INTRODUCTION

Atherosclerotic vascular diseases may include coronary vasculature (coronary heart disease, CHD), cerebral vasculature, and peripheral arterial vasculature. In spite of considerable efforts around the world for the prevention and the treatment of coronary artery disease (CAD), it still remains to be number one cause of death and disability. In recent years, demographics and health surveys have reported increasing CAD among individuals of all socioeconomic strata. Incidences of CAD-related death and disability have grown at an alarming pace in low-and middle-income countries like India. Adding to the seriousness of current scenario, most CAD victims in India happens to be in their productive age which may potentially impose huge socioeconomic burden and devastating consequences over the coming years. Conventional cardiovascular risk is attributed to life style changes and altered metabolic activity as seen in the rapidly increasing incidence of obesity, insulin resistance, diabetes mellitus, atherogenic dyslipidemia and elevated blood pressure.

Diabetes Mellitus (DM), often simply referred to as diabetes, is a group of common metabolic disorders that shares the phenotype of hyperglycemia, either because the body does not produce enough insulin or because the cells do not respond to insulin that is produced. Several distinct types of DM exist and are caused by complex interaction of genetic and environmental factors. The
metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.\textsuperscript{4,5}

The worldwide prevalence of DM has raised dramatically over the past two decades from an estimated 30 million cases in 1985 to 177 million in 2000.\textsuperscript{6} Based on current trends, more than 592 million individuals will have diabetes by the year 2035. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 diabetes is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. This is true in most countries and six of the top ten countries with highest rates are in Asia. Globally in 2013, an estimated 382 million people have type 2 diabetes and it accounts for 90-95\% of all diagnosed cases associated with the obesity. The disease affected more than 65.1 million Indians in 2013.\textsuperscript{7} The high incidence is attributed to a combination of genetic susceptibility plus adoption of high–calorie, low-activity life style by India’s growing middle class, population growth, aging and urbanization.\textsuperscript{8} DM increases with aging. The prevalence is similar in men and women throughout most age ranges.\textsuperscript{9}
DM is classified on the basis of pathogenic processes that lead to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The broad categories of DM are designated as type 1 DM, type 2 DM, gestational diabetes and other specific types of diabetes. Both type 1 and type 2 diabetes are preceded by a phase of abnormal glucose homeostasis during the course of disease. Type 1 diabetes is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. In addition, certain types of diabetes have been offered fanciful names like brittle diabetes, bronze diabetes etc.

Type 2 DM – formally Non-Insulin Dependent Diabetes Mellitus (NIDDM) or adult onset diabetes makes up about 90% cases of diabetes with other 10% primarily due to type 1 DM and gestational diabetes. Type 2 diabetes is characterized in part by elevated plasma levels of free fatty acids (FFAs) and glucose and is associated with a cluster of abnormalities such as central obesity, dyslipidemia, hyperinsulinemia, elevated plasma inflammatory markers, vascular abnormalities and hypertension. This cluster of abnormalities, referred to as metabolic or insulin resistance syndrome, is associated with increased risk for CAD. Insulin resistance is a fundamental defect that precedes the development of full insulin resistance syndrome as well as beta cell failure and type 2 diabetes.
Insulin resistance is characterized by hyperinsulinemia and hyperglycemia, and change in levels of adipocytokines that could lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension and vascular inflammation, all of which promote the development of CAD. It is well documented that high levels of insulin are associated with elevated “connecting peptide” (C-peptide) levels as both are produced in equimolar amounts. C-peptide was considered an inert substance, but recent studies have proven it is a bioactive peptide that affects various cell membranes, including endothelial, renal and nerve cell. The physiological effects of C-peptide are different from and complimentary to those of insulin. High levels of insulin and C-peptide co-exist and are suggested to promote atherogenesis thus contributing to increased risk for CAD. In general, C-peptide is composed of 31 amino acids and facilitates the correct folding of proinsulin to allow the cysteine disulphide bridges between alpha and beta chain of insulin to form. It is cleared by the kidneys and has a half life of about 20-30 minutes compared to insulin which is cleared through liver and has a half life of about 3-5 minutes. The measurement of C-peptide has been used as a marker of beta cell function and an index of insulin secretion. Direct measurements of endogenous insulin by immunoassay are problematic in patients undergoing insulin therapy because assays can cross-react with insulin analogs that the patient is taking. Moreover, these assays are affected by the presence of anti-insulin antibodies like islet cell antibodies, glutamic acid decarboxylase antibodies etc.
In addition, the extensive and variable hepatic extraction of insulin also makes it difficult to accurately estimate insulin secretion from peripheral insulin concentrations. Monitoring residual beta cell function through the measurement of C-peptide is a strategy endorsed by American Diabetes Association (ADA), and it recommends the use of C-peptide measurements as the outcome measure in clinical trials investigating methods to preserve beta cell function. Studies have linked low levels of C-peptide to diabetic complications, and evidence suggests that maintaining higher levels of C-peptide is especially beneficial for type 1 diabetics.\textsuperscript{14} Hence, C-peptide measurements play a key role in the evaluation of hypoglycemia, are useful aid in the classification of DM and may play a larger role in its management in the future.\textsuperscript{15}

