading cause of death in diabetic patients.

Diabetics are prone not only to overt manifestations of atherosclerotic heart disease, but also to the silent and sub-clinical manifestations of atherosclerosis. People with diabetes may be less likely to experience exertional angina or chest pain with exercise testing, thus potentially increasing the difficulty of diagnosing significant CAD. Type 2 diabetics are prone to silent myocardial ischaemia even before the development of overt CAD. Various Indian studies (Jalal et al. 1999, Sukhija et al. 2000, Agarwal et al. 2009) have reported the prevalence of silent ischaemia varying from 10% to 46% in T2DM patients.

Diabetic women are at increased risk of CAD, with a risk of cardiovascular death up to 7.5 times that of women without diabetes. The protective effect against CAD
observed among pre-menopausal women disappears after diabetes sets in. Vilbergsson et al. (1998) have reported that estimates of CAD mortality in diabetic men range from 1- to 3-fold the rate in non-diabetic men, whereas estimates in diabetic women range from 2- to 5-fold the rate in non-diabetic women. Several mechanisms have been proposed to explain the greater relative risk of CAD in diabetic women. Adverse changes induced by T2DM in some coronary risk factors, such as HDL-cholesterol, triglycerides, and blood pressure, have been found to be more pronounced in women than in men in some studies (Howard et al. 1998, Juutilainen et al. 2004, Zornitzki et al. 2007). It has also been proposed by Steinberg et al. (2000) that diabetes in women may interfere more with protective mechanisms in the vascular wall, leading to increased risk of CAD.

The impressive correlation between CVD and alterations in glucose metabolism has given rise to the hypothesis that atherosclerosis and T2DM may share common antecedents. Stern (1995) has given the common soil hypothesis for diabetes and CVD. The author has suggested that rather than atherosclerosis being a complication of diabetes, both conditions have common genetic and environmental antecedents, i.e. they spring from a ‘common soil’. Adverse environmental conditions (less-than-optimal nutrition in fetal and early life) are associated with an enhanced risk of both diabetes and CVD many decades later. According to Reaven (2005), diabetes and CVD are the constituents of the metabolic syndrome in which insulin resistance plays a contributory role. There is clustering of several metabolic disorders like dyslipidemia, hypertension, hyperglycemia and central abdominal obesity. Various other risk factors for CAD like inflammatory markers, atherothrombotic factors, fibrinolytic and coagulation factors have also been described in diabetic patients.

Taking into consideration that T2DM and atherosclerosis share common risk factors, the American Heart Association has stated that ‘diabetes is a cardiovascular disease’, as reported by Grundy et al. (1999). Diabetes has been accorded status of a CAD ‘risk factor equivalent’ by the US National Cholesterol Education Program (NCEP). According to NCEP III (2001), diabetic patients do not need specific CAD risk assessment; but instead, they may be managed as if they have CAD.
Various pathophysiologic mechanisms have been proposed that explain the increased risk of CAD in T2DM patients. Ahmed et al. (2010) and Laakso (2010) have recently reviewed the pathophysiology of CVD in T2DM. The pathophysiologic process of atherosclerosis in diabetic subjects is accelerated by several factors such as hyperglycemia, insulin resistance, abnormal lipid profile, oxidative modification of lipoproteins, altered rate of fibrinolysis and autonomic neuropathy. Endothelial dysfunction is a precursor to and also an effect of atherosclerosis. The vascular endothelium is a multifunctional organ system that resists thrombosis and atherogenesis and regulates blood flow by producing nitric oxide, the prime mediator of vascular reactivity. Diabetes impairs endothelial function through several proposed mechanisms (hyperglycemia, hyperinsulinemia, oxidative stress). Endothelial dysfunction is tightly linked to insulin resistance. The vasodilatory action of insulin is dependent on nitric oxide (NO) generation. Hyperglycemia inhibits production of NO and also leads to the reduction of NO synthesis due to elevated free fatty acid levels and increased production of reactive oxygen species (ROS), as reported by Inoguchi et al. (2000).

