2. Review & Literatures:

Cardiovascular disease (CVD) is one of the leading causes of death for both men and women worldwide. A 20% of the world's populations are contributed by the Indian subcontinent and one of the highest burdens of CVD in all over the world (Goyal & Yusuf, 2006). CVD, including coronary heart disease (CHD), arterial block myocardial infarction and stroke, is the largest and one of the primary cause of mortality in the world, and the majority of deaths occur in most of the developing countries such as India and China and also in maximum developed countries such as USA & Japan (NCD, 2010 & WHO, 2011). Cardiovascular disease is a term that refers to more than one disease of the circulatory system including the heart and blood vessels, whether the blood vessels are affecting the lungs, the brain, kidneys or other parts of the body. Recent studies indicated that environmental exposures, lifestyle factors (smoking, hypertension, and food habits), genetic determinants and inflammatory processes play an important role in the pathogenesis of CAD (Dent, 2010). Metabolic syndrome (MS) as CAD risk factors includes atherogenic dyslipidemia, hypertension and abdominal obesity. Regarding the habit and practices it may be concluded that unhealthy lifestyle, smoking habit and consumption of junk food and sedentary life style may generate a state of hyperglycemia and insulin resistance. And sustenance of this condition may be regarded as stepping stone of the proinflammatory state (Dandona et al., 2005; Espinola-Klein et al., 2011). The prevalence of

obesity and metabolic syndrome (MS) has reached epidemic levels in all around the world and related health risk is sharply increased throughout the last decade. Obesity is a chronic metabolic and inflammatory state associated with many cardiovascular and diabetogenic disorders (Pi-Sunyer FX, 2002; Baltaci et al., 2012).

Epidemiology of the Diseases

Epidemiology is the study on the frequency of disease and its determinants in the population and community (Last, 1995). The term derives from the word epidemic, and in the first half of the last century the major epidemics were infectious disease outbreaks. With the discovery of antibiotics (Fleming A, 1953) and the implementation of public health measures to control the spread of these diseases (Paneth, 2004), mortality due to infections decreased and life expectancy increased. As a consequence of these changes a non-infectious group of diseases became the main individual cause of mortality: cardiovascular diseases. Around the middle of the last century cardiovascular disease mortality began to increase rapidly, but very little was known about its origins and causes.

Studies on the Cardiovascular epidemiology began in the 1930's as a consequence of the observed changes in the causes of mortality. In 1932, Wilhelm Raab described the relationship between diet and coronary heart disease (CHD) in different regions (Raab W, 1932). In 1953 an correlation was drawn between cholesterol levels and CHD mortality in various populations (Keys A, 1953).

Several epidemiological studies were undertaken in the 1950s to unravel the causes of cardiovascular diseases (Doyle et al., 1957; Chapman et al., 1957). In 1948, the Framingham Heart Study was started by the USA Public Health Service. The main of this was to investigate the epidemiological basis risk factors for CVD (Dawber et al., 1951). That year, the National Institute of Health (NIM) was expanded to collaborate aiming to study particular these diseases. The Framingham Heart Study was transferred to the National Heart Institute established in 1949. Presently it is known as the National Heart, Lung, and Blood Institute. And it maintains it objectivity of research today. Since 1970 the Framingham Heart Study has also been precisely monitored under the affiliation of Boston University.

The first cohort study included 5209 healthy individuals between 30 and 60 years of age and they were enrolled in 1948 and that was the first this type of study with the large number of participants. In 1971, 5124 sons and daughters (and their spouses) of the cohort were recruited for the Offspring Study. Finally, in 2002, 4095 participants were involved in the Third Generation cohort of the study (Splansky et al., 2007). Different epidemiological studies in different part of the globe enabled the researchers to evaluate the most important risk factors and other determinants as a disease causing sources.

In recent years, the abundance of chronic diseases as major attributors to total global mortality has emerged and that conclude that CVD is one of the most prominent diseases out of all diseases. (Adeyi et al., 2007; WHO, 2008b). By the year 2005, the total number of deaths in cardiovascular diseases (CVD) increased globally to 17.5 million from 14.4 million

as counted in the year of 1990. Of these, 7.6 million were attributed to coronary heart disease and 5.7 million to stroke. It is notable that more than 80 percent of the deaths occurred in low and middle income countries (WHO, 2009e). This suggests that economic status, nutrition and lifestyle have impact on the disease outcome. The World Health Organization (WHO) estimated there would be about 20 million deaths from CVD by the year 2015. And this accounts for 30 percent of all deaths worldwide (WHO, 2005). By 2030, researchers highlight that non-communicable diseases will account for more than three-quarters of deaths worldwide. And CVD alone will be responsible for more deaths in low income countries than infectious diseases (including HIV/AIDS, tuberculosis, and malaria), maternal and perinatal conditions, and nutritional disorders combined (Beaglehole and Bonita, 2008). Thus, CVD is today the largest single attributes to global mortality. It will continue to dominate mortality pattern in the future (WHO, 2009e). So precautions, protective measures should be immediately taken to counteract this deadly situation.

