CHAPTER 2:
REVIEW OF LITERATURE
2.1. INTRODUCTION:

Researchers began to document regarding clustering of various elements of cardiometabolic risk in subjects in early 1960s and 1970s. The combination of cardiovascular and metabolic disturbances was first described as the clustering of hypertension, hyperglycaemia and gout by Kylin in 1923. Later, it was established that insulin resistance is the key abnormality associated with atherogenic, prothrombotic and inflammatory states relative to cardiovascular risk. Two decades later, Vague, in 1947 noted that upper body obesity known as android or male-type obesity was the type most often associated with the metabolic abnormalities seen with diabetes and cardiovascular diseases.

In 1977, Haller used the term "Metabolic Syndrome" for association of obesity, diabetes mellitus, hyperlipoproteinaemia, hyperuricaemia and steatosis hepatitis when relating the additive effects of risk factors on atherosclerosis. In the same year, Singer used the term for association of obesity, gout, diabetes mellitus and hypertension with hyperlipoproteinaemia (Singer, 1977). Gerald B. Phillips, in 1978, developed the concept that risk factors for myocardial infarction form a "constellation of abnormalities" including glucose intolerance, hyperinsulinaemia, hyperlipidaemia, hypercholesterolemia, hypertriglyceridemia and hypertension. There is association not only with heart disease, but also with aging, obesity and other clinical states. He suggested there must be an underlying linking factor, the identification of which could lead to the prevention of cardiovascular diseases. He hypothesized that this factor was sex hormone.

In 1988, Gerald M. Reaven proposed insulin resistance as the fundamental factor and named the constellation of abnormalities as "Syndrome X". Unfortunately, Reaven did not include abdominal obesity, which has also been put forward as the underlying factor, as part of the condition today. After several name changes over the past two decades including the term diabesity used in lay publications, name became "Metabolic Syndrome". The terms "Metabolic Syndrome," "Insulin Resistance Syndrome" and "Syndrome X" are now used exclusively to define a constellation of abnormalities that is associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease.

A number of expert groups have attempted to develop a unifying definition for the metabolic syndrome. The most widely accepted definitions have been produced by the World Health Organization (WHO) and European Group for the Study of Insulin Resistance (EGIR).
All groups agreed on the core components of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension. However, they provide different clinical criteria to identify such a cluster. For example, unlike the other two definitions, NCEP ATP III definition does not obligatorily require impaired glucose regulation or insulin resistance as an essential component. In addition, the levels set for each component and the combination of components required to identify subjects with potential cardio metabolic risk are slightly different in these three recommendations. Recently, a harmonized definition (H_MS) on cardio metabolic risk factors was released by an expert group from the International Diabetic Federation (IDF), National Heart, Lung, Blood Institute (NHLBI), World Health Federation and other international associations. The harmonized definition uses uniform cut-off points for all the risk factors and recommended that individuals with any three of the following components should be considered at potential cardio metabolic risk: Increased waist circumference (population specific) plus any 2 of the following: i) Blood pressure -130 mmHg systolic or ≥85 mmHg diastolic or on treatment for hypertension; ii) Blood glucose - ≥100 mg/dL or on antihypertensive treatment; iii) Lipid profile - TGs ≥150mg/dL or on TGs lowering drug; HDL-C <40mg/dL in men or <50mg/dL in women or on HDL-C lowering drug. The population and gender specific cut-off for waist circumference recommended on the basis of various epidemiological studies are as follows.
<table>
<thead>
<tr>
<th>Country/ethnic group</th>
<th>Waist circumference cut-off</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male (cm)</td>
<td>Female (cm)</td>
</tr>
<tr>
<td>Europids</td>
<td>≥94</td>
<td>≥80</td>
</tr>
<tr>
<td>In USA, ATPIII values (102 cm for males; 88 cm for females) are likely to continue to be used for clinical purposes.</td>
<td></td>
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<tr>
<td>South Asians</td>
<td>≥90</td>
<td>≥80</td>
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<tr>
<td>Based on a Chinese, Malay and Asian-Indian population.</td>
<td></td>
<td></td>
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<tr>
<td>Chinese</td>
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<tr>
<td>Japanese</td>
<td></td>
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<tr>
<td>Japanese</td>
<td>≥90</td>
<td>≥80</td>
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<tr>
<td>Ethnic South and Central Americans</td>
<td></td>
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<tr>
<td>Sub-Saharan Africans</td>
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<td></td>
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<tr>
<td>Eastern Mediterranean and Middle East (Arabs) population</td>
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</tbody>
</table>

Use South Asians recommendations until more specific data are available.

Use European data until more specific data are available.

Use European data until more specific data are available.

**Table I**: Country-wise cut off for waist circumference¹².
2.2 PATHOPHYSIOLOGICAL BASIS OF VARIOUS CARDIO METABOLIC RISK FACTORS IN SUBJECTS:

The pathophysiological basis of various cardio metabolic risk factors in subjects are not yet fully understood. These are affected by complex genetic and environmental factors and their interactions. The most accepted and unifying hypothesis to describe the pathophysiological basis of various cardio metabolic disorders are insulin resistance and abdominal obesity 13.

Insulin resistance is a condition in which there is an insufficient insulin action in liver, skeletal muscle and adipose tissue. Insulin resistance induces increased gluconeogenesis in the liver, decreased glucose disposal in the muscle, endothelial dysfunction in the arteries and increased release of free fatty acids (FFAs) from the adipose tissue 14. Elevated levels of circulating FFAs contribute to the development of insulin resistance by inhibiting insulin signalling. Plasma FFAs are derived mainly from adipose tissue by the action of lipases. Insulin inhibits lipolysis in adipose tissue and glucose production in the liver. Thus, when insulin resistance develops, the inhibitory effect of insulin on lipolysis is suppressed. The increased amount of lipolysis in adipose tissue produces more FFAs, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis. In addition, increased FFAs may result in ectopic lipid formation in the liver. Ectopic lipid accumulation in liver, muscle and pancreas further increases insulin resistance in these sites 15.

