CHAPTER 2

Review of literature
2.1. Search Strategies

A comprehensive literature search using electronic databases including PubMed, Medline, Science Direct, Cochrane database of systematic reviews, Cochrane central register of controlled trials, Pro-Quest and Blackwell online journals, EBSCO, SCOPUS, academic search premier, CINAHL, Biomed Central, Clinical Trials.Gov and web of science databases was undertaken to identify literature. Additional studies were added by manual searching of the reference lists of original investigations and review articles.

2.2. Search Duration

The custom range of search for publication dates was from 1980 to April 2015.

2.3. Key words

Obesity; overweight; visceral fat estimation; body fat distribution; epicardial fat; epicardial adipose tissue; pericardial fat; intra thoracic fat; echocardiography; Asian-Indians; Asian population; interventions for weight loss; physical activity; cardiovascular risk; anthropometrics; blood lipids; fasting blood glucose; high sensitive C-reactive protein.

2.4. Level of Evidence

Articles used in this review are graded independently in accordance to the criteria described by the Centre of Evidence-Based Medicine, Oxford, United Kingdom (Table 1 below).
Table 1: Level of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy / Prevention / Aetiology</th>
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<tr>
<td>Level 1</td>
<td>Evidence obtained from high-quality randomized controlled trials, prospective studies, or diagnostic studies</td>
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<td>Evidence obtained from lesser quality randomized controlled trials</td>
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<tr>
<td>Level 2</td>
<td>Prospective studies, or diagnostic studies (e.g. Improper randomization, no blinding, &lt;80% follow-up)</td>
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<td>Level 3</td>
<td>Case controlled studies or retrospective studies</td>
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<td>Level 4</td>
<td>Case series</td>
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<td>Level 5</td>
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2.5. Overweight and obesity prevalence in Asian-Indian population

The prevalence of cardio metabolic diseases is increasing in Asian-Indian population. Visceral fat has been identified as a front runner in all the causes of cardio metabolic diseases. Increasing prevalence of Diabetes and CAD in Asian-Indian population has been attributed to visceral fat accumulation. The visceral fat levels are comparatively high in normal weight Indians with relatively lower BMI than Caucasian individuals. BMI is found to be a poor indicator of cardiovascular disease risk in Asian-Indians. Based on these observations, WHO convened an expert consultation on classification of obesity. It was suggested to retain the current cut-off points of international classification for worldwide population. But they recommended the new cut-off points of 23, 27.5, 32.5, and 37.5 kg/m$^2$ for public health action. The additional trigger points identified as $> 23$ kg/m$^2$ for increased risk, and $>27.5$ kg/m$^2$ as representing high risk. Several studies have shown the increasing risk of cardiovascular diseases in Asian-Indians at lower BMI.$^{14,110}$
A meta-analysis was conducted to study the predictive ability of BMI, WC and waist-hip ratio in detecting new cases of diabetes, the relative risk of diabetes was found to be similar for all the three anthropometric measures used in the study.\textsuperscript{111} Naval et al studied the occurrence of risk factors of cardiovascular disease and further suggested the need for modification of obesity classification in Asian Indians.\textsuperscript{112} It is now known that the central obesity is associated with increased risk of diseases. Varghese et al studied the visceral and subcutaneous fat area measured by CT scan in young patients with CAD in a case-control study. Visceral fat area was found to be higher in patients with CAD which also correlated with lipids, fasting glucose and HS-CRP.\textsuperscript{113} The truncal fat was found to be more in Asian-Indians compared to Caucasians with same amount of total body fat. The insulin resistance syndrome and CAD were found to be better associated with central obesity in Indian population.\textsuperscript{114,115} Prasad et al found 3-5% higher body fat in South-Asians than whites, at any given BMI\textsuperscript{116}. Wulan et al examined the differences in body composition and the metabolic profile in a comparative study between Asians and Caucasians. Among the three major ethnic groups studied in Asia, Asian Indians were found to have the highest body fat.\textsuperscript{117} Singhal et al attempted to validate the measures of central obesity among young Asian Indian women. It was found that Fat mass index measurement was a better predictor of obesity compared to BMI.\textsuperscript{118} All these studies support the use of innovative methods of evaluation of central obesity, particularly in the Indian population for appropriate risk assessment.

The prevalence rates of truncal and generalized obesity were not found to be same in a large sample based observational studies in Indian population. The risk factor evaluation was conducted in Jaipur heart watch-2 study. The prevalence of truncal obesity was found to be 57.4% in females and 68.4% in males; whereas prevalence of generalized obesity was only
24.5% in males and 30.2% in females. HDL-C values were found to be abnormally low in majority of the participants among all the indices of dyslipidaemia in this population studied.\textsuperscript{119} Deepa et al conducted the Chennai Urban Rural Epidemiology Study (CURES:47) and found that the prevalence of combined obesity was found to be high among both genders. Moreover, in another study the isolated generalized obesity was more common in men whereas isolated abdominal obesity was more common in women.\textsuperscript{120} These two studies indicated that prevalence of central obesity is high compared to generalized obesity in Indian population, suggesting that risk factor assessment in adults should include identification and evaluation of central obesity.

The central obesity is the primary component of metabolic syndrome and increased inflammation. Insulin resistance syndrome is a common manifestation in metabolic syndrome in both diabetics and non-diabetic populations. Vega et al found the association between intra-abdominal obesity and metabolic syndrome in non-diabetics.\textsuperscript{121} These studies emphasized the need for monitoring the metabolic parameters in non-diabetic population with truncal obesity. Jeemon et al studied the association of Hs-CRP with established cardiovascular risk factors in the Indian population.\textsuperscript{122} As the inflammation is known to be accelerated in obese population, the assessment of inflammatory markers such as C-reactive protein has been found to be clinically important.