Insulin resistance and T2DM are associated with several changes in lipids and lipoproteins, which is known as diabetic dyslipidemia. The fundamental defect in lipid metabolism in patients with T2DM is the hepatic overproduction of large very low density lipoprotein (VLDL) particles, particularly VLDL1, as reported by Adiels et al. (2008). Overproduction of VLDL particles initiates a series of other changes in lipoproteins, resulting in high levels of remnant particles, small dense low density lipoprotein (LDL), and low high density lipoprotein (HDL) cholesterol levels. In addition to reduced levels of HDL-cholesterol and apolipoprotein A-I (apo A-I), there are abnormalities in the size and composition of the HDL particles (decreased particle numbers, changes in particle composition) in patients with T2DM. Reduced concentrations of HDL and apo A-I promote the accumulation of cholesterol in the vessel wall and lead to atherosclerosis. In addition, increased oxidation of LDL in diabetic patients has been associated with increased risk for CAD, possibly by promoting endothelial dysfunction.

Diabetes is associated with increased prothrombotic risk. The propensity for clotting is increased in patients with diabetes, as reported by Juhan-Vague and Alessi
The level of plasminogen activator inhibitor (PAI), which suppresses fibrinolysis, is elevated in the serum and atherectomy specimens of diabetic patients. In addition, increased concentrations of prothrombotic substances (such as tissue factor, fibrinogen and factor VII) have been found in diabetic patients, as reported by Schneider and Sobel (2001). Platelets in T2DM adhere to vascular endothelium and aggregate more readily than those in healthy individuals.

Autonomic neuropathy, which leads to an increased propensity for malignant arrhythmia, is another possible mechanism for the high morbidity and mortality from CAD in diabetic patients. Sympathovagal imbalance from parasympathetic denervation occurs in 40% to 50% of patients as reported by Bernardi et al. (1992). The resulting variation in areas of denervation in the myocardium may lead to arrhythmogenesis and sudden cardiac death.

On the molecular level, oxidative stress appears to play a role in diabetic atherogenesis. Hyperglycemia leads to increased production of ROS and to nonenzymatic glycoxidation of proteins, which alters their structure and function. Ultimately, these altered proteins, known as advanced glycation end products (AGEs), accumulate in patients with a chronically elevated glucose level as reported by Brownlee (1995). AGEs cause increases in vascular permeability, procoagulant activity, adhesion molecule expression and monocyte influx leading to vascular injury.

1.4 Risk factors for coronary artery disease

Various prospective epidemiological studies (Dawber et al. 1957, Kannel and McGee 1979, Cooper 1993) in the United States and Europe have lead to the development of the concept of risk factors and their relationship to the incidence of CAD. The incidence of CAD is compatible with the pattern of the distribution of CAD risk factors. The association is almost always a statistical one, and so the fact that a particular person has a particular factor merely increases the probability of developing a certain type of cardiovascular disease, it does not mean that the individual is certain to develop CAD. Conversely, the fact that an individual does not have a particular cardiovascular risk factor does not guarantee protection against CAD.
CAD has a multi-factorial etiology, with many of the risk factors being influenced by lifestyle. Diabetes, hypertension, obesity, dyslipidemia, lifestyle related factors (smoking, alcohol consumption, physical inactivity, socioeconomic status) and some non modifiable risk factors (age, sex and family history of CAD) are the major traditional risk factors for CAD identified from various studies (Kannel et al. 1961, Anderson et al. 1991) as shown in Figure 1.

**Figure 1: Various traditional risk factors for CAD**

Hypertension is an extremely common risk factor for CAD. It is one of the major risk factors contributing to premature mortality from cardiovascular diseases. As reported by Ezzati *et al.* (2002), hypertension is ranked third as a cause of DALYs losses in the world. According to Lawes *et al.* (2008), 80% of the disease burden attributable to hypertension occurs in low and middle income countries like India. The Framingham Heart Study has clearly demonstrated the association of hypertension with CAD in the general population, as reported by Lloyd-Jones *et al.* (2004). The overall prevalence of hypertension in Chennai Urban Population Study (CUPS) has been reported by Deepa *et al.* (2002b) to be 21.1%; the prevalence of CAD being significantly higher among hypertensives compared to normotensives. However, the role of hypertension as a risk factor for CAD in diabetic patients is not fully clear.
Obesity has been reported by Gutierrez-Fisac et al. (2006) as a major health problem with an increasing incidence in the recent 30 years in industrialized countries. There are two basic patterns of obesity, one in which excess fat is found primarily in the abdominal area (male-pattern or android obesity) and one in which excess fat deposits form around the hips and buttocks (female-pattern or gynecoid obesity). Android obesity, which is also found in some women (especially after menopause), is associated with an increased risk of cardiovascular disease, specifically CAD and stroke. A positive correlation between obesity and cardiovascular death and all other causes of death has been observed (Jousilahti et al. 1996, Spataro et al. 1996). The property of obesity that discriminates it from other risk factors is that, besides being an independent risk factor, it is also related to other major cardiovascular risk factors such as hypertension, dyslipidemia and diabetes mellitus. Therefore, obese cases with CAD deserve the highest priority in risk factor modification. But relation and role of obesity in CAD among diabetic patients is not clear. Some studies (Daousi et al. 2006, Yoo et al. 2009) have reported obesity to be a significant CAD risk factor in T2DM, while others (Bo et al. 1999, Song and Hardisty 2008) have reported that obesity is not a significant CAD risk factor among T2DM patients.