In the case of obesity, particularly abdominal obesity, the release of FFAs is increased. In addition, there is an increased production of several inflammatory cytokines and reduced production of anti-inflammatory adipokines 16. This imbalance in the production of inflammatory cytokines favours not only the inflammatory state associated with obesity but also induces insulin resistance by impairing insulin signalling transduction 17. Adipose tissue is a heterogeneous mix of adipocytes, stromal pre adipocytes, immune cells and endothelium, and it can respond rapidly and dynamically to alterations in nutrient excess through hypertrophy and hyperplasia 18. With obesity and progressive adipocytes enlargement, blood supply of adipocytes may be reduced with consequent hypoxia 19.

Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines which include glycerol, free fatty acids (FFA), pro-inflammatory mediators (tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6)),
plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP) 20. This results in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity related co-morbidities 21. Adipocytokines integrate the endocrine, autocrine and paracrine signals to mediate the multiple processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation and inflammatory responses which are thought to accelerate atherosclerosis, plaque rupture and atherothrombosis22,23. This shows that the adipose tissue is not only specialized in the storage and mobilization of lipids but it is also a remarkable endocrine organ releasing the numerous cytokines associated with pathogenesis of cardio metabolic risk in subjects.

In the case of insulin resistance, increased flux of FFAs to the liver increases the hepatic production of apoB containing triglyceride rich VLDL particles. ApoB serves as a structural protein for cholesterol and triglyceride containing lipoproteins that are carried from the liver to the site of use, whereas apoprotein A1-containing particles mediate the reverse transport from the peripheral tissue to the liver 24. Several studies have recently identified hepatic VLDL overproduction as a critical underlying factor in the development of metabolic dyslipidemia 25. The presence of hypertriglyceridemia induces changes in lipoprotein composition and reduction of HDL cholesterol.

The composition of LDL is modified producing small dense LDL (SdLDL). Potential atherogenic mechanisms of SdLDL particles is low affinity to the LDL receptor and long retention time in the circulation 26. In addition, SdLDL contains relatively smaller amounts of antioxidants compared to LDL cholesterol and therefore is more prone to oxidation forming oxidized LDL (OxLDL) particles. Recent studies have suggested that OxLDL may have an important role in the pathogenesis of obesity and insulin resistance 27.

Hypertension has been suggested to relate to insulin resistance in several mechanisms. First, in the presence of insulin resistance the vasodilatory effect of insulin in the endothelium may be suppressed resulting vasoconstriction 28. Compensatory hyperinsulinemia increases the activity of the sympathetic nervous system, where the effect on insulin action is preserved29. Renal Sodium reabsorption in the kidney is increased directly by adipose tissue and via increased sympathetic nervous activation. In addition, FFAs produced by adipose tissue may directly mediate vasoconstriction 30. Adipocytes also produce a variety of vasoactive peptides, which may impair the vasodilatory effect of insulin. Indeed, the relation between insulin resistance and hypertension is more evident in the case of obesity, suggesting that the effect may be mediated by adipose tissue. In addition, it has been suggested that LDL
and triglycerides may damage the arterial epithelium, impair Nitric Oxide release and cause endothelial dysfunction. Therefore, dyslipidemia characterized by elevated levels of apoB containing lipoproteins could cause hypertension by mechanisms only partly related to obesity and insulin resistance 31.

Results from multiple genome-wide studies have shown genetic basis for the individual components of the cardio metabolic risk factors in individuals like obesity, hypertension, dyslipidemia, hyperglycemia32. Such associations might facilitate or enable the development of the cardio metabolic risk in subject. In addition, some candidate genes have been suggested to affect more than one risk component. Although genetic contribution on the development of cardio metabolic disorders exists, the proportion of variance explained has been low 33,34. No genetic test is available that may be used in the diagnosis of such disorders. The lack of association is likely due to the complex interplay between gene and environment necessary for expression of this phenotype. Genetics of cardio metabolic risk involves a large number of genes having weak effects but they may interact with each other and work synergistically with environmental factors like diet, physical activity, alcohol intake, smoking etc. in the pathogenesis of the cardio metabolic risk in subjects 35.
2.3 GENDER DIFFERENCES IN CARDIO METABOLIC RISK FACTORS:

Men were traditionally considered to be at higher risk for cardio metabolic disorders than women. This was mainly due to misperception that females are naturally protected against cardiovascular diseases. However, the scenario started changing during 1990s. Since then, an increasing number of studies have been reported on status of cardiovascular health in women. Accumulating and emerging data demonstrated that a significant heterogeneity exists between men and women regarding cardio metabolic risk.

Recent data from the National Health and Nutrition Examination Surveys (NHANES) have shown that over the past two decades the prevalence of myocardial infarctions has increased in midlife (35 to 54 years) women, while declining in similarly aged men. Women with clinical manifestation of coronary heart diseases are in general older than men with higher expression of cardiovascular risk factors.

Although most of the cardio metabolic risk factors contribute to the health outcome in both men and women, the relative impact of individual risk factor might be different. Key sex differences in risk factors include distinctions in (a) glycemic indices, (b) body fat distribution, (c) adipocyte size and function, (d) hormonal regulation of body weight and adiposity and (e) the influence of estrogen decline on risk factor clustering.

Obesity is an independent cardio metabolic risk factor in women as well as in men. Willet and colleagues from the Nurses’ Health Study showed that even women with a modestly increased body mass index (<25 and >29 kg/m²) had twice the risk of coronary heart diseases as the leanest women (body mass index >21 kg/m²). Independent of overall obesity, the distribution of body fat is the most important determinant of cardiovascular risk. It has been shown that truncal obesity, the so-called android habitus, confers a far higher risk than the peripheral or ‘gynecoid’ body fat distribution. Both waist-hip ratio and waist circumference are highly correlated to the risk of coronary heart disease.