**Summary**

The prevalence of obesity has been found to be increasing in India in last two decades due to rapid change in the lifestyle and reduced physical activity. The prevalence was found to be underestimated with BMI as a measure of obesity. The prevalence of central obesity was
found to be proportionately more when compared to generalized obesity in most of the studies conducted in Indian population.

2.6. Clinical assessment and implications of visceral fat

Visceral fat is a major risk factor for cardio metabolic disorders through its inflammatory profile. The accurate quantification of VAT is of prime importance to prevent the pathologies related to its increased amount. The proportion of visceral fat or intra-abdominal fat was found to increase with age, whereas subcutaneous fat increases with an increase in the degree of obesity. Men have been reported to have higher amount of visceral fat compared to women, whereas total body fat percentage is higher in women. The quantification of visceral fat and defining its normal ranges may depend on gender and ethnicity.\textsuperscript{123,124}

Shuster et al reviewed the clinical importance and methods of analysis of VAT. The metabolic characteristics of VAT were found to be varying from SAT. The clear understanding of pathophysiological consequences of VAT increased the need for its quantification. A range of simple to expensive and cumbersome methods has been used to quantify the visceral adipose tissue. The accuracy of these methods is very important to study the effects of therapeutic interventions directed to reduce the quantity of visceral fat and further improve their health benefits.\textsuperscript{125} Waist circumference has been found to be most reliable measure of visceral fat and an important component of metabolic syndrome. But, it has been found to be confounded by subcutaneous fat.\textsuperscript{124,126} The correlations between skin fold measurements and intra-abdominal fat volumes showed poor correlation, suggesting that skin fold thickness measurements are better indicators of subcutaneous fat than visceral fat in
the body. BIA is a safe, radiation free and widely used clinical method used in body composition assessment which was earlier used to measure total body fat. Visceral fat levels estimated by BIA showed good correlation with CT and MRI. BIA and anthropometric methods are widely used for epidemiological studies, but these methods are not accurate to quantify the visceral adipose tissue. DEXA and whole body imaging methods have gained importance in quantification of total body fat and visceral fat components as they are rapid and precise. These methods have been increasingly used in the research studies, but not practically feasible in routine clinical use due to high cost and radiation exposure. DEXA is a precise method to differentiate the fat free tissue, fat tissue and bone mineral content, but it can distinguish different adipose tissues.

Bhat et al recommended the use of BIA and skin fold measurements rather than BMI after studying the body fat measurements using deuterium oxide dilution in Indian men.

Several studies demonstrated the reliability of abdominal ultrasound measurement in diagnosing intra-abdominal obesity. The abdominal fat index measured by ultrasonography has been found to be a reliable indicator of visceral fat, correlated with CT imaging. The ability of the researcher in accurately quantifying the tissue may influence the measurements; further research is required to prove the reproducibility of ultrasonography in measuring the abdominal adipose tissue or visceral adipose tissue. CT and MRI provide accurate estimation of total abdominal adipose tissue and can effectively differentiate subcutaneous and visceral adipose tissue. Volume of fat can be measured in voxels and translated to cubic centimetres. Voxels is defined as “contraction for volume element, which is the basic unit of CT are MRI”. A single or multiple slice measurements at predetermined landmarks are generated to measure the regional adipose tissue and even the total fat volume.
Visceral fat quantification has been used in several interventional studies using CT and MRI. Radiation exposure, unavailability of resources and high cost has made it a less feasible option to routinely use these imaging methods in clinical practice. Current research is focusing on simple, accurate and cost-effective methods to quantify visceral fat, which can also serve as a therapeutic target and potential research outcome. Tadashi Nakamura et al studied the association between visceral fat and CAD risk factors in non-obese individuals with diagnosis of CAD. Visceral fat area was detected to be increased in CAD compared to non-CAD. These findings suggested the role of visceral fat in the development of CAD in non-obese individuals.

2.7. VAT estimation in management of Obesity:

VAT quantification has been used in several interventional studies. Six months of moderate intensity aerobic exercise has been found to be effective in reducing the visceral fat area measured by MRI in non-obese women in a study conducted by Thomas et al. The aerobic exercise did not have significant effect on triglycerides and VLDL in these patients and therefore concluded that aerobic exercise has a preferential effect on visceral fat. High intensity exercise training was found to be highly effective in reducing the visceral fat quantity when compared with lower intensity exercise in a dose-response relationship study conducted by Irving et al.

Ohkawara et al carried out a systematic review and meta-analysis on dose-response link of exercise and visceral fat. Visceral fat reduction was observed with or without weight reduction in these studies. The results from the studies revealed that aerobic activity with 10 METS of weekly exercise involving brisk walking, jogging or stationary ergometer were
effective in reducing the visceral fat. Higher volumes of exercise were associated with more amount of visceral fat reduction compared to lower volumes of exercise in overweight individuals. A dose-response relationship was observed in obese individuals without metabolic disorders. \(^{100}\)

The regain of visceral fat deposition after weight loss may occur if the physical activity levels are not maintained. A follow-up study for a period of one year after weight loss induced by aerobic and resistance exercises were done to find that the subjects who did not adhere to the minimum of two days per week exercise regained visceral fat than those who adhered to the exercise program. The weight and visceral fat regain could be prevented with as little as 80 min/week of aerobic or resistance training. \(^{137}\)

**Summary:**

Visceral fat reduction occurs preferentially with aerobic exercise and the dose-response relationship was observed for this finding. Visceral adiposity regain occurs after the discontinuation of exercise. Epicardial fat is also a visceral fat which has close relationship with abdominal fat and its amount or thickness.