Dyslipidemia is an important risk factor for CAD. Elevated concentration of cholesterol and LDL-cholesterol and reduced HDL-cholesterol level raise the risk of CAD, as reported by Castelli (1988) in the Framingham heart study. Mohan et al. (2001) have reported that serum cholesterol, LDL-cholesterol and total cholesterol/HDL-cholesterol ratio are elevated in those with CAD compared to those without CAD. In diabetes, there is a derangement in the metabolism of lipids and fat, which leads to abnormal serum lipid pattern (diabetic dyslipidemia). Atherogenic dyslipidemia in diabetics is characterized by the three lipoprotein abnormalities: elevated VLDL, small LDL particles and low HDL-cholesterol (the lipid triad). Rajmohan et al. (2000) have reported that elevated serum cholesterol, LDL-cholesterol and low HDL-cholesterol are associated with CAD in subjects with T2DM.

Cigarette smoking is an important and reversible risk factor for CAD. Smoking is associated with adverse effects on serum lipids which include elevation of triglyceride
and reduction of HDL-cholesterol, formation of proatherogenic oxidized particles, activation of sympathetic nervous system, enhanced prothrombotic state and endothelial dysfunction as reported by Moarreaf (2004).

Research into the effect of alcohol on cardiovascular disease has indicated contradictory results (Mukamal and Rimm 2001, O'Keefe et al. 2007). Some studies have reported protective effects from moderate consumption. Although the exact mechanism is not understood, it appears that alcohol raises HDL-cholesterol. Others have reported that drinking four or more drinks per day can have deleterious effects. It raises blood pressure and puts the individual at significant risk of CVDs.

Physical inactivity is a common modifiable risk factor for CAD and is associated with at least a two fold increase in the risk of coronary events (Moarreaf 2004, Kokkinos 2008). Exercise has beneficial effects on weight control and several other important cardiovascular risk factors such as lipid profile, blood pressure as observed by Mora et al. (2007).

Socioeconomic status is associated with CAD risk factors, coronary morbidity and mortality. In industrialized countries, several studies (Sonmez et al. 2004, Harald et al. 2006) have shown that the lowest socioeconomic status groups have higher coronary morbidity and mortality rates and higher coronary risk factors profile. However, studies from developing countries have reported an inverse relation of socioeconomic status with CAD as compared to developed countries.

Advancing age is a risk factor used as a surrogate for atherosclerotic plaque burden. According to Vasto et al. (2010), there is a gradual but progressive accumulation of coronary plaques with ageing, accounting for the increasing risk of CAD with advancing age. Men are more likely than women to develop CAD. Estrogen protects against heart attacks and other forms of CVD. Estrogen increases HDL-cholesterol, which may explain how the hormone reduces the incidence of heart attacks in premenopausal women. Genetic factors also play an important role in the development of CAD.
Despite the long list of traditional risk factors, 50% of the CAD, especially among diabetic patients, still remains unexplained. This has led to the need for identification of newer risk factors, which might contribute to CAD. Inflammatory markers, coagulation and fibrinolytic factors, lipoprotein(a), homocysteine are some of the newer risk factors which might contribute to CAD (Tsimikas et al. 2006, Packard and Libby 2008). Studies on migrant Indians have suggested that excess risk for CAD seen among Indians can be partly explained by some newer factors (Chambers et al. 2000, Enas 2000).