Men and women display a conspicuous sex dimorphism in body fat distribution with substantial variation that may be exclusive to our species. In his seminal observations, Vague referred to android and gynoid obesities when describing adipose tissue accrual in the upper body (trunk and abdomen) in men and lower body (hips and thighs) in women, respectively. The teleological explanation for differential fat partitioning is presumably due to evolutionary and sexual selection pressures which favour storage of excess calories in different depots. However, the precise biologic mediators leading to topographical
differences in body fat distribution remain to be fully elucidated.41

With regard to sex differences in central obesity as shown by computed tomographic measurements, the amount of VAT is up to 2-fold higher in men than in premenopausal women.42 In men, VAT accrual generally increases with the amount of total body fat, whereas in women, VAT accumulation is less a function of total adiposity. It has been convincingly demonstrated that even after accounting for total body fat mass, premenopausal women have a lower ratio of VAT to total body fat than men. Women had less visceral fat despite having a higher total body fat, BMI and abdominal SAT. Premenopausal women therefore appear to accumulate a substantial amount of total body fat before increases in visceral fat are observed. Moreover, it has been demonstrated that for the same waist circumference, men have more VAT than women.43 Thus, a large waistline alone, although a convenient measure, may not be an accurate indicator of visceral obesity. Data from corroborative findings from a more recent meta-analysis suggested that men experience greater reductions in visceral fat and potentially greater improvements in metabolic profile than women despite similar levels of weight loss. The sex differences in distribution and impact of visceral adipose tissue factors responsible for better metabolic profile in men require further study.

Total cholesterol and low-density lipoprotein cholesterol (LDL) levels in men and women are similar up to 20 years of age. In the third and fourth decades, cholesterol levels increase more sharply in men than in women. HDL levels are higher in women than in men from young adulthood onwards. Some studies have described a decrease in HDL levels following the menopause. The loss of protection from HDL is considered to be a major factor for the increased coronary risk in postmenopausal women. It has been suggested that low levels of HDL are more predictive of coronary artery disease in women than in men. Because of the higher level of HDL in women, a modification of the current National Cholesterol Education Program (NCEP) guidelines has been proposed with more aggressive targets for HDL in women. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that a modest increase in HDL levels in men with coronary heart disease and normal LDL levels resulted in a significant reduction in the risk of major cardiovascular events. So far, similar data for women are not available.36
Elevated levels of triglycerides have been associated with an increased risk of CHD in men and women. However, the role of plasma triglycerides as an independent risk factor is still elusive. First, there are methodological difficulties in interpreting triglyceride. Second, strong interactions exist between triglycerides and other lipid factors. Elevated triglycerides are often seen with lower HDL levels and this combination has been associated with increased cardio metabolic risk. A meta-analysis including more than 46000 men and nearly 11000 women showed for men and women respectively, a 32% and 76% increase in cardiovascular risk associated with a 1μmmol/1 increase in triglycerides. After adjustment for HDL and other risk factors, these risks were decreased to 14% in men and 37% in women, but this remained statistically significant for both genders. It seems that elevated triglycerides increase cardiovascular risk more in women than in men, implying a gender difference in the role of triglycerides in atherosclerosis. Therefore, analogous to the gender-specific approach for HDL, the latest NCEP guidelines have suggested that the optimal levels for triglycerides may be lower for women.

Diabetes mellitus is a powerful cardio metabolic risk factor. Up to 75–80% of adult diabetic patients die of cardiovascular diseases and 75% of these deaths are caused by coronary heart disease (CHD). Compared to diabetic men, who have a two-fold to three-fold increased risk of CHD, diabetic women are reported to have a three-fold to seven-fold increased risk. Thus, diabetes seems to eliminate the premenopausal ‘female advantage’ in the prevalence of cardio metabolic disorders. Mortality from myocardial infarction is significantly higher in diabetic women than in non-diabetic women and in men with or without diabetes mellitus. Lipid abnormalities frequently found in patients with diabetes type II are elevated triglycerides, low HDL levels and small dense LDL. Decreased HDL and very low-density lipoprotein levels predict CHD mortality in diabetic women but not in non-diabetic women or diabetic and non-diabetic men. Because of the poor prognosis for women with diabetes, aggressive treatment of cardiovascular risk factors, such as dyslipidemia, should be a high priority.

Isolated systolic hypertension is a common finding in elderly women with a prevalence of 30% in women over 65 years of age. The Systolic Hypertension in the Elderly Program (SHEP) has shown that both men and women with isolated systolic hypertension benefit from blood pressure control. However, large long-term clinical trials have included both men and women and a meta-analysis of these studies did not show significant gender differences in blood pressure and clinical outcome.
Analysis of the published reports on the role of a number of risk factors with emphasis on possible differences between men and women revealed, except for female hormonal status, no risk factor has been recognized as acting on one gender but not on the other. These findings indicated that the pathogenesis of coronary heart disease is very similar for men and women. Yet, in individuals with diabetes mellitus, HDL and triglycerides levels have been found to have a greater impact on CHD risk in women compared to men. In addition, there are indications that risk factors such as smoking, family history and inflammation characterized as C-reactive protein, have a more negative influence on CHD in women than in men. On the other hand, the evidence showed that lipoprotein (a) is a stronger cardiovascular risk factor in men than in women. Therefore, for optimal treatment and prevention of cardio metabolic disorders, it is necessary to acknowledge that women and men did not show a similar response to risk factors or to treatment. Therefore, it is essential that studies present results according to gender, in order to comprehend to what extent preventive measures of cardio metabolic risk are similar for men and women.
2.4 CARDIO METABOLIC RISK PROFILE IN WOMEN - ROLE OF MENOPAUSE:

The hypothesis that menopause and consequent biological modifications are related to cardio metabolic risk in women is derived from the observation that incidence and mortality rates for coronary heart disease in women below menopause are substantially lower than in men but tend to rise approaching those of men at older ages \(^5^2\). However, it is difficult to disentangle the effect of age from that of menopause on cardio metabolic risk, because the two variables are strongly related and an apparent higher risk from menopause may simply be due to the rise of coronary heart disease incidence and mortality with increasing age\(^5^3\).

The overall epidemiological evidence on the relationship between menopause and age and cardio metabolic risk is still controversial. Most information is derived from different cohort studies and case–control studies. As for the cohort studies, the 20-year follow-up of the Framingham Study showed a 2-fold increase in relative risk in postmenopausal versus premenopausal women; in the 24-year follow-up of the same cohort, based on 43 cases of fatal and non-fatal MI, the MI incidence rate was 1.4 in premenopausal and 3.9 in postmenopausal women. In a cohort of Swedish women, based on 25 cases of MI, the relative risk were 2.0 (95% CI: 0.2–19.1) for women aged more than 40 years at menopause, 2.2 and 1.4 for women aged more than 45 years and more than 50 years, compared with premenopausal women. In 6-year follow-up of the American Nurses’ Health Study, after strict allowance for age, compared with premenopausal women, never HRT users with natural menopause had a relative risk of 1.1, and those with surgical menopause had a relative risk of 1.7\(^5^4\).