Not only the developed countries, but also individuals from the developing/under developed countries are highly victim of this situation. The diseases are primarily epidemic in urban locations and are rapidly increasing in rural areas also (Fuster et al., 2010). Due to the epidemiological transition phases (changes of lifestyle, environmental factors and other determinants) and increasing urbanization associated with increase in CVD risk factors (smoking, sedentary lifestyle, obesity, hypertension and hypercholesterolemia). And due to the lack of proper health policies from the Govt./organization directives aimed at CVDs are poised to accelerate further (Gupta et al., 2011). There is an uneven distribution of age-

matched CVD mortality around the globe. The lowest age-adjusted mortality rates are noticed in the more urbanized/industrialized countries.

Multiple (depending on the geographical location and demographic profile) set of major risk factors consistently play a major role in explaining trends in CVD incidence and death globally. Taken together, the data indicate that unhealthy diet, use of tobacco , physical inactivity, use of excess alcohol are the major contributors to the occurrence of CVD (Anand et al., 2008; Clarke et al., 2009; Critchley et al., 2004; Lopez-Jaramillo et al., 2008; Mayosi et al., 2009; Rosengren et al., 2004; Stein et al., 2005; Yusuf et al., 2004).

Tobacco use has been the most extensively documented, which suggests that tobacco use in the United States from 1900 to 1990 associates with CVD. (Fox et al., 2004; Mirzaei et al., 2009; Shopland, 1995). Another extensive study also describe the real pictures in the United Kingdom, a 38-year follow-up study of male individuals showed that baseline differences in tobacco use, high blood pressure, and cholesterol were significantly associated with a 10- to 15-year shorter life expectancy from age 50 (Clarke et al., 2009). The study is of great significance for developing countries because many of the baseline variable of risk common in the late 1960s in the United Kingdom are the standard in many developing countries today. But further analysis is required to predict definitive.

There are a few studies that provide more direct insight into the causes of recent increases in CVD incidence and mortality in low and middle income countries. (Critchley et al., 2004).There has been a steady rise in global cigarette and other form of tobacco/nicotine

consumption since the early 1970s. In 2010, researchers estimate that 6.3 trillion cigarettes or more than 900 cigarettes for every person on the earth—will be consumed. This increase in the total number of smokers around the world is driven predominantly by global population growth and is expected to continue unless smoking rates are significantly reduced. By the year 2020, if current smoking and population growth trends continue, the global annual cigarette consumption might rise to a huge gathering (ERC, 2007; Guindon and Boisclair, 2003; Shafey et al., 2009). This increasing burden of tobacco/ nicotine use is increasingly falling developing countries.

Extensive evidences suggest that rapid dietary changes associated with nutritional transition. The decreases in physical activity in many rapidly urbanizing societies are another dominant risk factors for CVD. (Stein et al,. 2005). The nutritional transition currently occurring in many low and middle income countries and that has established a new phenomenon where it is not unlikely to notice both under-nutrition and obesity coexist in the same populations (Caballero, 2005; Dangour and Uauy, 2006; Reddy et al., 2003). Under-nutrition has been the hallmark of the low and middle income countries of Africa, Latin America, and South Asia. WHO has estimated that while the undernourished global population has diminished to approximately 1.2 billion, the overweight population has increased to the similar figure. Moreover of these, an estimated 300 million are clinically obese (Misra and Khurana, 2008). As an associated problem, the global prevalence of overweight in children (ages of 5 and 17 years) is 10 percent (Bhardwaj et al., 2008).

Epidemiological evidence suggests that dietary changes specifically the increasing consumption of energy-dense foods have contributed to an increase in CVD incidence in developing countries (Hu, 2008). Traditionally, monitoring of dietary consumption trends in low and middle income countries has been difficult due to poor assessment, documentation and quality of date. This measure usually overestimates consumption, but trends remain valid indicators of the broad changes. The load of communicable and non-communicable diseases (NCDs) is highlited to get reversed in 2020 from its distribution in 1990 (Nutrition Transition in India, 1947-2007). India's economic growth and urbanization, a large number of the population has moved towards unhealthy lifestyles with decreasing physical activity and increasing stress levels. The average life span has increased due to improvements in medical care; the rapidly ageing population, more prone to NCDs. Finally, most NCDs share common risk factors, whose prevalence is 53% in India and they generally occur as co-morbidities (Fig: 1). The probability of dying between ages 30 and 70 years from the four main NCDs is 26%. Cardiovascular diseases are the largest cause of mortality, accounting for around half of