There is emerging evidence that inflammatory risk factors are among the most important risk factors for CAD. Inflammatory processes and specific immune mechanisms are involved in atherogenesis. A significant role of inflammatory markers like C-reactive protein (CRP), interleukin-6 (IL-6), vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecule (ICAM) in CAD has been reported in many studies. Various studies have identified defects in coagulation and the fibrinolytic cascade to play a major role in the pathological mechanisms leading to CAD. These two cascades consist of activators and inhibitors which regulate clot formation and vascular potency. Diabetes is considered to be a hypercoagulable and hypofibrinolytic cascade. An increased level of fibrinogen and PAI-1 has been shown to be associated with CAD in diabetic subjects (Schneider et al. 1993, Deepa et al. 2002c, Gorog 2010). Lipoprotein (a) is a complex of apo A and LDL. It can inhibit plasminogen activity leading to impaired fibrinolysis and has been shown to be associated with CAD in diabetic patients (Mohan et al. 1998, Velmurugan et al. 2003). Homocysteine, a sulphur-containing amino acid, is an atherothrombogenic moiety which triggers platelet adhesion in culture and has been shown to be strongly associated with CAD in several studies (Moghadasian et al. 1997, Dardik et al. 2000).

1.5 Inflammation and coronary artery disease

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. The inflammatory theory of CAD, also known as ‘immunological hypothesis’, is now widely accepted for explaining the vulnerability of plaque and the occurrence of clinical event. Inflammation is involved in the onset and development of atherothrombotic disease, which is accompanied by the emergence of numerous inflammatory biomarkers cytokines, interferons, chemokines etc.
(Ross 1999, Blake and Ridker 2002). Also, a close relation is present between the inflammatory markers and glucose metabolism abnormalities. Thus a common inflammatory basis for both diabetes and CAD could be plausible.

Inflammation participates in atherosclerosis from its inception and development to its ultimate endpoint, thrombotic complications (Ross 1999, Libby 2006, Packard and Libby 2008). Each of the cardiovascular risk factors (smoking, hypertension, diabetes, lipids and lipoproteins) may be associated with the generation of biologically active agents that may lead to dysfunctional changes in the endothelium as shown in Figure 2. Increased levels of oxidized LDL in dyslipidemia, angiotensin II in hypertension, AGEs in diabetes and cytokines in obesity lead to endothelial dysfunction, leading to initiation of inflammation. Endothelial dysfunction leads to increased endothelial permeability to lipoproteins and other plasma constituents, expression of adhesion molecules and elaboration of growth factors that lead to increased adherence of monocytes, macrophages and T lymphocytes.

**Figure 2: Various traditional risk factors in inflammation and CAD**
Adapted and modified from Chyu and Shah (2001).
According to the response to injury hypothesis of atherosclerosis by Ross (1993), the lesions of atherosclerosis represent a specialized form of a protective, inflammatory fibroproliferative response to various forms of insult to the artery wall. Depending upon the nature and duration of the insult, the protective response may become excessive and over many years in its excess, become a disease process.

Figure 3: ‘Response to injury’ hypothesis for atherosclerosis; Adapted and modified from Ross (1993).

The first step of atherogenesis is the development of fatty streak consisting of small sub-endothelial deposits of monocyte-derived macrophages. The presence of several selectin and integrin classes of molecules, including ICAM-1 and VCAM can lead to increased adherence of monocytes and lymphocytes to the endothelium. Once adhered to the arterial endothelium, monocytes penetrate the endothelial lining and enter the
intima of the vessel wall by diapedesis between endothelial cells. This process requires a chemoattractant gradient which is mainly due to monocyte chemoattractant protein-1 (MCP-1). In the vascular wall, macrophages accumulate lipids and become large foam cells. Foam cells, in turn, release growth factors and cytokines that promote migration of smooth muscle cells and stimulate neointimal proliferation. These foam cells continue to accumulate lipid and support endothelial cell dysfunction. Foam cells, T cells and smooth muscle cells eventually form the fatty streak as shown in Figure 3.

Ultimately, the formation and release of numerous growth regulatory molecules and cytokines form a network which is established between cells in the lesion, leading to progression of the lesion to a fibrous plaque or advanced, complicated lesion. As a result, the fibrous cap becomes thin and friable and can rupture, thus creating a thrombus that can lead to myocardial infarction or other complications.