In a Dutch study of 12195 women including 824 deaths from CVD, the overall relative risk was 0.982 per year delay of menopause and the inverse relation was greater at younger age. In a study from Norway, including 2767 cases of coronary heart disease, the relative risk was 0.84 for women aged more than 53 years at menopause compared with those aged more than 40 years. In the US National Health and Examination Survey (NHANES) I Study, based on 84 cases of fatal acute MI, a moderate and not significant association was observed with age at menopause\(^5^5\).

The relative risk of cardiovascular disease was found to be 3.2 in women with natural menopause and of 2.7 in those with surgical menopause at age more than 45 years, compared with women with natural menopause when aged more than 51 years. Study found increased risks of coronary heart disease in women with menopause either at young (35–40 years) or
later age (56–60 years), the association being stronger in non-HRT users\textsuperscript{56}. Thus, there is some suggestion that after allowing for age, postmenopausal women are at higher risk of coronary heart disease, although there is substantial heterogeneity in the results across various studies on menopause, and age at menopause and coronary heart disease. This is not easily explained by the different type of studies (cohort or case–control), the inclusion of fatal or non-fatal diseases, the inclusion of hormone therapy users, the cut-points selected for age at menopause and other identified factors. Part of these discrepancies may depend on difficulties in the collection and analysis of epidemiological data on menopause. Besides uncertainties in the definition of the peri-menopausal period, age at menopause is difficult to establish in women after hysterectomy and in those using HRT. Moreover, similar to any other time factor, it is important to make an extremely strict age-adjustment to obtain an unbiased quantification of risk\textsuperscript{57}.

Although the epidemiological studies do not show a large immediate effect of menopause on coronary heart disease events, ovarian hormone deprivation after menopause is associated with an increase in CVD risk factors. Estrogens improve endothelial function and vascular reactivity and reduce the progression of coronary atherosclerosis both in animals and in early post-menopausal women. When administered in combination with estrogens, progestogens may, in some instances, interfere with the endothelial effect of estrogens. In post-menopausal women, data on the anti-atherogenetic effect of progestogens are scanty and mainly limited to medroxyprogesterone acetate and gestodene. Combining more androgenic progestogens with estrogens also negatively affects peripheral vascular resistance and vascular reactivity. Lipid, glucose and insulin metabolism are improved by estrogen replacement therapy, but this effect may be reversed by the combination of estrogen with androgenic progestogens, whereas combination with non-androgenic progestogens has a more favourable metabolic profile\textsuperscript{58,59}.

It is well known that endogenous and exogenous estrogens stimulate hepatic synthesis of angiotensin that in turn increases plasma levels of aldosterone through an activation of the rennin angiotensin system. Therefore, in predisposed women estrogens may cause sodium and water retention. Progestogens have different effects on sodium metabolism that may range from extreme sodium retention to sodium excretion. Synthetic progestogens cause an increase of hepatic angiotensin and plasma angiotensin, thereby enhancing Sodium retention. Progesterone competes with aldosterone at kidney level causing a dose-dependent natriuretic effect. Similar effect on Renal excretion of Na+ is shared by dydrogesterone, whereas a
newer progestogen, drospirenone, have a more complex effect on sodium balance having direct anti-aldosterone activity. Drospirenone has a powerful antimineralocorticoid effect that is effective in counter balancing the increase of aldosterone that may be induced by estrogen administration especially in predisposed women and in those predisposed to develop arterial hypertension. Furthermore, in hypertensive women drospirenone is effective in reducing blood pressure either alone or in combination with other anti-hypertensive agents.60

Some cardiovascular effects of estrogen may be counteracted by progestogens. Progesterone receptors are present in the arterial wall and there is evidence that the arterial effects of progestogens are mediated through progesterone receptors as well as through down-regulation of E2 receptors. Progestogen therapy can stabilize arteries in a state of vasomotor instability but may also induce vasoconstriction of estrogenized vessels and precipitate arrhythmia. According to their chemical structure, progestogens have different metabolic and vascular effects that may enhance or abolish the effects induced by estrogen therapy on cardiovascular risk factors and on vascular functions.61

Therefore, the overall effect of hormone replacement therapy on blood pressure is related, on one hand, to the individual response to the activation of the renin angiotensin system and on the other hand, to the dose and type of molecules used. Higher doses of estrogens may induce sodium retention as do synthetic and androgenic progestogens. Micronized progesterone, dydrogesterone and drospirenone have an antimineralocorticoid effect (that is higher for drospirenone) and therefore antagonize the sodium retention effect of estrogens. These progestogens should be preferred in women with borderline hypertension, in those with arterial hypertension well controlled by anti-hypertensive therapy and in women with a tendency to sodium retention.62

Evidence from many observational studies suggests that estrogen replacement therapy after menopause can provide protection against heart disease. However, the results of randomized studies using estrogen and progestogens in women averaging >60 years of age failed to confirm the results of the observational studies. Moreover, awareness and knowledge regarding the cardiovascular risk in women, vis-a-vis, their menopausal status is suboptimal. Therefore, further studies are necessary to better evaluate various cardiovascular risk factors in women in relation to their menopausal status to understand risk/benefit ratio of various therapies available. Until then, prevention of events due to atherosclerosis should rely on diet and fitness and low-dose aspirin therapy.63
2.5. EPIDEMIOLOGY OF CARDIO METABOLIC RISK FACTORS:

Cardiovascular diseases (CVD) are the number one reason of death globally and are predictable to remain the leading cause of deaths. An approximate 17.5 million people died from cardiovascular diseases in 2005, signifying 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million were due to stroke. Around 80% of these deaths occurred in low and middle-income countries (LMIC). An approximate 20 million people will die from CVD every year, mainly from heart attacks and strokes if right action is not taken, by 2015 64,65.