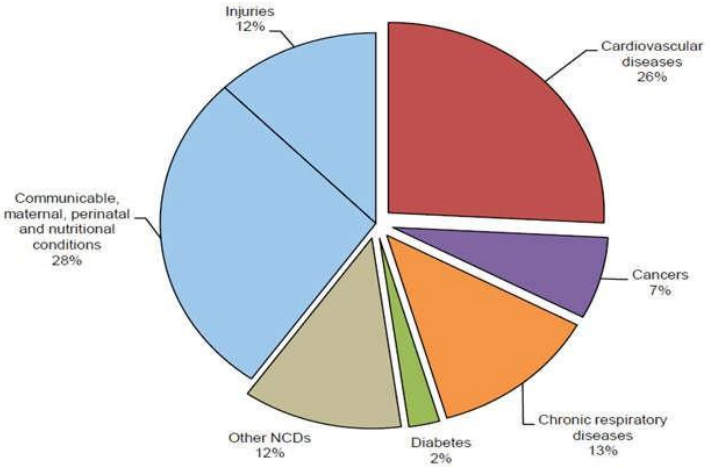

Fig-1: Proportional Mortality-India (% of total deaths, all ages, both sexes) (IHPS, 2011 & WHO, 2014)

all deaths resulting from non-communicable diseases (NCDs). Overall, CVDs accounted for around one-fourth of all deaths in India in 2008. CVDs are expected to be the fastest growing chronic illnesses between 2005 and 2015, growing at 9.2% annually, and accounting for the second largest number of NCD patients after mental illnesses (IHPS, 2011 & WHO, 2014).

Several hematopoietic factors are regarded as reliable marker for the CVD outcome. Risk factors include hyperglycemia and hyperlipidemia. Although low density lipoprotine-cholesterol (LDL-C) remains the primary risk factor in atherogenesis which produce largely in the insulin resistance condition. It is the first lipid target of therapy in CVD. Research has moved to include other lipid fractions such as HDL-C and triglycerides that may be contributing to the risk of CVD. Triglycerides (Jim & Deepak, 2007), Dyslipidemia, hypercholesterolemia, hyperglycemia in association with sedentary lifestyle, food habit, excessive smoking have been demonstrated as individual or in combine risk factors of CVD (Chattapadhyay & Ramanakumar, 2005). However, in recent past, inflammation in atherosclerosis has been shown to play a curtail role in CVD , which has bee extensively explored (van der et al,. 2012). During hypercholesterolemia, infectious agents or non-infectious stress-related signal leads to an increase in the increasing pro-inflammatory and inflammatory cytokines like IL-6, IL-10, TNF-α etc, which are hallmarks of inflammatory processes in the body (Kaperonis et al,. 2006). Atherosclerosis is a progressive process affecting peripherally multiple vascular beds. The main patho-physiological consequences in the sequential progressive event of plaque formation by accumulation of oxidized LDL in endothelial cell that gives rise to coronary artery disease (CAD), cerebrovascular disease, and

peripheral arterial disease (PAD) (Munger et al., 2004). The risk of atherosclerotic disease is markedly increased among individuals with diabetes. The increased risk is independent of and additive to, other cardiovascular risk factors.

Events in Atherosclerosis

Atherosclerosis is an abnormal epidermal injury, with smooth muscles proliferation, inflammation, plaque formation, foam cell development, infiltration and last platelets aggregation in arterial cavity. The plaque formation is started from deposition of lipids specially oxidize LDL in endothelial cells and progressively blocks the blood vessels.

1. In hyperglycaemic or hyperlipidemic condition the small LDLs are interact with extracellular matrix (ECM) & diffuse the endothelial cell (EC) wall and deposit underlying ECM by the help of adhesion molecules.
2. In here these accumulating LDL interact with the ROS (reactive oxygen species) and oxidise. This oxidised LDL induces the migration of monocytes into subendothelial cells.
3. The oxidised LDL also can stimulate the overlying endothelial cells to unregulated cellular adhesion molecules, chemoactractent proteins. Growth factors and inhibits the nitric oxide (NO) production.
4. Monocytes are engulfed oxidised LDL and convert to macrophage.

5. Matured macrophages are released cytokines IL6, INF gama and TNF alpha etc. These cytokine have autocrine characters which recruits additional monocytes as well as macrophages.
6. Monocytes macrophages interaction with oxidise LDL produce foam cell which is the main component of atherosclerosis.
7. Foam cell production induces the vascular smooth muscle cells (VSMCs) proliferation in internal elastic lamina.
8. Smooth muscle cells migrate towards tunica intima where they are accumulates over the foam cells.
9. VSMCs produce a new ECM that give rise a fibrous cap.
10. The resulting complex plaque is vulnerable to destabilization, rupture, and superimposed thrombosis leading to an acute vascular occlusion (Fig: 3).