The concept of the involvement of inflammation in atherosclerosis has spurred the discovery and adoption of inflammatory markers for cardiovascular risk prediction. Various risk factors for inflammation include increased levels of cytokines (IL-1, IL-6, TNF-α), chemokines (MCP-1, CXCL8, CXCL10), cell adhesion molecules (VCAM-1, ICAM-1, P-selectin, E-selectin) and acute phase reactants like CRP (Ridker et al. 2000a, Ridker et al. 2000b, Ridker et al. 2000c, Ridker 2003, Aukrust et al. 2008). CRP is the most extensively studied inflammatory marker. Data from multiple large-scale prospective studies have demonstrated that CRP strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, and sudden cardiac death (Koenig et al. 2004, Pai et al. 2004). CRP levels have been reported to be high in studies on Indians with cardiovascular disease (Nyandak et al. 2007, Jaswal et al. 2008). Although studies on markers of inflammation has provided substantial insight into the pathophysiology of atherothrombosis, the clinical utility of measuring these markers remains uncertain.

1.6 Monocyte chemoattractant protein-1

MCP-1 (also known as CCL2: chemokine C-C motif ligand 2) is a CC chemokine which acts as a potent chemoattractant for monocytes and plays a significant
role in inflammation. Chemokines (chemotactic cytokines) are small heparin-binding proteins which constitute a large family of peptides (60-100 amino acids) structurally related to cytokines. The main function of chemokines is to regulate cell trafficking. Chemokines share a similar genomic structure consisting of three exons and two introns. Chemokines are secreted in response to signals such as pro-inflammatory cytokines where they play an important role in selectively recruiting monocytes, neutrophils and lymphocytes. Once induced, the directed migration of cells expressing the appropriate chemokine receptors occurs along the chemokine gradient. This allows cells to move toward high local concentrations of chemokine, as reported by Callewaere et al. (2007). According to Deshmane et al. (2009), chemokines are classified into four subfamilies based on the number and location of the cysteine residues at the N-terminus of the molecule: CXC, CC, CX3C and C. The largest family of chemokines is the CC chemokines, because of the first two of the four conserved cysteine residues. The genes encoding the CC chemokines are located on chromosome 17.

MCP-1 is the most thoroughly characterized CC chemokine. Human MCP-1 gene is located on chromosome 17q11.2. Human MCP-1 is a monomeric protein composed of 76 amino acids which is derived by proteolytic cleavage of a 99-amino-acid precursor, as reported by Van Coillie et al. (1999). MCP-1 is secreted in two predominant forms with apparent molecular weights of 9 and 13 kDa. These proteins have the same protein core and differ by the addition of O-linked carbohydrates to the larger form. The secondary structure of human MCP-1 consists of four regions of β-sheet. These include residues 9-11 (βα), 27-31 (β1), 40-45 (β2), and 51 to 54 (β3). In addition to the four strands of sheet, there are two helical regions. A long helix extends from approximately residue 58 to residue.

MCP-1 is produced by many cell types, including endothelial, fibroblasts, epithelial, smooth muscle, mesangial, astrocytic, monocytic and microglial cells, as reviewed by Deshmane et al. (2009). Monocyte/macrophages are the major source of MCP-1. MCP-1 regulates the migration and infiltration of monocytes, memory T lymphocytes and natural killer cells. MCP-1 has also been shown to stimulate a subset of CD4+ and CD8+ lymphocytes and memory T-lymphocytes in vitro. Despite the
ability of MCP-1 to stimulate chemotaxis in several leukocyte types involved in chronic inflammation, injection of MCP-1 in vivo leads predominantly to recruitment of monocytes. MCP-1 also stimulates several cellular events associated with chemotaxis, including Ca^{++} flux and expression of integrins. Besides chemotaxis, MCP-1 is one of the most potent inducers of histamine release from basophils, as reported by Kuna et al. (1992). Because of this capacity, MCP-1 has been implicated as an important mediator in allergic inflammation. MCP-1 is also involved in the apoptotic pathway, as reported by Zhou et al. (2006). MCP-1 mediates its effects through its receptor CCR2. There are two alternatively spliced forms of CCR2 namely CCR2A and CCR2B, which differ only in their carboxy-terminal tails, as reported by Charo et al. (1994). CCR2A is the major isoform expressed by mononuclear cells and vascular smooth muscle cells. Monocytes and activated natural killer cells express predominantly the CCR2B isoform.