Obesity is thought to be the primary cause of type 2 diabetes in people, who are genetically predisposed to the disease. Rates of diabetes have increased markedly over the past 50 years in parallel with obesity. Indeed, this new unprecedented phenomenon has been referred to as “Diabesity”.\textsuperscript{16} The International Diabetes Federation (IDF) says that, “Diabetes and obesity are the biggest public health challenges of the 21\textsuperscript{st} century”. Even in India, obesity has reached epidemic proportions, with morbid obesity affecting 5\% of the country’s population.\textsuperscript{17}

Obesity is the state of excess adipose tissue mass. Although often viewed as equivalent to increased body weight, this need not be the case – lean but very
muscular individuals may be overweight by numerical stands without having increased adiposity. Obesity is therefore more effectively defined by assessing its linkage to morbidity or mortality. Although not a direct measure of adiposity, the most widely used method to gauge obesity is Body Mass Index (BMI) which is equal to weight/height\(^2\) (in kg/m\(^2\)). Other measures to quantify obesity include anthropometry (skin fold thickness), densitometry (under water weighing), CT or MRI and electrical impedance. A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention especially in the presence of risk factors that are influenced by adiposity such as hypertension and glucose intolerance. Worldwide, the proportion of adults with a body mass index (BMI) of 25 kg/m\(^2\) or greater increased between 1980 and 2013 from 28·8% (95% CI 28·4-29·3) to 36·9% (36·3-37·4) in men, and from 29·8% (29·3-30·2) to 38·0% (37·5-38·5) in women. Prevalence has increased substantially in children and adolescents in developed countries; 23·8% (22·9-24·7) of boys and 22·6% (21·7-23·6) of girls were overweight or obese in 2013. The prevalence of overweight and obesity has also increased in children and adolescents in developing countries, from 8·1% (7·7-8·6) to 12·9% (12·3-13·5) in 2013 for boys and from 8·4% (8·1-8·8) to 13·4% (13·0-13·9) in girls.\(^1\)

The distribution of adipose tissue in different anatomic depots also has substantial implication for morbidity. Specifically, intra abdominal and abdominal subcutaneous fat has more significance than subcutaneous fat present in the
buttocks and lower extremities. This distinction is most easily made clinically by determining waist to hip ratio with a ratio >0.85 in women and > 0.9 in men being abnormal. Many of the most important complications of obesity such as insulin resistance, diabetes, hypertension, hyperlipidemia and hyperandrogenism in women are linked more strongly to intra abdominal and/or upper body fat than to overall adiposity.\textsuperscript{19}

Obesity has major adverse effects on health. It is associated with increase in mortality with a 50-100\% increased risk of death from all causes compared to normal weight individuals, mostly due to cardiovascular causes. Mortality rates rise as obesity increases, particularly when it is associated with increased intra abdominal fat. It is also apparent that the degree to which obesity affects particular organ systems is influenced by susceptibility genes that vary in the population.\textsuperscript{20}

Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and decreasing with weight loss. Insulin resistance is more strongly linked to intra abdominal fat than to fat in other depots. The molecular link between obesity and insulin resistance in tissues such as fat, muscle and liver has been sought for many years. Major factors considered include:

1. Insulin receptor down regulation.
2. Increased FFAs capable of impairing insulin action.

3. Intracellular lipid accumulation.

4. Various circulating peptides produced by adipocytes including cytokines e.g. Tumour Necrosis Factor (TNF–α) and Interleukin-6 (IL-6), Retinol Binding Protein (RBP-4) and adipokines- adiponectin and resistin, have altered expression in obese adipocytes and are capable of modifying insulin action.21

Although the cause of DM is multifactorial; obesity, however, is a major risk factor for DM and as many as 80% of patients with type 2 DM are obese.22, 23 Alterations in body fat distribution are associated with changes in lipids and lipoproteins and increased coronary heart disease risk. Individuals with diabetes may have several forms of dyslipidemia. In obese patients with type 2 diabetes mellitus, a distinct “diabetic dyslipidemia” is characteristic of the insulin resistance syndrome whose prominent features include high serum triglycerides, low high density lipoprotein-cholesterol (HDL-C) and a qualitative change in low density lipoprotein (LDL) particles.24 Current standards of care involve determination of serum lipid levels in patients with diabetes and measures designed to correct obesity and hyperglycemia such as exercise, dietary modifications and hypoglycemic therapy. Patients with type 2 DM-associated dyslipidemia remain exposed to a high residual risk of CVD associated
complications even if they are managed according to these standards of care, making it one of the major unmet needs in the treatment of diabetics. For that matter, an understanding of complex interplay of how treating dyslipidemia reduces the risk for CVD events in diabetic patients and an ability to assess high risk patients is necessary.