### 2.8. Anatomy and physiological implications of Epicardial Adipose Tissue:

The knowledge about anatomy of EAT is limited to the laboratory studies, mainly studied in rats and mice with little amount of fat. EAT is now known to embryologically evolving from brown tissue. It shares the common origin as abdominal adipose tissue and it further evolves as a white adipose tissue in adults. EAT originates from splanchnopleuric mesoderm in contrast to the pericardial fat which originates from primitive thoracic mesenchyme. EAT is located between myocardium and visceral pericardium; it covers 80%
of the heart and weighs about 20% of total weight of the heart.\textsuperscript{74,76,138-140} The amount of epicardial fat in atrioventricular and interventricular grooves has been found to be maximum in cadaver based studies.\textsuperscript{141} EAT shares the same microcirculation as myocardium and thus interacts during paracrine and endocrine mechanisms. The distribution of EAT is not even all around the heart, the thickness and volume has been found to be predominant on the right free wall of the heart and also adjacent to the coronary vasculature. The increased thickness and close proximity of EAT to the coronary arteries has been found to increase the risk of coronary artery stenosis.\textsuperscript{77,142,143}

EAT is known to play its normal physiological function acting as buffer to prevent the torsion to the arteries produced by the pulsation and also provides energy to the cardiac muscle. It is thrice in amount over the right ventricle compared to that on left ventricle. The microscopic examination of EAT reveals the presence of adipocytes, ganglion, inflammatory and immune cells. EAT differs from other fat depots by smaller size of the adipocytes and higher rate of fatty acid synthesis. The hypertrophy and hyperplasia of adipocytes in obese may lead to increase in release of inflammatory substances.\textsuperscript{75,138,144,145}

The human and animal research displayed the beneficial effects of EAT on coronary vasculature in normal weight individuals and pathological effects in obese. EAT has anti-atherogenic, anti-inflammatory effects under normal conditions, whereas it contributes to development of coronary artery disease in obese population as a pathological effect. The amount of EAT has been found to have direct relationship with the disease risk, the volume and thickness was found to be more in patients with coronary artery disease compared to others.\textsuperscript{77,81,146}
2.9. Relationship of Epicardial Adipose Tissue with anthropometric parameters

EAT was found to have direct relationship with BMI and central obesity indicated by increased WC. EAT has been found to be increased, even in healthy and asymptomatic individuals with increased BMI across different ages. However, WC is known to be a better indicator of visceral fat than BMI. EAT was found to be better associated with waist circumference and visceral fat quantity measured by imaging methods than BMI.\(^\text{147,148}\) It was also found to be high in non-obese or normal weight patients diagnosed with coronary artery disease\(^\text{149}\). This indicates that EAT is an independent and better predictor of coronary artery disease than BMI, as it is increased in subjects who are prone to develop CAD\(^\text{150,151}\).

It was observed that visceral fat or intra-abdominal fat estimated by MRI had good correlation with EAT. WC is a strongest predictor and a risk factor for cardiovascular diseases. WC measures both subcutaneous and visceral fat in the abdomen and showed excellent correlation with EAT; however, it was found to be more accurate in predicting the visceral fat. The measurement of visceral fat has been found to be clinically more important in the management of obesity. EAT measurement has been found to be a better indicator of visceral adiposity than anthropometric measures routinely used in practice.\(^\text{86,152}\)

2.10. Relationship of Epicardial Adipose Tissue with age and gender

Based on the cadaver studies, it was observed that epicardial fat amount increases with age between 20-40 years and after that age does not have an influence on the amount and thickness.\(^\text{141,153}\) But the comparison of EAT values of obese and non-obese individuals across different age groups has not been studied in different populations and the influence of age on epicardial fat remains controversial. If the combined relationship of age and BMI is known
with reference ranges based on ethnicity, the predictive ability of EAT may be improved. The obese children and adolescents were found to have increased EAT compared to non-obese Korean population.\textsuperscript{154} This indicates that obesity is a major contributor than the age for epicardial fat deposition. It also indicates that therapeutic regimens focusing on reduction of epicardial fat should be started from childhood and need to be perceived aggressively for adolescents and younger age groups. However, it remains to be seen if EAT can be used a reliable method to study the fat loss in younger age groups.

Gender differences in the epicardial adipose tissue deposition are not exactly known.\textsuperscript{155} Increased visceral fat or intra-abdominal adiposity in males was associated to hormones and android pattern of obesity. Post-menopausal women also have increased risk of visceral fat accumulation due to the influence of hormones.\textsuperscript{70,123,156} There is limited literature to know whether epicardial fat deposition also follows the same pattern in women. There is less evidence on weight loss interventions leading to EAT reduction whether are influenced by gender differences.

\textbf{2.11. Relationship of Epicardial Adipose Tissue with metabolic syndrome}

Metabolic syndrome or syndrome ‘X’ is a syndrome of modern world, people suffering from chronic health diseases due to high intake of unhealthy food and physical inactivity. The central obesity is a major and most important characteristic of this syndrome according to International Diabetic Federation (IDF) and National Cholesterol Education Program (NCEP). Additionally if two of the four findings of high blood pressure, increased fasting blood glucose, high serum triglycerides and low high-density cholesterol levels are found, the diagnosis of metabolic syndrome is made. The reference ranges according to
NCEP-ATP III Guidelines (National Cholesterol Education Program- Adult Treatment Panel-III) are generally followed to interpret the results and diagnose metabolic syndrome.\textsuperscript{157,158}

The latest research indicates that visceral adipose tissue plays a major role in the development of metabolic syndrome. As the prevalence of metabolic syndrome is increasing and owing to its potential consequences, the visceral fat estimation has gained importance.\textsuperscript{159,160} Several studies have indicated that visceral fat estimation by imaging methods may help in accurate prediction of metabolic syndrome. The subjects with metabolic syndrome have been found to have higher epicardial adipose tissue thickness compared to subjects without metabolic syndrome.\textsuperscript{83,148} The early detection of metabolic syndrome may help in initiation of interventions aiming at weight loss, thus helping in primary and secondary prevention of cardiovascular diseases.