MCP-1 plays an important role in the inflammatory process within the artery wall and hence it might act as a risk factor for CAD. The target cell specificity of MCP-1 for monocytes makes it a key candidate for the signal that brings circulating monocytes into the vessel wall (Fuster et al. 1992, Rollins 1996, Ikeda et al. 2002). Monocytes differentiate into macrophages in the artery wall and take up cholesterol to become foam cells, a major component of fatty streak. The recruitment of monocytes to the arterial wall is one of the major steps in the inflammatory cascade leading to atherosclerosis.

MCP-1 is also involved in the progression of atherosclerotic disease and plaque rupture, as reviewed by Gonzalez-Quesada and Frangogiannis (2009). MCP-1 induces smooth muscle cell proliferation and promotes neovessel formation in the plaque; leading to rapid progression of the lesion. MCP-1 may play a role in disruption of the atherosclerotic plaque by inducing matrix metalloproteinase expression and release. MCP-1 is also involved in the healing response after an acute coronary event. Myocardial infarction triggers a local inflammatory reaction that results in formation of a scar and is closely intertwined with remodeling of the infarcted ventricle. MCP-1 expression is markedly but transiently induced in infarcted hearts and regulates the healing response.
MCP-1 mediates macrophage recruitment and timely clearance of dead cells from the infarct, as reported by Frangogiannis et al. (2005). MCP-1 is also the molecular link between oxidized lipoproteins and foam cell recruitment into the vessel wall, as reported by Cushing et al. (1990).

Obesity and obesity-associated T2DM are frequently related to a low-grade chronic inflammatory state. Studies using murine models of obesity indicate that MCP-1 is overexpressed in adipose tissue of obese mice leading to higher systemic MCP-1 concentrations (Sartipy and Loskutoff 2003, Takahashi et al. 2003). MCP-1 release can also be stimulated with insulin resistance-associated mediators such as TNFα, IL-1, IL-6 and growth hormone, whereas anti-inflammatory agents such as IL-10, metformin and thiazolidinediones suppress MCP-1 release (Fasshauer et al. 2004, Bruun et al. 2005, Fain and Madan 2005). The hyperinsulinemia that accompanies obesity leads to an over-expression of MCP-1, which in turn modifies the function of adipocytes. In addition to the above, some studies have identified MCP-1 expression in certain other diseases like delayed-type hypersensitivity reactions in the skin, rheumatoid arthritis, HIV infection and malignancy (Bernasconi et al. 1996, Soria et al. 2008, Rantapaa-Dahlqvist et al. 2007).

MCP-1 has been assessed in various studies on its role in atherosclerosis or atherosclerosis-related diseases. Circulating MCP-1 level has also been associated with peripheral artery disease, myocardial infarction, stroke, acute coronary syndromes (de Lemos et al. 2003, Petrkova et al. 2004, Arakelyan et al. 2005). Cardiovascular risk factors such as smoking, hypertension, obesity, high cholesterol and positive family history have been found to track with circulating levels of MCP-1 (Deo et al. 2004, Martinovic et al. 2005).

Circulating MCP-1 concentration has been shown to be elevated in various studies on patients with CAD (Hoogeveen et al. 2005, Martinovic et al. 2005, Herder et al. 2006a, Ardigo et al. 2007). An independent association of MCP-1 with CVD mortality in diabetic patients has been reported by Piemonti et al. (2009). However, a lack of association of circulating MCP-1 concentration with CAD and various coronary
risk factors has also been reported in some studies (Mosedale et al. 2005, Liang et al. 2006, Liang et al. 2008). Piemonti et al. (2003) have reported lack of an independent association of MCP-1 with CVD mortality in diabetic patients. Herder et al. (2006b), in a large population based study, have reported that MCP-1 serum concentration is not associated with impaired glucose tolerance, T2DM or several parameters of obesity. As evident from the literature, data on the relevance of MCP-1 in the pathophysiology of CAD, especially among diabetic patients is inconsistent. Coll et al. (2007), in review on the role of MCP-1 as a biomarker for atherosclerosis, have reported that the role of plasma MCP-1 concentration as a biomarker of atherosclerosis is not clear and the MCP-1/CCR2 pathway should be further explored as a diagnostic, prognostic and therapeutic target.