Women are supposed to experience excessively high mortality from CVD. By 2040, women in countries like Russia, Brazil, India, China, and South Africa will represent a higher proportion of CVD deaths in comparison to men. It was projected that by 2040, women population in China will become 49.5 per cent of the total population and they will account for 54.6 percent of CVD deaths. The increase of CVD deaths in Brazil and China among working-aged women between 2000 and 2040 will be higher than that for men. Projections suggested that coronary heart disease (CHD) mortality for all developing countries will increase by 120 percent for women and 137 percent for men. Estimations for the next two decades enclose tripling of CHD and stroke mortality in Latin America, the Middle East, and even sub-Saharan Africa. The proportion of increase will surpass the increase in other regions, except Asian and Pacific Island countries. The increase in more-developed nations, largely attributable to a growth of the population of older people at risk 66. Data available from the World Health Organization MONICA Project indicated that the coronary event rate in men was highest in Finland (North Karelia, 835) and lowest in China (Beijing, 81). For women, the maximum occurrence rate was in the UK (Glasgow, Scotland, 265) and the lowest in Spain (Catalonia, 35) and China (Beijing, 35). These data revealed results from 35 MONICA Project populations collected during the mid-1980s until the mid-1990s 67.

Data from the INTERHEART study showed that rates of CVD have risen greatly in low-income and middle-income countries. Nine potentially modifiable risk factors associated with myocardial infarction (MI) were identified. These varied by populations. The effect of the risk factors is remarkably noticeable in young men and women, demonstrating that most premature MI is avoidable. Two-thirds of an acute MI worldwide is related to smoking and abnormal lipids. High blood cholesterol is predicted to cause about 4.4 million deaths which sum up to 18 percent of strokes and 56 percent of global CHD. A blood cholesterol level of
less than 5.0 millimoles per liter (mmol/L) is recommended for both primary and secondary prevention of CHD\(^{68,69}\).

Approximately 66 percent of men and women in the UK have blood cholesterol levels of 5.0mmol/L and above. According to data published by World Health Organisation, approximately 600 million people with high blood pressure are at risk of heart attack, stroke and cardiac failure. In African-Americans, hypertension develops at much earlier age compared to whites. The cause for this difference may be due to a complex interchange between environmental response to diet, stress and a potential genetic/physiological difference in Sodium/Potassium excretion. A study of hypertension in Canada, United States and in six European countries: Germany, Finland, Sweden, England, Spain and Italy showed the average blood pressure was 136/83 mmHg in the European countries and 127/77 mmHg in Canada and the United States, among men and women ages 35–74 years. Blood pressure measurements for all age groups were highest in Germany and lowest in the United States. The measurement of blood pressure in England revealed that 34 percent of men and 30 percent of women have high blood pressure or are being treated for hypertension. The number of men and women not being treated for high blood pressure are 67 % and 78%, respectively. In Asia, a steep increase in stroke mortality goes together with a rapid rise in the prevalence of hypertension. Projections suggest that in China, hypertension will increase from 18.6 percent to 25 percent between 1995 and 2025. In India, the equivalent figures are 16.3 percent to 19.4 percent\(^70\).

Coronary heart disease (CHD) mortality is at least 40% higher in UK Indian Asians compared with European whites. Traditional coronary risk factors including smoking, hypercholesterolemia, and hypertension do not clarify their increased CHD risk compared with whites. Diabetes mellitus and insulin resistance are more common among Indian Asians. The exact mechanisms underlying the increased CHD mortality in Indian Asians are not known. Myocardial infarction (MI) was seen to occur at a lower age in Indian population compared with the group population of countries to which they have migrated and mortality from MI was ten times higher. Although insulin resistance may be involved in the early event of risk factors and CHD in Indians, there is some data to suggest that other aspects of the lipid profile such as the lipoprotein (a) [Lp(a)] level, affect risk in Indian patients. Lp(a) was an independent risk factor for CHD in type 2 diabetic patients in South India\(^72\).

Epidemiological studies have shown that South Asians also are more likely to have central obesity, increased waist/hip ratio (WHR) and glucose intolerance compared with
Caucasians\textsuperscript{73}. Studies observed a strong tendency for insulin resistance in lean Asian Indians. The latter were much more insulin resistant than lean Caucasians. The curve of insulin sensitivity against percent body fat was relatively steep in Caucasians. This was not the case in Asian Indians. In the latter group increasing adiposity was accompanied by some decrease in insulin sensitivity. The mechanisms underlying the low insulin sensitivity in Asian Indians, whether due to physical inactivity, dietary differences, or hereditary factors, still continue to be evaluated\textsuperscript{74}.

Asian Indian women had a higher rate of CHD than do other ethnic groups, despite similar conventional risk factors and lipid profiles. It may partly be explained by the differences in the prevalence of atherogenic HDL-C and low-density lipoprotein cholesterol LDL-C sizes and their subclass concentrations among Asian Indian women compared with Caucasian women\textsuperscript{75}. In a study conducted by Ranjith \textit{et al.}, that examined differences in major cardiovascular risk factors and clinical outcome in South African Asian Indians of different age groups and gender, who presented with acute coronary syndromes, it was observed that diabetes mellitus and hypertension were less frequent in young male patients. Total cholesterol was elevated in 65 to 70\% of all patients while high-density lipoprotein (HDL) levels were significantly lower in men compared with women for all age groups\textsuperscript{76}.

In the study by Chambers \textit{et al.}, they investigated CRP concentrations in a representative sample of Indian Asian and European white men living in West London, UK. They found that CRP levels were elevated in Indian Asians and were closely associated with increased central adiposity and markers of insulin resistance in Asians compared with Europeans\textsuperscript{77}.

The defined reasons underlying increased central obesity among Indian Asians compared with European whites are not known. The genetic factors in the first-degree relatives of Indian Asian CHD patients may play a major role in explanation of increased abdominal obesity in this racial group\textsuperscript{78}. That is in agreement with the data that suggested that CRP concentrations may be influenced by genetic factors, although the molecular basis remains to be identified\textsuperscript{79}. On the basis of the reported relationship between CRP and risk of CHD, it was observed that increased CRP concentrations and/or the processes underlying elevated CRP are associated with an increase in population CHD risk among Indian Asians compared with European whites. The extent of this effect on CHD risk is comparable to a rise in diastolic blood pressure or an increase in total cholesterol. The studies suggested that
inflammation or enhanced cytokine production and/or their acute phase consequences may contribute significantly to the increased CHD mortality in Indian Asians\textsuperscript{80,81}.