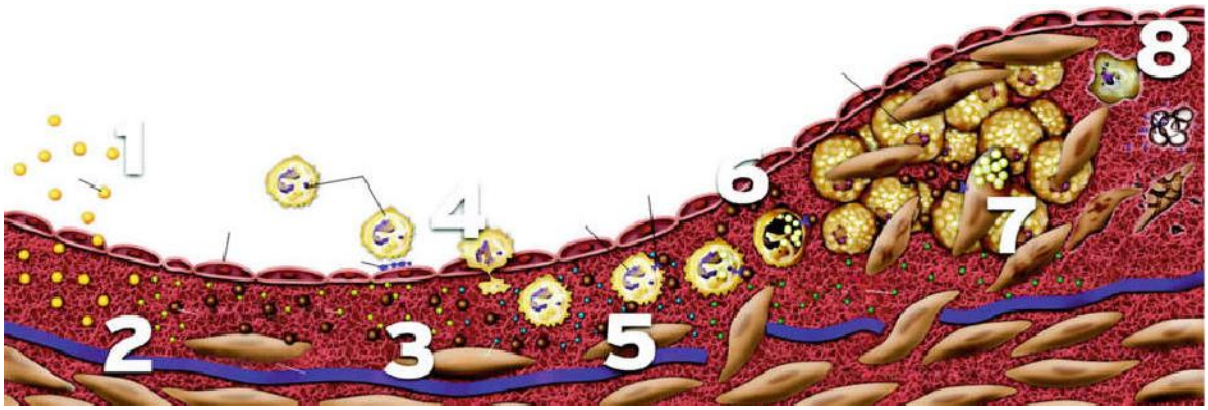

Fig 2: The stages of development of an atherosclerotic plaque. (1) LDL is taken up by the endothelium. (2) Oxidation of LDL by macrophages and VSMCs. (3) Release of growth factors and cytokines. (4) Attraction of additional monocytes. (5) Foam cell accumulation. (6) SMC proliferation. (7, 8) Formation of plaque (Faxon et al., 2004).

Atherosclerosis promotes most of the death and disability in patients with diabetes, particularly in the type 2 diabetic population (Beckman et al., 2002). An important investigation schedule, the Verona Diabetes Study evaluated that cardiovascular disease is responsible for 44% of all diabetic patient population (Brun et al., 2000). As a key feature diabetes contributing to the promotion of atherosclerosis which is a most morbid health hazard of DM in whole population in world. For that reason diabetes increases the risk of death from cardiovascular disease (Brun et al., 2000). Insulin resistance is an another key factor in the pathogenesis of diabetes type 2 patient. Insulin resistance and its attendant

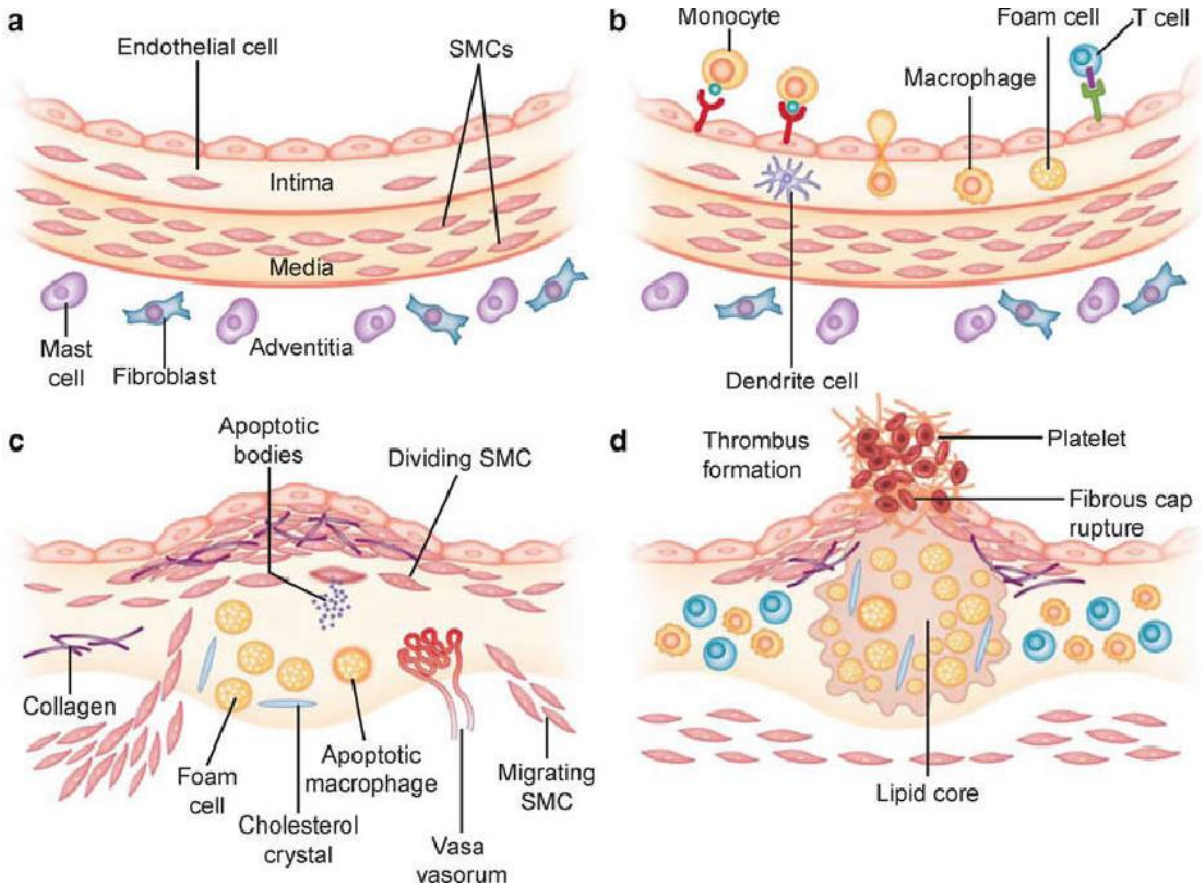

Fig-3. Development of atherosclerotic plaque with superimposed thrombus (Libby et al., 2011).

metabolic abnormalities may be one of the most important cause much of the increased cardiovascular risk of diabetes (Watson et al., 2003). In recent research the Cardiovascular and cerebrovascular event rates are higher in diabetic individuals with peripheral artery disease (PAD) than in comparable non-diabetic populations (American Diabetes Association, 2003).