1.7 dimeric Pyruvate kinase M2

Pyruvate kinase type M2 (abbreviated: M2-PK or PKM2; formerly also termed: pyruvate kinase type K, type K4 or type III) is one of four isoenzymes of pyruvate kinase (PK), the glycolytic enzyme which catalyzes the last step within glycolysis. PK is a rate-controlling enzyme of the glycolytic cascade that catalyses the formation of pyruvate and ATP from phosphoenol pyruvate and ADP (Tanaka et al. 1967, Nowak and Suelter 1981). Besides its well-known role in glycolysis, PK has been reported to be the cytosolic receptor for thyroid hormone, to influence microtubule stability and to interact with phospholipids (Kato et al. 1989, Vertessy et al. 1999).

In mammals, PK exists in the form of four isozymes designated M1, M2, L, and R, which are differentially expressed in different cell types, as reported by Tanaka et al. (1967). The four isoenzymes of pyruvate kinase (type M1, type M2, type L and type R) differ widely in their kinetic characteristics and regulation mechanisms. Tissues with different metabolic functions express different pyruvate kinase isoenzymes.

The M1-type and M2-type isozymes of pyruvate kinase are produced from a single gene by alternative splicing. This gene is located on chromosome 15q22 as shown by Tani et al. (1988). Selection of exon 10 generates the M2 type, which occurs in most
tissues, whereas the M1 type is expressed by use of exon 9 only in skeletal muscle, heart and brain. The pyruvate kinase isoenzymes type M1 and M2 differ solely by 23 amino acids (Noguchi et al. 1986, Dombraukas et al. 2005).

M2-PK is expressed in some differentiated tissues, such as fat tissue, lung, retina and pancreatic islets form (Takenaka et al. 1996, Dabrowska et al. 1998). It is also expressed in all cells with a high rate of nucleic acid synthesis, which include all proliferating cells, such as normal proliferating cells, embryonic cells, adult stem cells, and tumor cells in particular. During embryogenesis a shift takes place from M2-PK to the respective tissue specific PK isoenzymes, whereas during tumorigenesis these tissue specific pyruvate kinase isoenzymes disappear and PKM2 is over-expressed (Eigenbrodt and Glossmann 1980, Steinberg et al. 1999, Christofk et al. 2008). Knockdown of M2-PK expression with short hairpin RNA and the replacement of M2-PK with PKM1 has been shown by Christofk et al. (2008) to reduce the ability of human tumor cell lines to form tumors in nude mouse xenografts.

M2-PK can occur in a tetrameric form with a high affinity for its substrate phosphoenolpyruvate and in a dimeric form with a low affinity for phosphoenolpyruvate (as shown in Figure 4). In the cells with high rate of proliferation such as tumor cells, M2-PK is mainly present in the dimeric form (dM2-PK). Under these conditions, all phosphometabolites above pyruvate kinase such as glycerate 3-phosphate and fructose 1,6-diphosphate accumulate and are then available as precursors for synthetic processes such as nucleic acid, phospholipid and amino acid synthesis. Consequently, ATP and GTP levels are low and energy is provided by glutaminolysis. When the fructose 1,6- diphosphate levels reach a certain high value, the dimeric form of M2-PK reassociates to the tetrameric form. Then glucose is converted to lactate until the fructose 1,6-diphosphate levels drop below a minimum signal level. As a consequence M2-PK dissociates to the dimeric form and this oscillating cycle starts again.
Figure 4: Metabolic consequences of dimeric and tetrameric forms of pyruvate kinase M2
Adapted and modified from Mazurek (2008).

In tumor cells the dM2-PK, termed tumor M2-PK, is the predominant form. It is released from tumors into the blood and from tumors of the lower gastrointestinal tract also into the stool of tumor patients. The amount of tumor M2-PK has been shown to be increased in plasma samples from patients with melanoma, renal cell carcinoma, lung, breast, thyroid, cervical, ovarian and gastrointestinal tumors and to correlate with tumor stage (Hardt and Ewald 2008, Landt et al. 2010). Plasma tumor M2-PK can also be used in the follow-up of patients to monitor success or failure of therapy (Mazurek et al. 2002, Mazurek 2008).