There were numerous studies on the relationship between epicardial fat measurement and parameters of metabolic syndrome. Iacobellis et al first studied this relationship in the year 2003 in Caucasians. A strong relationship existed between EEATT and abdominal fat measured by MRI. EEATT measured through echocardiography also linked with the clinical parameters of metabolic syndrome such as lipids, blood pressure, fasting blood sugar levels and waist circumference.\textsuperscript{86} Karadag et al did a comparative study on the relationships of epicardial fat and anthropometrics with parameters of metabolic syndrome in elderly and younger age groups. EEATT was particularly found to be a useful method in the determination of visceral fat in advanced age groups.\textsuperscript{161} Although it was identified to be a reliable indicator of visceral fat in obese children, Mazur et al\textsuperscript{162} reported that EEATT was not found to be an independent predictor of metabolic syndrome. The prognostic value of EEATT differs in children compared to the adults.
The high risk threshold values for cardio-metabolic risk stratification and therapeutic interventions targeting the fat were proposed in a study conducted by Iacobellis et al.\textsuperscript{87} Lee et al studied the predictive ability of EEATT in identifying incident metabolic syndrome as part of a prospective cohort study named as Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population. 23.9% men and 16.8% women were found to have developed metabolic syndrome after an average of 2.2 years of follow-up.\textsuperscript{163}

The measurement location of epicardial fat measured by single slice CT scan was found to be important in predicting metabolic syndrome and coronary atherosclerosis. Increased epicardial fat volume measured at left main coronary artery correlated with Coronary Artery Calcium (CAC) score and had highest odds ratio (OR 1.56, p = 0.042).\textsuperscript{147} In a study conducted by Park et al\textsuperscript{164}, the power of EEATT to predict metabolic syndrome and CAD was found to be stronger in Asian population with BMI < 27kg/m\textsuperscript{2}.

Women with metabolic syndrome had higher epicardial thickness suggesting that EEATT is a reliable marker of cardiovascular risk in post-menopausal women.\textsuperscript{165} Lima-Matinez et al studied the cut-off values of EEAT for predicting metabolic syndrome in Venezuelan population of 20 to 65 years. An EAT value $\geq$ 5 mm had good sensitivity and specificity (84.62% and 71.11% respectively) for predicting metabolic syndrome in the Venezuelan population with an odds ratio of 8.25.\textsuperscript{166} Shetty et al studied EEATT, weight, BMI and WC in 350 asymptomatic Asian-Indians and found a moderate correlation of epicardial fat thickness with all the three anthropometric measures in their community based study.\textsuperscript{167}
Pierdomenico et al conducted meta-analysis to study the relation of EEATT and the metabolic syndrome. EEATT was found to be a reliable indicator of metabolic syndrome with a thickness of 1.15 mm difference in comparison to subjects without metabolic syndrome. Caucasians were found to have a higher difference of 1.75 mm. This study emphasized the importance of establishing cut-off values to predict metabolic syndrome for different ethnicities.\textsuperscript{168} Simon Rabkin conducted a systematic review to find out the relationship between epicardial fat and metabolic syndrome. Most of the studies were conducted in European population and the total epicardial fat volume was measured by CT and MRI in few studies, whereas EATT was measured using echocardiography in majority of studies. This meta-analysis demonstrated strong correlation of epicardial fat thickness and volumes with the principal clinical indicators of obesity and abdominal obesity measured by MRI, CT, or DEXA. EAT showed moderate correlation with indices of metabolic syndrome.\textsuperscript{169}

EEATT values were found to be high in normal weight hypertensives of age more than 40 years as per Pierdomenico et al. The cut-off value of 3.1 mm had 100% sensitivity and 79% specificity in this study conducted in Caucasian subjects.\textsuperscript{170} Hypertensive patients with metabolic syndrome were found to have higher risk of cardiovascular mortality than hypertensive patients without the syndrome.\textsuperscript{171} EEATT was also found to be related to altered blood pressure response to exercise stress testing.\textsuperscript{172} Eroğlu et al found EATT thickness values to be further increased in patients with uncontrolled hypertension than in those with controlled hypertension.\textsuperscript{173}
EEATT value > 5 mm was associated with lower ejection fraction, increased left ventricular mass, and abnormal diastolic function, suggesting that increased epicardial fat causes cardiac abnormalities and thus increasing the risk of cardiovascular diseases. Sengul et al found epicardial fat to be associated with autonomic dysfunction indicated by blunted heart rate recovery. EEATT value of ≥ 5.5 mm was associated with the blunted heart rate recovery and metabolic syndrome with sensitivity of 84% and specificity of 52.

Summary:

EAT and its association with metabolic syndrome was studied previously. The influence of ethnicity on EEATT in prediction of metabolic syndrome has been observed. The cut-off values for prediction of metabolic syndrome using EEATT values have been published based on some ethnic populations. The cut-off values of EEATT to predict metabolic syndrome has not yet been published in Asian-Indian population. EEATT has been found to be a reliable marker of metabolic syndrome in children and adolescents. The predictive ability, sensitivity and specificity of EEATT are yet to be ascertained for routine clinical use, even though it has been identified as a reliable marker.

2.12. Relationship of Epicardial Adipose Tissue with Cardiovascular Diseases

Increased epicardial adipose tissue volume or thickness is strongly associated with increased risk of cardiovascular diseases. As the epicardial fat shares the same blood supply as myocardium, the increased thickness of fat may have an effect on coronary circulation. Effect on cardiac function due to epicardial fat has been extensively studied. The studies in cadavers have shown that the atherosclerotic plaques were more prominent in the arteries which are in close contact with epicardial fat deposits. Epicardial fat increases the risk of
cardiovascular diseases through inflammatory and metabolic responses, the risk of the disease increased independent of increased BMI. The cardiovascular disease is high even in normal weight individuals with increased ectopic fat and abnormal metabolic profile.

The abdominal fat as a predisposing factor for cardiovascular diseases has been established in earlier studies. Several researchers explored the relationship between EAT and CAD using CT and MRI. Echocardiography has also been used to study the role of epicardial fat as an independent predictor of CAD.