Both type 2 diabetes and metabolic syndrome are spreading rapidly all over the world because of changes in obesity, sedentary lifestyle, and the aging of the population (Cameron et al., 2004). Both metabolic syndrome and type 2 diabetes appear due to insulin resistance and induce an increased risk of atherosclerosis and cardiovascular disease (CVD). Recent research has disclosed some evidence that substances like C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α play a major role in promoting development of unfavorable vascular outcomes in both conditions.

CRP is the known inflammatory marker which has been endorsed as an independent risk factor for CVD (Ridker et al., 1997; Ridker et al., 2002). The CRP is an acute-phase reactant that is synthesized in the liver and activates the complement pathway through the immune system. So it establishes a link between metabolic outcomes with the immune status in an individual. Many pro-inflammatory cytokines like as TNF and IL-1 originated from vascular endothelium and adipose tissue and these have major role in diabetes mediated atherosclerosis formation. The macrophages secrets IL-6 due to a massive accumulation of oxidized LDL in endothelial cell (EC) which give a positive signal to incensement of the oxidative stress. Not with standing infection may be the original cause that initiates this process. CRP has been shown to balance partialy of endovascular health towards a pro-atherogenic state by decreasing the synthesis of nitric oxide (NO). It is known that NO play a role as vesodialator, upregulating endothelin-1, and activating cell adhesion molecules. Several studies demonstrate that inflammation of the endothelium can be determine by assay

of high-sensitivity C-reactive protein (hs-CRP), which is a good predictor of future cardiovascular incidents (Ridker et al., 1997; Ridker et al., 2002).

In every cell the free radicals are very common those are produced from electron transport chain. Inflammatory molecules are also produced during metabolic dysregulation. Life style disorders, habit to consume junk foods, the oxidative equilibrium in cells of tissues and organs potentiate inflammatory responses which can ultimately trigger human-diseases like cardiovascular or cerebro-vascular disease (Peroxisomes, oxidative stress, and inflammation. World J Biol Chem. 2012). In regard to the free radicals and their metabolism, hydrogen peroxide and other reactive species help in defining the oxidative status of cells.

Uric acid (UA) is the metabolic end product of purine metabolism. It acts as a powerful antioxidant components to cellular materials (Rodrigo et al., 2013). The elevated UA levels are directly or indirectly related to systemic inflammation, arterial hypertension, and particularly in cardiac diseases. The endothelial dysfunction and pathological remodeling of blood vessels are the way of action for that in different tissues. The physiological UA levels act as a powerful antioxidant (Rodrigo et al., 2013).

The inflammation of endothelium initiates more oxidative stress and vigorously generates free-radicals that can support vascular damage, endothelial-injury, plaque-rupture as well as mitochondrial dysfunctionation. The sequence of these process farther induce oxidative-stress and free-radicals production and athero-thrombosis (Hsueh & Quinones, 2003). Inflammatory protein marker CRP have been shown to a valid predictor which can correlate

major cardiovascular pathogenesis like myocardial infarction (Ridker et al., 1997; Ridker et al., 2002). A prospective study evaluates that low-grade systemic inflammation is not only promote diabetes. But it initiates complications in vascular bed (Stehouwer et al., 2002 & Duncan et al., 2003).

Recently, a research study elucidated the relationship between CRP and the metabolic syndrome in emerging the process in cardiovascular diseases. In two different studies (Ridker et al., 2005 & Sattar et al., 2003) the age-adjusted comparative risk of future anomalies was the same in subjects and both equally elevate the risk factors with high CRP without the metabolic syndrome and in individuals with low CRP with the metabolic syndrome. But when, individuals with both increased CRP levels and the presence of the metabolic syndrome, the relative risk of cardiovascular events was doubled. But in combination with high CRP level in presence of metabolic syndrome the relative risk of the occurrence is highly increased. This indicates that CRP is an important determinant of disease outcome (Rutter et al., 2004).

Some prospective factors are important as pro-inflammatory markers that have a tendency to work together. And additive effects impact pronounced disease outcome and another few emerging pro-inflammatory molecules and there are tended to accumulate in vessel walls to initiate several pathophysiological conditions (Ceriello & Motz et al., 2004). Interestingly, they appear to be elevated in obese insulin-resistant individuals who have a special feature of abdominal or central obesity (McLaughlin et al., 2002). level all are

interlinked to each other and implicatively the induced CVD. Since inflammatory markers are elevated in the presence of cardiovascular risk factors, they give information that inflammation is a potent component of the metabolic syndrome, including diabetes.