Studies demonstrated that CRP concentrations were also closely associated with levels of HDL cholesterol, triglycerides, glucose, blood pressure, and a composite insulin resistance score in different racial groups. The similar data was reported in North American and European populations, which have additionally shown that CRP concentrations and other inflammatory markers, including white cell count and fibrinogen, are strongly correlated with plasma insulin and insulin-mediated glucose uptake\textsuperscript{82}.

In a study by Mohan \textit{et al.}, it was established that CRP showed a strong association with coronary artery disease (CAD) and diabetes mellitus, even after adjusting for age and gender in an urban south Indian population. The association of body fat with diabetes mellitus seems to take place through hs-CRP. However, CRP didn’t appear to mediate the relationship between body fat and CAD. The relationship between CRP and dietary nutrients was investigated in young Asian Indians residing in a major metropolitan city in north India. Raised CRP levels (>3 mg/L) were noted in 9% study subjects (8.6% males and 12.8% females). Saturated fat appear to be the single most important nutrient contributing to increase in serum CRP levels after adjustment for other covariates. The probability of having a raised CRP level in subjects eat more than 10% energy as saturated dietary fat were twice that compared to subjects having a normal saturated fat intake. Elevated CRP levels in adolescents and young adults in Asian Indians in north India were observed in 21.8% of the overweight subjects and 24.5% of the subjects with high (>85th percentile) percentage body fat (%BF). Levels of CRP correlated significantly with body fat (%), WHR, biceps skinfold and triceps skinfolds for males only. The findings of significant prevalence of elevated CRP levels in adolescents and young adults having increased generalized and abdominal adiposity may be important for the development of cardio metabolic risk in Asian Indian adults\textsuperscript{83,84}. 
2.6. CARDIO METABOLIC RISK AND ANAEMIA:

Using the historical definition by the World Health Organization, anaemia is defined when Hb concentration is less than 13 g/dL for men or less than 12 g/dL for women. Anaemia is prevalent in patients with CHF but the exact rates vary widely. A recent meta-analysis of 1,53,180 patients with CHF, reported in 34 published studies from 2001 to 2007, estimated the prevalence of anaemia to be 37.2% (10–49%). Similarly, the latest prospective STAMINA-HFP (Study of Anaemia in a Heart Failure Population) Registry estimated a prevalence of 34% in a cohort study. The variability in the estimated prevalence of anaemia is partly attributable to use of different definitions of anaemia. Patients with CHF and anaemia tend to be older than their non-anaemic counterparts. Concerning the gender, in studies of CHF and anaemia enrolling a preponderance of men, the proportion of women steadily increases as Hb concentration falls to the point that women can predominate among patients with CHF and severe anaemia.

The major factors contributing to CHF-related anaemia involve chronic kidney disease (CKD), renin-angiotensin system, hematinic abnormalities, mainly iron deficiency, chronic inflammation and haemodilution. Iron deficiency is common in patients with CHF especially when accompanied by CKD, whereas vitamin B12 and folic acid deficiencies or iron overload are not. It is of interest that the incidence of iron deficiency is increasing with the severity of heart failure. In half cases, iron deficiency is absolute with low transferrin saturation and serum ferritin, usually associated with decreased iron stores and reduced iron deposits in the bone marrow. In the other half cases iron deficiency is functional-relative, with low transferrin saturation and normal or elevated serum ferritin, usually associated with normal or elevated iron stores and iron deposits in the bone marrow.

Although the exact role of anaemia in promoting cardiovascular disorders (CVD) is currently not well understood, maintenance of adequate tissue oxygenation in the anaemic state is achieved by both non-hemodynamic and hemodynamic adaptations. Non-hemodynamic adaptations include increase in erythropoietin production and increase in intra-erythrocytic concentrations of 2,3-diphosphoglycerate. Hemodynamic changes include systemic arterial dilatation, which leads to a decreased systemic vascular resistance and reduced afterload, which in turn may increase stroke volume. Anaemia also results in decreased blood viscosity, which increases venous return and thus, augments preload. Finally, the presence of anaemia activates the sympathetic nervous system, which results in...
an increase in heart rate. Increased preload, heart rate and stroke volume as well as reduced after load, all of which act to raise cardiac output\textsuperscript{90,91}.

It is important to recognize that although studies may demonstrate an association between anaemia and CVD outcomes, this does not necessarily imply that anaemia is the cause and therefore, a treatable cause of CVD. That is, confounding from unmeasured factors, or residual confounding from measured factors may be playing a role. Two examples include (1) anaemia may be associated with an unmeasured risk factor such as inflammatory status, which in turn is the cause of both the anaemia and the causal risk factor associated with CVD; (2) anaemia may be a marker of the severity of underlying heart disease. For example, in patients with heart failure, anaemia may be due to hemodilution associated with the severity of heart failure\textsuperscript{92,93}.

There has been increasing appreciation of the significance of anaemia in the pathophysiology, treatment and prognosis of heart failure. Once considered a downstream complication of heart failure, anaemia is now emerging as a crucial and potentially modifiable factor in the overall treatment strategy for patients with chronic heart failure. Although the reports of prevalence of anaemia vary widely, it is unequivocal that anaemia is prevalent in patients with heart failure regardless of the clinical setting\textsuperscript{94}.

The prevalence of anaemia was reported to be 37.2\% in a recent meta-analysis of a total of 153,180 patients with heart failure across 34 published studies over a seven-year period (2001–2007). This is consistent with the findings from the prospective STAMINA-HFP (Study of Anaemia in a Heart Failure Population) using the WHO definition of anemia\textsuperscript{95}. A recent Canadian study of a population-based cohort of 12,065 patients with new-onset heart failure from hospital discharges identified a prevalence of anaemia of 17\%. In this study, more than half of the patients (58\%) were classified as having anaemia of chronic disease based on International Classification of Diseases. As might be expected, in addition to variations in definitions, the different practice settings have different mechanisms and different prevalence rates of anaemia. For example, those patients in acute decompensated states likely experience more dilutional anaemia simply due to hypervolemia. Overall, the prevalence of anaemia varies widely, ranging from 14\% to 56\% in outpatient registries to 14\% to 61\% in hospitalized patients.\textsuperscript{96,97}.