Silaghi et al examined the link between epicardial fat and age along with fat distribution and coronaropathy in cadavers. Epicardial fat volume showed good correlation with age, waist circumference, and heart weight, but did not correlate well with BMI, subcutaneous adipose tissue in abdomen and legs. This study proved that epicardial fat volume plays an important role in the development of CAD. Apfaltrer et al found relationship between epicardial fat and CAD based on the race. The amount of epicardial fat was found to be more in white males compared to the age and gender matched black males.

Epicardial fat volume was found to be associated with coronary stenosis and vulnerability for plaque formation which was confirmed by coronary angiography performed as per Rajani et al. In a report by Okada et al., increased epicardial fat volume was found to be strongly associated with severity of CAD in non-obese CAD patients. Enhos et al investigated the relationship between EAT volume and collateral circulation in stable CAD patients, to suggest that non-invasive cardiac fat imaging methods might be useful in assessing collateral circulation in coronary arteries. The sensitivity and specificity of epicardial fat volume for prediction of atherosclerosis were 72% and 70% respectively as per
Djaberi et al. This study indicated that increased EAT volume is a good predictor of CAD in both normal and obese individuals.  

Bettencourt et al investigated epicardial fat volume, CAC and coronary angiography by MSCT in non-obese individuals without known history of CAD. Abdominal visceral fat was found not to correlate well with epicardial fat in non-obese population. Increase in EAT was associated with an increase in CAC score in non-obese individuals suggesting that epicardial fat volume measurement is a useful predictor of CAD even in non-obese population with less amount of abdominal visceral fat. De Larochellière et al studied subcutaneous abdominal adipose tissue, visceral abdominal adipose tissue, epicardial adipose tissue and hepatic fat fraction using MRI in large number of non-obese healthy individuals. Visceral abdominal adipose tissue and epicardial adipose tissue were linked with markers of cardiometabolic risk of all the fat tissue components in normal weight individuals suggesting that increased epicardial fat is a possible risk factor of CAD in normal weight adults.

The location of EAT also plays a very important role in atherosclerosis. The EAT thickness in left atrioventricular groove provided an accurate assessment or presence of atherosclerosis in patients who underwent CT and coronary angiography in a study conducted by Wang et al. Higher levels of intra-thoracic fat, epicardial and pericardial fat were found to be associated with cardiovascular disease risk markers and subclinical atherosclerosis indicated by higher coronary artery calcium scores in a study performed by Huang et al. The intra-thoracic fat volumes also had a strong relationship with lipids, HS-CRP and insulin levels indicating that cardiac fat imaging can be a valuable indicator of progressive atherosclerosis compared to anthropometrics.
Ahn et al utilised echocardiography to predict coronary artery diseases and recognised that the increased thickness was associated with high incidence of CAD confirmed by coronary angiography. But the results from study done by Chaowalit et al who also used echocardiography to study EATT did not find good correlation with conventional coronary angiography. Jeong et al found strong relationship of EEATT with presence and severity of CAD.

In a study conducted by Ahn et al, the sensitivity and specificity of EAT predicting CAD were found to be very high with cut-off values of 5 mm thickness in the patients who underwent coronary angiography. Wang et al proposed the use of EEATT as an independent predictor for major coronary events in the hospital. Guauque-Olarte et al and Hirata et al studied the transcriptome of human epicardial tissue, mediastinal adipose tissue and subcutaneous adipose tissue. They detected increased inflammation in EAT in patients with CAD. The epicardial fat cells showed increased fold of expression of interleukin-6 compared to the visceral adipocytes studied by Zdychova et al, also indicated that inflammatory substances released from epicardial adipocytes contributed in the pathogenesis of CAD.

The coronary flow reserve which is considered as an early indicator of endothelial dysfunction has been studied by Atakan et al in patients on hemodialysis. This study proved that EAT which is significantly high in hemodialysis patients contributed to development of coronary atherosclerosis. Detection of subclinical atherosclerosis in the absence of traditional risk factors is found to be very important in recent studies, further improving the cardiovascular risk stratification. Nelson et al determined the associations between EEATT,
carotid intima thickness; Framingham Risk Score and CAC score in primary prevention population. EEATT values that figured more than 5.0 mm was observed to have strong correlation with CAC scores and weak correlation with scores and Carotid Intima Media Thickness, suggesting that EEATT is most likely to detect carotid atherosclerosis compared to the traditional risk factors.\textsuperscript{61} Studies have also indicated that increased EAT volume significantly correlates with obstructive CAD, MI and major cardiac events. In a study conducted by Comert et al, EEATT values were seen to correlate well with slow coronary flow and thus is proposed as an independent predictor of subclinical atherosclerosis.\textsuperscript{191} EEATT values exceeding 10 mm and 8mm when measured over right ventricle and right apex were found to have good sensitivity and positive predictive value (more than 70%) in predicting coronary artery stenosis of more than 50%, compared to coronary angiography in a study conducted by Toufan et al.\textsuperscript{192} The diagnostic value of EEATT measurement as an indicator of coronary artery stenosis has been found to be acceptable and cut-off values of EEATT measurement at different regions have been suggested in this study.

**Summary:**

The stage and severity of atherosclerosis both in obese and non-obese individuals can be predicted with imaging methods. The sensitivity and specificity of EEATT in predicting CAD has been found to be good. Epicardial fat is also proposed as a reliable indicator of major cardiac events and the coronary reserve flow in diagnosed CAD patients. The cut-off values for the presence of CAD may vary based on several factors and ethnicity is found to be an important factor.
2.13. **Research on Epicardial Adipose tissue in Asian-Indian population:**

The volume and thickness of EAT values, the cut-off values for prediction of metabolic syndrome varied among different ethnic groups.\(^\text{193}\) The lack of literature on sensitivity and specificity of EAT as a risk marker has further limited its use in routine practice. EAT thickness values of obese population studied in Asian countries including India were found to be relatively low compared to European population.\(^\text{164}\) Even though higher EAT values were observed in Asian population with metabolic syndrome, the cut-off values for EAT were not established specific to population. EAT values were found to be related to anthropometric parameters in Indian population.\(^\text{167}\) But, the cut-off values for EAT, as a marker of metabolic syndrome and CAD is yet to be studied in Indian population.