dM2-PK is a metabolic parameter characteristic for proliferation. Inflammation is accompanied by increased cell turnover and rapid division and a return to normal cell turnover once inflammation has resolved, as reported by Sipos et al. (2005). Given the relationship of dM2-PK to cell division and the role of inflammation in CAD, it has been postulated in the present study that the plasma concentration of dM2-PK could be
elevated in patients with CAD. Hence dM2-PK could act as a marker of inflammation in CAD. It has been reported to be elevated in different acute and chronic inflammatory conditions. Elevated dM2PK levels have been detected in rheumatic diseases, diabetic nephropathy, chronic heart diseases, inflammatory bowel disease (Oremek et al. 2003a, Oremek et al. 2003b, McDowell et al. 2004). These conditions were not due to malignancy, suggesting that dM2-PK could rather be an indicator of inflammation than cancer per se. There is no reported study on the role of dM2-PK in inflammation among CAD patients.

1.8 Significance of the present study

The pathogenesis of the long term complications in diabetes mellitus is not fully understood, and controversies exist about why they occur in some patients and not in others. The clustering of classical cardiovascular risk factors is insufficient to account for the excess CAD in patients with diabetes. As evident from literature, inflammation plays an important role in CAD; but very few studies have assessed inflammatory risk factors for CAD among the diabetic patients. Hence there is urgent need to explore various newer risk factors for CAD among T2DM patients.

Some of the comparative studies on migrant Indians have suggested that the excess risk for CAD seen among Indians can be partly explained by the newer risk factors (Chambers et al. 2000, Enas 2000). There are very few studies from India exploring the role of inflammatory risk factors in CAD; especially among T2DM patients. There is no previous report from North India on the role of MCP-1 in CAD among T2DM patients. Also there is no previous study from India on dM2-PK in CAD or diabetic patients.

Much of the knowledge of risk factors for CAD in diabetics has been acquired from studies conducted in the Western population or in the migrant Indian population. The results of these studies cannot be generalized since association of risk factors with CAD differs in Indians as compared to western populations and the differences might range from the frequency of presence of classical risk factors to their total absence or irrelevance in these populations. According to the available data in native Indians, it has
been suggested that some of the cut-offs for risk factors might be different from those in Western populations. The lower BMI (< 23 kg/m²) cut-off value for Asians is one such example (Snehalatha et al. 2003, Pan et al. 2004). Therefore, criteria for desirable levels of risk factors based on data for developed countries may be inappropriate for Indians (Janus et al. 1996, Sharma and Ganguly 2005). Furthermore, Indians who migrated to affluent countries have a higher demographic transition state than those residing in India. For these reasons, the observations in the migrant population do not hold true for the Indian population.

Most of the previous studies on CAD risk factors in native Indians are from the general population and not on diabetic patients. Only a meager amount of published literature on CAD in diabetic patients is available from native Indians. Hence it is imperative to undertake studies in India to identify both traditional and newer CAD risk factors among diabetic patients. The major studies on CAD in T2DM patients are from South India. However, there are differences in CAD prevalence and risk factors among South Indians and North Indians, as reported by Begom and Singh (1995).

Punjab is a state in North western part of India. Punjabi society has achieved a socioeconomic status similar to that of developed countries, especially with respect to living conditions and nutritional intake. Physical activity and occupational activity has declined as a result of increased mechanization of life. According to PSCST (2005) and Sidhu et al. (2006), all these conditions have contributed to increasing prevalence of obesity and associated diseases (diabetes and CAD) in Punjab. Bhatti et al. (2007) have reported a high prevalence of CAD (18.5%) among diabetic patients in Punjabi population. There is no recent report addressing the risk factors for CAD in diabetic patients from Punjab. Prospective studies on the relative role and importance of traditional and newer risk factors in Punjab are urgently needed for the formulation of active public health policy to reduce the twin epidemics of diabetes and CAD.

Amritsar is a city in state of Punjab, India. The 2001 Indian census has reported the population of the city to be over 1,500,000. An increase in urbanization accompanied by the rise in socioeconomic status during the past few years in Amritsar has lead to
changes in lifestyle pattern and an increasing prevalence of CAD and diabetes in Amritsar. However, to the best of my knowledge, there is no reported study on risk factors for CAD among T2DM patients from Amritsar. Hence, in the present study, an attempt has been made to assess traditional and newer risk factors for CAD among T2DM patients.

The objectives of the present study are:

1. To study various traditional risk factors for CAD among T2DM patients.
2. To study newer risk factors (MCP-1 and dM2-PK) for CAD and their association with traditional risk factors in T2DM patients.