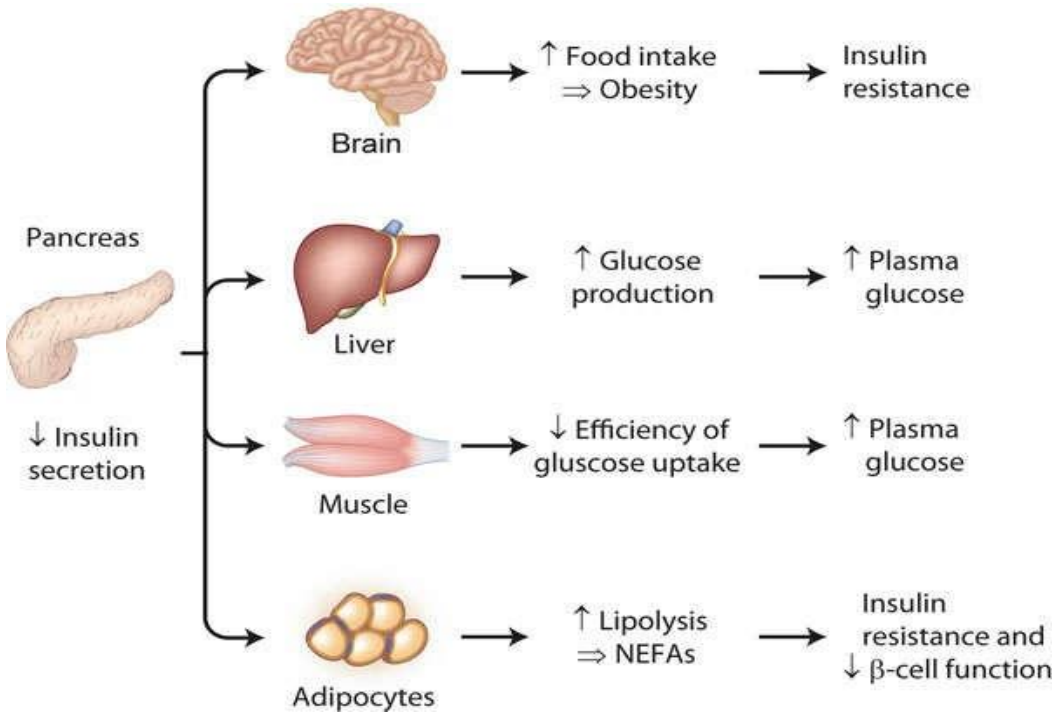

Fig-4. Impaired insulin secretion results in decreased insulin levels and decreased signalling in the hypothalamus, leading to increased food intake and weight gain, decreased inhibition of hepatic glucose production, reduced efficiency of glucose uptake in muscle, and increased lipolysis in the adipocyte, resulting in increased plasma NEFA levels (Van Gaal et al., 2006).

These pro-inflammatory cytokines like TNF-α, IL-10 and IL-6 correlate with both insulin resistance and hyperinsulinemia. Studies have linked the role of inflammatory cytokines to dyslipidemia, hypertension, and insulin resistance (Festa et al., 2000 & Yudkin

et al., 1999) implicating them in the genesis of CVD. Dislipidemia, hypertension, insulin In healthy vessels, endothelial cells synthesize NO. This is a potent vasodilator that inhibits platelet activation and the migration of vascular smooth muscle cells. Diabetes impairs NO-mediated vasodilatation by inhibiting production of NO and NOS(Williams et al., 1996). A number of mechanisms (mainly excessive ROS formation) contribute to the decreased bioavailability of endothelium-derived NO in diabetes (De Vriese et al, & Hennes et al., 2000). The effects of endothelial cell dysfunction increase arterial susceptibility to atherosclerosis by accumulating free fatty acid in endothelial cells.

The CRP may also be a risk factor for peripheral artery disease (PAD). C-reactive protein has procoagulant role related to its ability to enhance expression of tissue factor (INF) (Cermak et al., 1993 & Vinik et al., 2001). C-reactive protein may be regarded as a metabolic inflammatory marker. It is also related to the immunological process and inflammatory condition. Immunological inflammatory molecules TNF-α and high level of CRP indicate the similar term of disease outcome. C-reactive protein also inhibits endothelial cell nitric oxide (NO) synthase, prostaglandin (PGI_2) resulting in abnormal regulation of vascular tone, and increases production of plasminogen activator inhibitor-1 (PAI-1). This factor inhibits the formation of fibrinolytic plasmin from plasminogen (Vinik et al., 2001) and creates an inducing environment to stimulation of mononuclear cells tissue factor.

In addition to reducing NO the state of conditions, diabetes increases the production of vasoconstrictors, such as endothelin-1, which is further promote to migration. Report

suggests that diabetes also stimulates other atherogenic pathways in vascular smooth muscle cells. For example, hyperglycemia activates protein kinase C (PKC) and nuclear factor kappa-B (NFKβ), increasing the production of reactive oxygen species that activate the formation of atherosclerotic lesions (Inoguchi et al., 2000).