The true frequency of anaemia in patients with heart failure is not only influenced by the definition used, but also differs according to the patient population and demographics in which anaemia is being assessed. Unfortunately, the precise cut-off to define anaemia in heart
failure has mostly been arbitrary and there is no consensus about definition of anaemia specific to patients with heart failure. Although a historical definition of anaemia was put forwarded by the World Health Organization (WHO). Such a definition has not been subjected to rigorous clinical validation, particularly in the setting of heart failure. Considerable variability exists in defining anaemia, particularly in the setting of chronic kidney disease (CKD), which often coexists with heart failure. Moreover, the threshold haemoglobin level at which anaemia treatment should be initiated is an even more complex and controversial clinical question.

Anaemia is a health problem mainly affecting developing countries. With economic growth and associated sociodemographic changes, the burden from under nutrition and infectious diseases has diminished. Concomitantly, changes in diet and other lifestyle factors have led to an increase in life expectancy but also to an increased prevalence of cardio metabolic diseases and other chronic diseases. The cardio metabolic disorders are characterised by a clustering of cardiovascular risk factors and being a powerful determinant of type 2 diabetes has been reported to be increasing in developing nations. An association between inflammation and the cardio metabolic risk has been reported in various populations. As inflammation is associated with anaemia, theoretically there could be a connection between anaemia and the cardio metabolic risk, if the anaemia is mainly caused by inflammation.
2.7. CARDO METABOLIC RISK, OXIDATIVE STRESS AND ANTIOXIDANTS:

Oxidative stress is a well-recognized mechanism playing an important role in many pathological conditions and several human diseases have been closely related to oxidative stress. A number of cell functions appear to be regulated by free radical molecules, which may also act as intracellular and intercellular signals. Also, the protein redox state is implicated in the regulation of several cellular activities, including cell differentiation and activation of specific metabolic pathways. Oxidative stress has been associated with all the individual components of various cardio metabolic risk complications in subjects. Three major cardio metabolic risk factors: impaired glucose tolerance, dyslipidemia and hypertension are caused by the same underlying mechanism—endothelial dysfunction primarily mediated by oxidative stress.

It is now apparent that visceral adipose tissue is an endocrine organ that secretes many bioactive molecules, known as adipocytokines. The production of adipocytokine is of particular interest, because their local secretion by perivascular adipose depots may provide a new mechanistic link between obesity and its associated cardiovascular complications. Increased oxidative stress to adipocytes causes dysregulated expression of inflammation-related adipocytokines. Increasing evidence supports the central role of adipose tissue in the development of systemic inflammatory state, which contributes to obesity-associated vasculopathy and cardiovascular risk. These adipocytokines are generally divided into pro-inflammatory cytokines such as tumor necrosis factor-a, interleukin-6, monocyte chemo attractant protein-1, plasminogen activator inhibitor-1 and anti-inflammatory cytokines such as adiponectin. Imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines is responsible for oxidative stress especially to endothelial cells and underlies the pathogenesis of the obesity associated insulin resistance, impaired glucose tolerance, type-2 diabetes mellitus, hypertension, dyslipidemia and vasculardisease.

In a recent study, the role of oxidative stress in the pathophysiologic interactions among the constituent factors of cardio metabolic risk in subjects has been evaluated. Although some of the constituent characteristics of the metabolic syndrome are known to share common pathogenic mechanisms of damage, the impact of hereditary predisposition and the regulation of gene expression as well as the role of environment and dietary habit in determining inflammatory process triggered oxidation are still unclear. However, excessive free radical production and oxidative damage are found to be associated with cardio metabolic disorders in several experimental demonstrations and human observations.
High concentrations of H$_2$O$_2$ promote insulin signalling and induce typical metabolic actions of insulin. This result could be considered as the first documentation on the link between ROS and insulin. In particular, H$_2$O$_2$ uses the same pathway of insulin and causes downstream propagation of the signal producing typical metabolic actions of insulin. H$_2$O$_2$ induces an increase in glucose uptake by adipocytes and muscles and also stimulates GLUT4 translocation and lipid synthesis in adipocytes. Insulin receptor substrate (IRS) proteins are effectors for tyrosine kinase activity of the insulin receptor (IR) upon insulin binding. These proteins are involved in a critical step of insulin signalling. In normal physiological state, insulin signalling molecules are distributed between the cytosol and internal membrane pools. Whereas, after insulin stimulation, tyrosine residues on IR and IRS are phosphorylated through activated insulin receptor kinase. This leads to the enrolment of PI 3-kinase in the plasma membrane and in internal membrane pools. Subsequently, the activation of small GTPase Rac induces cytoskeletal reorganization that propagates the insulin signals. Finally, this induces to typical metabolic effects of insulin such as increased glucose uptake.

In conditions of increased oxidative stress, stress-responsive signalling cascades are activated, such as the MAP kinase cascades. This induces to increase Ser/Thr phosphorylation of IRS molecules. Modified IRS molecules are released from internal membrane pools and are subjected to increased protein degradation. In these conditions, insulin fails to gain normal metabolic effects. This happens because IRS molecules are decreased in content and cannot be normally tyrosine phosphorylated when hyper phosphorylated on certain Ser/Thr residues. It is important to note that, receptor substrates are able to directly modify the expression of glucose/metabolic genes such as GLUT4 and adiponectin. In animal models of obese mice, an increased H$_2$O$_2$ generation by adipose tissue could be observed prior to diabetes onset. This event came with decreased mRNA levels of SOD, catalase and glutathione peroxidase. Developing diabetes in these mice increased these alterations, which remained unobservable in other tissues.

Obesity and related insulin resistance are frequently related with increased accumulation of lipids (triglycerides) in the liver. Increased numbers of lipid peroxidation markers have been observed in the liver, in animal models of diabetes and obesity. Oxidation-induced disruption of cellular redistributed signalling molecules in response to insulin stimulation was associated with impaired insulin action. An animal model of oxidative stress provided support for this notion. In this in vivo model, oxidative stress was induced in rats using an inhibitor of glutathione biosynthesis enzyme. The reduction in tissue levels of glutathione, a cellular antioxidant, increased markers of oxidative stress and
impaired glucose homeostasis. Some studies in humans have evidenced the pivotal role of oxidative stress in insulin resistance states such as metabolic syndrome, obesity, and type 2 diabetes mellitus.  