Apart from lipoprotein abnormalities in diabetes associated with or without obesity, it has been identified that obesity, mainly abdominal obesity is also associated with decreased levels of the vascular protective adipokine, adiponectin. It is the gene product of the adipose most abundant gene transcript – 1 (apM 1) gene; bearing structural homology to collagen VIII, X and complement C1q as well as TNF – α. It is a 244 – amino acid polypeptide with molecular weight of 30 kDa that is exclusively secreted by adipocytes of white adipose tissue and acts as a hormone with anti-inflammatory, anti-atherogenic and insulin sensitizing properties. Thus, by several mechanisms, adiponectin may decrease the risk of type 2 DM, including suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in liver, stimulation of fatty acid oxidation and glucose uptake in skeletal muscle, and stimulation of insulin secretion.\textsuperscript{25,26}

Circulating adiponectin levels in normal subjects has been reported as 5-20 µg/ml, thus accounting for approximately 0.01% of total plasma proteins.\textsuperscript{27} Adiponectin secretion, in contrast to secretion of other adipokines, is paradoxically decreased
in obesity. It is possible that accumulation of visceral fat might produce inhibiting factors for adiponectin synthesis or secretion such as TNF–α. Plasma adiponectin levels are higher in women than men and in non-obese diabetics as compared to obese diabetic subjects. The levels are decreased in obesity, insulin resistance, type 2 DM and dyslipidemia, and are particularly low in patients with coronary artery disease (CAD).

Plasma concentrations of adiponectin have been positively associated with age and have been shown to be unaffected by food intake. It has been proposed that adiponectin may be a link between markers of inflammation, endothelial dysfunction, obesity and risk factors of type 2 DM. Due to interactions of genetic factors including single nucleotide polymorphisms (SNPs) of adiponectin gene and environmental factors, hypoadiponectinemia causes obesity, resulting in insulin resistance, metabolic syndrome and increasing the risk of type 2 DM. Furthermore, hypoadiponectinemia may be a novel and important risk factor for CAD and hypertension. Adiponectin concentration is negatively associated with plasma TG, LDL-C and positively associated with HDL-C. Higher levels are also associated with reduced risk of acute myocardial infarction in men and reported to improve insulin sensitivity.

Activity of adiponectin is associated with leptin, resistin and with steroid and thyroid hormones, glucocorticoids, and nitric oxide. It suppresses the expression
of extracellular matrix adhesive proteins in endothelial cells and atherosclerosis potentiating cytokines. Anti-atherogenic and anti-inflammatory properties of adiponectin and the ability to stimulate insulin sensitivity have made adiponectin an important biomolecule for physiological and pathophysiological studies with the aim of potential therapeutic applications.\textsuperscript{36}

In contrast, TNF – \(\alpha\), IL – 6 and leptin are able to induce insulin resistance. Leptin, a 16 kDa protein produced primarily in adipose tissue is a pleiotropic hormone that is involved in body weight regulation, puberty, reproduction and immune function.\textsuperscript{37} Leptin, the product of \textit{ob} gene, is a peptide that is strongly correlated with adiposity and is a potential determinant of obesity and its complications. Leptin, together with other adipocytokines, affects insulin sensitivity and is accepted to play a role in pathogenesis of obesity-related disorders. Increased serum leptin is considered as a component of metabolic syndrome. Resistance to leptin in beta-cells might prevent the inhibitory effect of leptin on insulin secretion resulting in hyperinsulinemia, which might exhaust pancreatic beta-cells leading to the development of T2DM. Leptin is associated with BMI and body fat in non-obese and obese subjects and in patients with type 2 DM. Serum leptin concentrations also has a gender dimorphism, with higher serum levels in women than that in men. Although, leptin levels are increased in obesity, obese subjects with type 2 diabetes display reduced leptin levels which may be due to altered fat distribution.\textsuperscript{38} On the other hand, data collected from
several studies have reported increased or unchanged leptin levels in diabetic patients.\textsuperscript{39, 40}

The complex interplay between leptin, adiponectin, insulin and C-peptide in obese/non-obese diabetics is far from being fully elucidated and warrants extensive work to cross-bridge the existing lacunae.