Platelet aggregation is enhanced in diabetes. And a role of NO has been linked to this phenomenon. Elevated glucose level activates protein kinase C and decrease the production of platelet-derived NO. In this situation oxidative stress is also increased extensively. A report suggests that in diabetes, platelets also have elevated expression of glycoprotein Ib and IIb/IIIa receptors, enhancing their thrombotic potential. This is occurred after plaque rupture in blood vessels (Vinik et al., 2001). In addition to potentiating platelet aggregation, diabetes augments blood coagulability by enhancing the tissue factor expression and decreasing anticoagulants levels. Consequently, it is more likely that atherosclerotic plaque rupture would end up in thrombus formation (Carr ME, 2001). Thus, alterations in the metabolism in diabetes adversely affect different cell types within the vascular wall. The enhanced thrombotic potential is one of the main characteristic of diabetes.

Both hypertension and diabetes are potent risk factor for cardiovascular disease and support endothelial dysfunction mediated by an impaired NO availability. (Ghiadoni et al., 2012). The role of reactive oxygen species (ROS) in the pathophysiology of cardiovascular diseases has been explained, as ROS is associated with cardiac and vascular anomalies leading to hypertension and atherosclerosis (Dhalla et ai., 2000). But the direct cause and

effect relationships have not been clearly defined. Although ROS originate from different sources, the vascular NADPH seems to be one of the main sources in cardiovascular complications (Elnakish et al., 2013). The enzyme superoxide dismutase (SOD) has an intracellular antioxidant defence properties which catalyses the superoxide radical into H_2O_2 and O_2 (Dhalla et ai., 2000). SOD has a defensive role in atherogenesis (Cathcart et al., 1989) and promotes hypertension modulating vasodilation, vasoconstriction, vascular remodeling, and cardiac hypertrophy (Fukai & Ushio-Fukai, 2011).

Inflammation has a role in the development and progression of atherosclerosis. It produced cytokines to predict cardiovascular risk (Hansson, 2005). A report evaluate that obesity produce constant low-grade inflammation that altered the secretion of cytokines (Chapman & Sposito, 2008) which increase the risk of diabetes mellitus (DM) andmetabolic syndrome (MS). And also inducing insulin resistance, hypertension and dyslipidemia, thus contributing to development of cardiac disease (Rana et al., 2007). The progression of atherosclerosis is controlled by the balance between inflammatory factors, these are interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-1 (IL-1), tumor necrosis factor (TNF-α) (Mountantonakis & Deo, 2012). IL-6 is produced not only by immune cells but also by adipocytes, endothelial cells, vascular smooth muscle cells and ischemic cardiomyocytes (Kanda & Takahashi, 2004). It stimulates acute-phase reactant proteins, such as CRP, serum amyloid A and fibrinogen (Guo et al., 2012). CRP is a systemic marker of inflammation produced by the liver may promote atherosclerosis by reducing endothelial nitric oxide synthase (eNOS) expression, mediating the negative effects of oxidized low-density

lipoprotein (LDL) on endothelial cells such as expression of adhesion molecules (Anand & Yusuf, 2010; Chen et al., 2012).