Oxidative stress with an imbalance between ROS and antioxidant defence mechanisms, contributes to the etiology of hypertension in animals and humans. ROS are generated by multiple cellular sources, including NADPH oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived Nitric Oxide synthases (eNOS), cyclo-oxygenase and lipo-oxygenase. Superoxide anion is produced by stimulation of angiotensin /angiotensin II type I receptor (AT1R) and NADPH oxidase by Angiotensin II. Superoxide anion is the predominant ROS species produced by these tissues, which neutralizes Nitric Oxide (NO) and leads to downstream production of other ROS such as Hydrogen Peroxide, hydroxyl radicals and per-oxynitrite. Hypertensive patients have impaired endogenous and exogenous antioxidant defence mechanisms, increased plasma oxidative stress and an exaggerated oxidative stress response to various stimuli. Hypertensive patients also have lower plasma ferric-reducing ability of plasma (FRAP), lower vitamin C levels and increased plasma 8-isoprostanes, which correlate with both systolic and diastolic blood pressure (BP). Various single-nucleotide polymorphisms (SNPs) in genes that codify for antioxidant enzymes are directly related to hypertension including NADPH oxidase, xanthine oxidase, superoxide dismutase (SOD 3), catalase, glutathione peroxidase (GPx 1) and thioredoxin.

ROS directly damage endothelial cells and degrade NO. Various neurohormonal systems including the renin-angiotensin-aldosterone system and sympathetic nervous system also contribute to oxidative stress, inflammation and vascular immune dysfunctions. The increased oxidative stress, inflammation and autoimmune vascular dysfunction in human hypertension results from a combination of increased generation of ROS, an exacerbated response to ROS and decreased antioxidant reserve. There are also direct interactions of the central nervous system, inflammation and BP. Increased oxidative stress in the rostral ventrolateral medulla (RVLM) enhances glutamatergic excitatory inputs and attenuates GABAergic inhibitory inputs to the RVLM, which contributes to increased sympathetic nervous system (SNS) activity from the paraventricular nucleus. Activation of the AT1R in the RVLM increases NADPH oxidase and increases oxidative stress and superoxide anion. It will increase SNS outflow causing an imbalance of SNS/Peripheral nervous system (PNS) activity with elevation of BP. There will be an increase heart rate, alterations in heart rate variability and heart rate recovery time, which can be blocked by AT1R blockers.
Atherogenic dyslipidemia is an important component of the cluster of cardio metabolic risk factors in subjects. There are three major components of dyslipidemia that are the part of cardio metabolic risk factors: an increase in triglyceride-rich lipoproteins (TRLs) both fasting and postprandial, a reduction in high-density lipoprotein (HDL) and elevated small, dense low density lipoproteins (LDL) particles. Because the metabolism of all lipoproteins is highly interrelated, it is believable that a common fundamental metabolic defect explicates all of the lipoprotein changes in the dyslipidemia related to insulin resistance. It is indeed rare that they are found separately in insulin resistant individuals. During the postprandial state, dietary fatty acids are transferred from the intestine to peripheral tissues as chylomicron triglycerides. In blood of the peripheral tissues, chylomicron triglycerides are lipolyzed by lipoprotein lipase (LPL), conceding the delivery of nonesterified fatty acids to cells and resulting in production of smaller, cholesteryl ester-enriched chylomicron remnants. These particles are fast removed. Some studies have examined the relation between postprandial lipemia and insulin resistance, plasma glucose and insulin response to a dinner in healthy nondiabetic subjects. Postprandial triglyceride levels, as an indirect measurement of chylomicron remnant particles were found to be significantly related to insulin action. A significant relation of triglyceride levels to postheparin plasma LPL activity was also demonstrated. Because LPL is an insulin-sensitive enzyme, which is suppressed in insulin resistant individuals, its deficiency might contribute to the abnormal levels of remnant particles in insulin resistance.

A correlation between elevated LDL and low HDL and oxidative stress in animal models is well established. LDL receptor-deficient mice fed a cholesterol-enriched diet developed elevated LDL levels and consequently oxidative stress. These observations extend to human studies. High plasma oxidative stress markers are positively correlated with elevated plasma triglycerides and are inversely correlated with low HDL in a group of metabolic syndrome patients with end-stage renal disease, after all other factors like presence of obesity, hypertension and/or type II diabetes mellitus were adjusted.

Lipid peroxidation, as an index of oxidative stress, is correlated with low HDL levels, irrespective of age, gender and presence of the other cardio metabolic risk components. It is also now accepted that the numerous positive effects of some statins in the cardiovascular system are independent of their lipid lowering effect and a consequence of a direct decrease in oxidative stress. For example, short-term pravastatin treatment reduced myocardial infarct (MI) size in hypercholesterolemic rabbits through reduction in peroxynitrate and nitrotyrosine formation. Similar results, with regards to the atherogenic index were achieved with
rosuvastatin, which lowered oxidative stress by elevating the expression of antioxidant enzymes (SOD, catalase, glutathione, glutathione peroxidase), LDL, triglycerides, and C-reactive protein (CRP) and elevated HDL. In cross-sectional studies, obese subjects have higher levels of oxidative stress biomarkers compared with their leaner counterparts. Also, weight gain significantly increases the concentration of these biomarkers. There are multiple sources for oxidative stress in relation to obesity. Some of them are inherently related to increased adiposity and fat distribution, whereas others are the result of co-morbidities or behavioral changes associated with being obese. Increased adipose tissue and in particular, visceral adiposity are significantly correlated with systemic levels of oxidative stress biomarkers.

Adipose tissue-mediated systemic oxidative stress and systemic inflammation may be secondary to increased leptin-to-adiponectin ratio and increased levels of other adipokines, such as tumor necrosis factor and plasminogen activator inhibitor. Obesity is associated with several co-morbidities, including hypertension, insulin resistance, diabetes mellitus, and hyperlipidemia: each of these co-morbidities alone can increase the oxidative stress burden. Maintaining a healthy lifestyle by eating a balanced diet rich in antioxidants and being physically active are associated with reduced oxidative stress. Unfortunately, this protection is less effective among obese subjects, who are more sedentary having reduced intake of dietary antioxidants and lower serum vitamin levels.
2.8.REFERENCE:

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