2.14. **Relationship of Epicardial adipose tissue with lipids and C-reactive protein**

Epicardial fat is also found to be an independent marker of progression of coronary artery disease with or without lipid abnormalities. The association between epicardial fat and indices of metabolic syndrome was found to be greater in Asians.\(^\text{194}\) The aerobic exercise has proven effects on lipids with or without actual weight loss.\(^\text{195}\) High-sensitivity C-reactive protein has been found to be a potential adjunct for global risk assessment and a useful therapeutic target in the primary prevention of cardiovascular disease. EAT was found to be associated with abnormal lipid profile and several inflammatory markers. C-reactive protein was found to be associated with obesity and increased adipose tissue.\(^\text{196, 197}\)

2.15. **Reliability of echocardiography in epicardial fat estimation**

Traditionally, anthropometric measures were used to assess the body fat distribution for cardiovascular risk assessment. But more recently, imaging methods have gained lot of
research and clinical interest. Several imaging methods have evolved for estimation of VAT mass. Among the several imaging methods used, MRI is well established, but ultrasound and Magnetic Resonance Spectroscopy (MRS) are also emerging as useful methods for quantitation of VAT. Ultrasound is the most cost-effective and a convenient imaging tool whereas MRS has been shown to have high sensitivity and specificity.\textsuperscript{133,198} Although, researchers have started using EEATT widely as visceral fat indicator and therapeutic target in obesity management, the accuracy of measurement is very important for its routine use. The studies on the reliability of EEATT measurements were reviewed.

Iacobellis et al suggested that EEATT is best measured at end-systole. However, majority of the studies measured it at end-diastole. The varying methodologies used to measure EEATT might have influenced the magnitude of effect of the therapeutic interventions in some of the earlier studies. The inter-rater and intra-rater reliability of EEATT was critically checked prior to the intervention and it was found to be good in most of the studies. The majority of clinical studies have reported excellent inter observer and intra observer agreement for EEATT measurement (ICC 0.90 to 0.98 and 0.93 to 0.98), respectively. EEATT changes correlated well with the post intervention visceral fat changes measured by computer tomography changes in lipid profile and certain inflammatory markers supporting the positive findings achieved in response to the therapy. Thus, it may still be recommended as a potential therapeutic target for future interventions involving primary prevention strategies.\textsuperscript{86,145}
2.16. Effects of therapeutic interventions on epicardial fat

Epicardial fat measurement has drawn a lot of attention from clinicians and researchers in the recent years. As EEATT measurement is identified as a simple and cost effective marker of visceral fat and metabolic syndrome, the focus is now on its reduction and clinical applications. Weight loss induced by some pharmacological and non-pharmacological interventions is found to alter the regional fat compartments including epicardial fat. The weight reduction is primarily achieved by dietary modification and improvement in physical activity levels. Therapeutic interventions altering the fat metabolism and drugs which are known to modify the adipose tissue and its pathogenic profile play a significant role in cardiovascular disease prevention. The statin groups of drugs are widely used in the management of cardio metabolic disorders, but the effects on visceral adipose tissue are not well known. Growth hormone deficiency is significantly linked with the increased visceral fat. It is important to know the role of replacement therapy in prevention of cardiac complications. It is also interesting to know the positive effects of fat reduction surgeries on cardiac diseases in severe obese individuals. The studies on pharmacological and non-pharmacological interventions influencing EEATT have been reviewed.

2.16.1. Effect of low calorie diet on EEATT:

Iacobellis et al studied the effect of 6-month very low-calorie diet in 20 morbid obese individuals with BMI more than 35 kg/m². The diet program resulted in the improvement of cardiac functions which correlated better with EAT changes than with BMI and body fat changes. This dietary intervention without any physical activity resulted in decrease in EEATT by 32% from the baseline which was significantly more than decrease in weight (20%), BMI (19%) and WC (23%).

Effect of Aerobic exercise on Epicardial Adipose Tissue Thickness in Overweight and Obese Individuals-a Randomized Controlled Trial
Kim et al studied the effect of low calorie diet in 27 moderately obese men (BMI 30.5+/-0.7 kg/m²). The 12-week interventional study resulted in reduction of VAT (29.8%) measured by computed tomography scan which was two times more than the reduction of EEAT (17.2%). The effect of diet induced weight loss was comparatively less on BMI (11%) and body fat percentage (16.6%) suggesting that weight loss effects were more on VAT than anthropometric values.\(^\text{86}\)

Both studies suggest that moderate and very low calorie diet is effective in reducing EEAT. The effect of diet was more on EEAT and visceral fat measured by CT scan than the actual reduction in body mass and other anthropometric indices. However, it is not known whether similar effects can be seen in overweight and mild obese subjects with cardio metabolic risk profile. It remains to be seen if the preferential VAT reduction is seen only in those patients presenting higher levels of visceral fat at baseline.