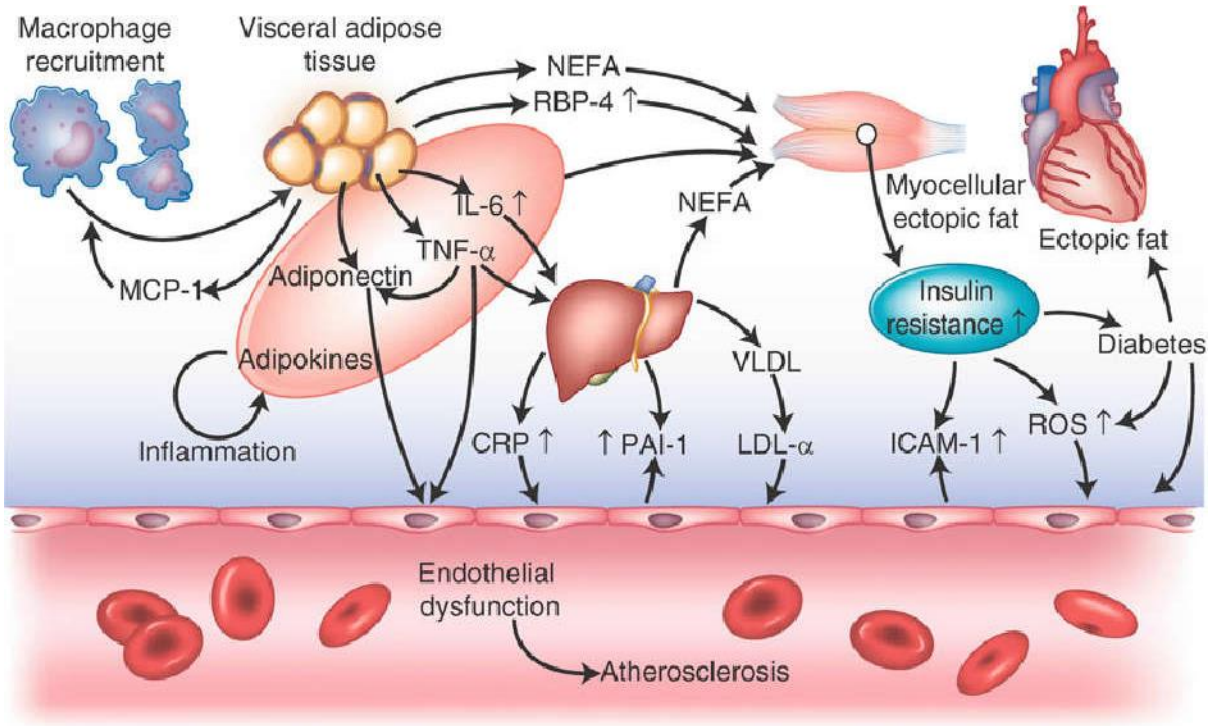

Fig-5. Intraabdominal fat contributes to insulin resistance and cardiovascular dysfunction through cytokine (IL-6, TNF- a , and adiponectin), NEFA and retinol binding protein 4 (RBP-4) production (Kahn et al., 2006)

Thyroid hormones have the ability to elevate the mobilization of stored triglycerides by inducing adipose tissue lipolysis (Pucci et al., 2000). The free fatty acid and glycerol level in blood circulation is dramatically increase in hyperthyroidism, (Nikkilä & Kekki, 1972; Heimberg et al., 1985), which continuously increase the delivery of free fatty acids to the liver for allowing them re-esterification to triglycerides. Thyroid hormones stimulate hepatic

fatty acid β-oxidation, (Pucci et al., 2000) as a result of these divergent actions hypothyroidism most likely results in enhanced hepatic triglyceride accumulation (Walsh, J.P, 2011; Pagadala et al., 2012; Eshraghian; Hamidian, 2014). Hepatic fat accumulation is responsible for increased production of very-low-density lipoprotein (VLDL) which produced metabolic syndrome (MS), as well as in Type 2 diabetes mellitus (T2DM) (Taskinen, M.R, 2003; Adiels et al., 2008). The clearance of VLDL particles in the circulation is diminished in hypothyroidism due to impaired activity of lipoprotein lipase, resulting in decreased lipolysis of VLDL. It also reduced hepatic VLDL removal via LDL receptor-related protein 1 (Moon et al., 2013) which normally help to minimize the VLDL abundance in circulation.

Thyroid dysfunction effects on cardiovascular hemodynamics and cardiac function. Tri-iodothyronine (T_3) increases thermogenesis and decreases systemic vascular resistance. It decreases effective arterial filling volume, promotes renal reabsorption of sodium and increases blood volume (Klein & Ojamaa, 2001). An increased blood volume together with direct effects of tri-iodothyronine on the heart enhances cardiac inotropy and chronotropy, thereby stimulating cardiac output.

The type I diabetes mellitus subdivided in two categories: (i) Type-1A-diabetes mellitus (T1ADM) and (ii) Type-1B-diabetes mellitus (T1BDM). The T1ADM is reported to be caused by the destruction of the pancreatic-β cells by auto immunologic assault (Yoon & Jun, 2005; Waldron-Lynch & Herold, 2011). The T1BDM on the other hand, has been

reported to that the T1BDM be induced by stress or other environmental factors. We have the recently research reported the appearance of a stress-induced protein of MW 11,000 kDa, identified to be dermcidin isoform-2 (DCN-2) in the circulation of the individuals with T1BDM (Ghosh et al, .2012). It has been reported that the T1BDM occurred as a major form of T1DM than T1ADM due to dermcidin induced inhibition of glucose uptake, rather than destruction of the pancreatic β cells (Ghosh et al,. 2011). Some disease conditions sharply augment the human plasma dermcidin (DCN-2) as such when patients suffering from acute myocardial infarction (AMI) have high the level of DCN-2 is significantly high in their plasma (Ghosh et al,. 2011 & Bank et al,. 2014). As because diabetes is the major risk factor for the genesis of AMI and atherosclerosis, so, diabetic patients (both type-1 and type-2) have high level of DCN-2 in their plasma which increase the stress induction in diabetic patients. (Ghosh et al,. 2012). In all these instances stress and DCN have been correlated to the patho-physiological conditions.

Few reports demonstrated that the early elevation of cardiac troponin T (Trop T) than CK-MB in relation with symptomatic evidence of that the myocardial infarction (MI). Since then, Trop T has replaced creatine kinase-MB (CK-MB) as the preferred biochemical markers for the diagnosis of MI. The decision for including cardiac Trop T in the diagnostic field was made due to its high sensitivity and also, even small amounts of myocardial necrosis. An induction of Trop T presence all times not the underlying cause for myocardial injury. Hence, besides acute myocardial infarction (AMI), there is a potential disease with troponin release, including acute pulmonary embolism, heart failure, myocarditis, and end

stage renal disease (Alpert et al., 2000). Troponin T is protein of the myocardial sarcomere more sensitive and specific marker for cardiac injury that is not detectable in the healthy state. Trop T is released within 4-6 hours of cardiac injury peaking after 12 to 24 hours. Elevation of trop T reflects even minor myocardial damage and remains detectable for up to 14 days. Thus the trop T has a predictive value for myocardial ischaemia several times higher than CK-MB (Aviles et al., 2002 .