\subsection*{2.16.2. Effect of lipid lowering therapy on EEATT:}

Statin therapy was found to reduce the epicardial fat thickness; the amount of reduction was more with intensive therapy in a study conducted by Alexopoulos et al. The reduction of epicardial fat was linked to anti-inflammatory effects of statin drugs in this study. The CAC scoring was also done to study the progression of atherosclerosis during the study period. Whether the regression of epicardial fat is associated with altered progression of atherosclerosis is not known.\(^\text{199}\)

Park et al compared the effects of Atorvastatin and Simvastatin/Ezetimibe on EEATT in patients who underwent coronary intervention as part of a retrospective cohort study. Atorvastatin resulted in better reduction of EEATT compared to Simvastatin, although
the cholesterol reduction and Hs-CRP changes were same in both the groups. The effect of statins was observed on lipids, Hs-CRP and EEATT without any change in BMI in this study following Post coronary intervention.\(^{200}\)

The exact mechanism of EEATT lowering effect of statins was unknown. The use of statin might decrease the production of pathological adipokines in the epicardial fat, subsequently resulting in reduced EATT. Future research may focus on various types of statins and their effects on EEATT in prospective randomized controlled trials in asymptomatic high risk individuals.

2.16.3. Effect of Growth Hormone Replacement Therapy on EEATT

EEATT was found to be increased in untreated Growth Hormone Deficiency adolescents when compared to treated GHD subjects and healthy controls. Ferrante et al demonstrated a 29% reduction in EEATT after 6-months and 40% reduction from baseline after 12 months of Growth Hormone Replacement Therapy. No significant changes were observed in BMI and WC in this study.\(^{201}\)

EEATT is found to be a valuable marker of VAT reduction during growth hormone replacement therapy treatment. Further research can be focused on long term implications of visceral fat changes associated with rhGH therapy

2.16.4. Effect of bariatric surgery on EEATT:

Van Schinkel et al found that Roux-en-Y Gastric Bypass surgery induced weight loss causes larger reduction in pericardial fat than epicardial fat in obese patients with type 2 DM after 16 weeks. The surgery induced weight loss was not related to improvement in
cardiovascular function. Gaborit et al studied the effect of bariatric surgery on EAT volume in morbidly obese patients. The EAT volume loss was found to be less when compared to loss of abdominal fat volume.

Willens et al observed the preferential effect on visceral abdominal fat during rapid weight loss period after laparoscopic bariatric surgery. However, this preferential VAT reduction occurred only in patients presenting with higher levels of baseline values with maximum amount of weight loss. The amount of reduction of excess weight in relation to the ideal body weight was more than the EEATT reduction in this study. Gastric bypass surgery induced weight loss lead to higher loss of visceral fat volume compared to subcutaneous fat volume, higher loss of paracardial fat volume than epicardial fat volume in a study conducted by Van Schinkel et al.

The studies on weight loss effects on regional body fat compartments following bariatric surgery are limited. Further research is required to learn the effects of EAT reduction and the possible role in prevention of cardiac diseases with associated changes in the cardiac functions following bariatric surgery.

2.16.5. Effect of exercise on epicardial fat:

Sengul et al studied the influence of the EEATT on Heart Rate Recovery (HRR) and peak Vo2 values in men. The EEATT values were found to have association with lower HRR, suggesting that obese men have autonomic dysfunction and reduced cardiorespiratory fitness. This study also suggested that moderately obese men with increased EEATT values demonstrate altered autonomic response and their cardiorespiratory endurance is also reduced. Sengul et al also investigated the relationship between EEATT and blood pressure
and found that increased epicardial fat was related to change in blood pressure responses during exercise test. These two studies established the need for monitoring the exercise program in obese population with increased EATT. Nakazato et al studied effect of weight loss on EATT using non-contrast CT scan in asymptomatic subjects. This long term cohort study proved that epicardial fat is regressible and cardiovascular risk can be reduced with long duration exercise.

Jonker et al. studied the effects of six months of moderate intensity aerobic exercise on fat volumes measured with the help of MRI men with type 2 DM. The exercise program is seen to be effective in reducing the epicardial fat volume along with other measures, but the cardiac function did not change. Fu et al studied the effect of dietary education and exercise in non-diabetic obese individuals with metabolic syndrome and age-matched healthy men. Epicardial fat thickness was measured using MRI. A significant reduction of epicardial fat was detected along with the weight loss in this study.

The literature on effects of exercise on EEATT is limited. Only two prospective clinical trials have been conducted. Kim et al studied the effect of 12 weeks of supervised aerobic exercise program with isocaloric diet on EEATT in obese middle-aged Japanese men. The percent change in EEATT was observed to be twice as high compared to WC, BMI, and bodyweight after exercise training. The reduction of EEATT also correlated well with changes in blood pressure, quantitative insulin sensitivity check index and abdominal fat measured by computer tomography in response to exercise training. This was the first study to prove the positive effect of exercise or any form of physical activity on EEATT. However, the non-exercising control group was not included and the study was only conducted in obese men.

Effect of Aerobic exercise on Epicardial Adipose Tissue Thickness in Overweight and Obese Individuals-a Randomized Controlled Trial
The mortality rate due to cardiovascular diseases is very high in chronic kidney disease patients. Wilund et al evaluated the efficacy of endurance exercise in patients on haemodialysis. EEATT reduced by 11% in exercise group while there was no change in control group after 4 months of exercise with no exercise, suggesting that endurance training during haemodialysis may reduce the cardiovascular disease risk. The EEATT reduction was associated with reductions in other risk factors such as serum oxidative stress and serum alkaline phosphatase.\textsuperscript{211}

A six month moderate intensity aerobic exercise program did not significantly reduce the epicardial fat volume measured by CT scan, whereas there was significant reduction in abdominal and subcutaneous fat volumes in patients with type 2 Diabetes Mellitus.\textsuperscript{208} The reduction of EAT in superior interventricular groove correlated with an improvement of indicators of insulin resistance in non-diabetic men with metabolic syndrome after three month weight loss program including diet and exercise in a study conducted by Liang et al.\textsuperscript{212} The abdominal fat and epicardial fat were significantly reduced after 16 weeks of home based treadmill training in post-menopausal women along with a reduction in waist circumference.\textsuperscript{213} A successful weight reduction program involving lifestyle modification over a period of one year was associated with a reduction of EATT and an improvement in ventricular diastole function in severe obese individuals in a study conducted by Fenk et al.\textsuperscript{214} A systematic review and meta-analysis was conducted by Rabkin et al on comparison of effects of various treatment methods on EAT. Diet and bariatric surgery were found to cause significant reduction in EAT, whereas there was no significant reduction in exercise. There were very few studies found on EAT reduction with exercise induced weight loss therapy.\textsuperscript{215}
The effect of exercise parameters such as intensity, duration or dose-response relationship is not established. Till date, there is no literature on effect other exercise training methods on EEATT. EEATT has been identified as a reliable marker of cardiovascular disease and also an effective therapeutic target. It has been proved that EEATT regresses even without significant weight loss. Echocardiography measures EAT linearly at a single location and may not reflect the total volume. However, echocardiographic examination is relatively accurate, easier and more accessible for cardio metabolic risk stratification than the MRI or computerized tomography scanning. EEATT may be considered for all large sample based studies concentrating on primary and secondary prevention of cardiovascular diseases as it is cost effective and is proved to have good reproducibility.\textsuperscript{107,216}

Visceral fat is presently considered as an important component of the metabolic syndrome more than the waist circumference. Although, visceral fat reduction is associated with improvement of the cardio-metabolic profile, the amount of visceral adipose tissue loss needed to induce favourable metabolic changes is not known. Since, EEATT is considered as a reliable marker of visceral adipose tissue, the amount of loss of EEATT required to induce favourable changes in the cardiovascular risk still remains to be studied. Decrease in epicardial fat was observed to be proportionally higher than the overall decrease in adiposity as per the data available from most of the interventional studies amongst the limited literature available. Epicardial fat loss was also seen to be substantially high compared to loss in other body fat compartments, suggesting favourable changes in visceral fat and cardiovascular risk profile with the therapeutic interventions. It was also interesting to note that epicardial fat reduction may also take place without a change in the body mass and anthropometrics following pharmacological interventions. But, the amount or dose of the therapeutic
interventions needed for significant loss of EEATT is not known. The consistency and magnitude of the effect on EEATT varied depending upon the intervention. The percentage of reduction of EEATT ranged from 8.6 to 32 percentage of the initial measurement. The results of these studies cannot be generalized as they were limited to some populations. If appropriate intensity or dose of the therapy required to have a significant effect on this surrogate marker is demonstrated, it may well be considered as a clinical end point in clinical studies.82,108,217,218

The studies on measurement of EAT and its relationship with cardiovascular disease risks has mostly been limited to European-Caucasian subjects. The prediction of cardio metabolic risks using EEATT values and the effect of therapeutic interventions in other ethnic groups remains to be studied. The determination of normal upper limit values of EEATT in various ethnic groups may help to study the response to the weight loss interventions more accurately. Future research can be also focused on comparative effects and combined effects of various therapeutic interventions in multi-ethnic studies. The association between regression of EEATT with interventions and risk of coronary events remains to be demonstrated in long term follow up studies.

Summary:

EEATT has been found to be a marker of visceral adiposity and a potential therapeutic target in cardiovascular and metabolic disorders. The pharmacological and non-pharmacological interventions resulted in reduction of EEATT, although the consistency and magnitude of this effect has not been well characterized. There is limited research on the dose-response relationship and effect of combination of two or more therapies. Further research is required to study the clinical applications of EEATT in primary and secondary
prevent treatment of cardiovascular and metabolic disorders. There is level 2 evidence on effect of lifestyle modifications on EEATT in obese individuals.

2.17. Epicardial fat as a predictor of mortality:

EAT volume had good predictability of mortality rates in patients on haemodialysis in a study conducted by D'Marco et al. The risk of death estimated in a follow-up study conducted for 4 years calculated an increase by 6% with an increase of the epicardial fat volume by 10 cc.\(^{219}\) In a study conducted by Jennifer Kuk et al, VAT was found to be a better predictor of all-cause mortality in men.\(^{220}\)

2.18. Summary of literature review:

- The prevalence of obesity and its related complications are high and are increasing in India and other South-Asian countries. BMI is not a good predictor of future cardiovascular events and BMI cut-off values have been modified for South-Asian population.
- VAT is found to be more dangerous than SAT. VAT is characterized by storage of lipids and is a source of inflammatory markers.
- The estimation of VAT is very important in clinical management of obesity and can be measured reliably by imaging methods.
- EAT is an indicator of the quantity of VAT in the body, related to metabolic syndrome and increased risk of CAD.
- EAT is found to be high in overweight and obese individuals. The values were comparatively high in Caucasian and European population compared to Asian population.
• EATT can be measured by imaging methods such as MRI and CT scan. Echocardiography offers simple, cost-effective and reliable measurement of EATT.

• Echocardiography is found to have good reliability in measuring EAT. The cut-off and threshold values for high risk individuals have been studied in different populations.

• Reduction in EATT is associated with improvement in the cardio-metabolic profile and decreased risk of CAD in obese population.

• EEATT is proposed as a therapeutic target in obesity management. Pharmacological and non-pharmacological interventions are found to be effective in reducing the epicardial adipose tissue thickness. Statin group of drugs used in obesity management is also found to effective in reducing epicardial adipose tissue thickness.

• Bariatric surgery is found to have regressive effect on EATT.

• Lifestyle modifications cause reduction in EEATT along with an improvement in cardio-metabolic risk profile.

• Exercise is detected as an effective means in reducing EEATT. Despite there were few non-randomized controlled trials conducted earlier, there have been no prospective randomized controlled trials conducted to study the effect of aerobic exercise on EEATT in primary prevention population.

• The clinically significant change in EEATT leading to an improvement in cardio-metabolic risk profile is also not known.

• The mortality rate due to non-communicable diseases which are associated with obesity is high in Indian population. Several studies have emphasized the need for prevention of obesity and its related complications with lifestyle modifications.