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EFFECT OF THERAPEUTIC INTERVENTIONS ON ECHOCARDIOGRAPHIC EPICARDIAL ADIPOSE TISSUE THICKNESS: A REVIEW

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ABSTRACT

Increased Echocardiographic Epicardial Adipose Tissue has been identified as a major risk factor for atherosclerosis. Echocardiographic measurement of Epicardial Adipose Tissue has been recognized as a simple, reliable and cost effective method to estimate visceral fat and future risk for coronary events. Echocardiographic Epicardial Adipose Tissue Thickness is also considered as an effective therapeutic target. The effect of pharmacological, surgical and life style interventions on Echocardiographic Epicardial Adipose Tissue Thickness was reviewed in this study. The databases searched include Medline, PROQUEST and CINAHL. Seven studies have been selected which had at least one arm that was a surgical, pharmacological, dietary, and exercise intervention. The articles published in English through 2013 were reviewed. The weight loss induced by all these interventions was associated with a reduction of Echocardiographic Epicardial Adipose Tissue, although the consistency and magnitude of this effect has not been well characterized. There is limited research on the dose-response relationship in response to diet induced and exercise induced weight loss. Further research is required to study the clinical application of Echocardiographic Epicardial Adipose Tissue measurements before and after therapy in prevention and management of cardiovascular and metabolic disorders

KEYWORDS: Epicardial Adipose Tissue Thickness, Echocardiography, Therapeutic interventions, Review, Visceral fat

INTRODUCTION

The incidence and prevalence of obesity and metabolic syndrome continues to increase globally along with those of co-morbidities of obesity such as cardiovascular diseases in the past few decades. [1] Visceral fat has been found to be more significantly associated with atherosclerosis and Coronary Artery Disease (CAD) in obese compared to subcutaneous fat [2]. The accurate quantification of visceral fat allows better risk stratification of cardiovascular diseases and may also serve as a therapeutic end point. The quantification of visceral adipose tissue (VAT) is done by non-invasive imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI), which are cumbersome and expensive. Epicardial adipose tissue (EAT) measurement through echocardiography has been found to be a simple, reliable and inexpensive marker for cardiac and visceral adiposity. [3, 4]

Epicardial adipose tissue (EAT) is recognized as true visceral fat around the heart and also a source of several inflammatory mediators in high risk cardiac patients. It has been well recognized as a predictor of visceral fat, metabolic syndrome and CAD. [5-10] Iacobellis et al proposed the measurement of EAT on the free wall of the right ventricle from both parasternal long and short-axis views using **t**ransthoracicechocardiography. Echocardiographic epicardial adipose tissue (EEATT) measurement was found to correlate well with anthropometric measures and clinical parameters of metabolic syndrome .[7]The reproducibility of EEATT measurement has been found to be excellent in previous studies and its reliability was good when compared with MRI for prediction of visceral adipose tissue and intra-abdominal fat. EEATT has been used for both diagnostic purposes and therapeutic interventions that can modulate the adipose tissue. [8]

Epicardial fat measurement has drawn a lot of attention from clinicians as well as researchers in the recent years. Since EEATT measurement has been identified as a simple and cost effective marker of visceral fat and metabolic syndrome, the focus is now on its reduction and clinical applications. [8] The weight loss induced by pharmacological and non-pharmacological interventions has been found to alter the regional fat compartments [11] including epicardial fat [12]. The weight reduction is primarily achieved by dietary modification and improving 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 its effects on visceral adipose tissue are not well known [16]. Growth hormone deficiency is significantly associated with increased visceral fat, and it is important to know the role of replacement therapy in prevention of cardiac complications [13]. It is also interesting to know the positive effects of fat reduction surgeries on cardiac diseases in severe obese individuals [18]. The objective of this study is to review the effects of various pharmacological and non-pharmacological interventions on epicardial adipose tissue thickness measured using echocardiography, a potential target and surrogate marker for cardiovascular diseases.

Method of Review

The databases searched include PubMed, OVID, PROQUEST and CINAHL. Seven studies were selected which had at least one of the following as therapy arms - surgical, pharmacological, dietary, and exercise intervention. The articles published in English between January 2003 to October 2013 only and were on humans were reviewed. The search strategy consisted of combination of three main concepts :(1) epicardial adipose tissue, epicardial fat (2) echocardiography, echocardiographic epicardial adipose tissue (3) weight loss, weight reduction interventions, diet, low calorie diet, exercise, bariatric surgery, statins, and hormone replacement therapy. All possible and relevant keyword combinations were used for search.

Effect of Therapeutic Interventions on EEATT

Effect of Low Calorie Diet on EEATT

Two studies have examined the effect of diet-induced weight loss on EEATT. Iacobellis et al of a 6-month very low-calorie diet (900 kcal/day) on 20 severely obese (BMI 45 ± 5 kg/m^2) subjects. This very low calorie diet intervention composed of three phases (complete meal replacement, partial meal replacement and long-term maintenance) which was found to have resulted in improvement of cardiac functions. The cardiac changes were better correlated with epicardial fat thickness changes than with BMI changes. The effect of weight loss on EEATT was proportionally higher than overall adiposity drop. This dietary intervention without any physical activity resulted in decrease in EEATT by 32% from the baseline which was significantly greater than the decrease in body weight (20%), BMI (19%) and Waist Circumference (23%)[14].

Kim et al studied the effects of low calorie diet in 27 moderately obese men (BMI 30.5+/-0.7 kg/m^2) .This 12-week interventional study resulted in reduction of visceral adipose tissue (29.8%) measured by computed tomography which was two times more than the reduction of EEAT(17.2%). The effect of diet induced weight loss was comparatively less on body mass (11%) and percentage fat mass (16.6%) suggesting that diet induced weight loss effects were more on visceral fat than anthropometric values [15].

Both the above mentioned studies suggest that moderate and very low calorie diet-induced weight loss may represent an effective strategy for reducing EEAT. The effect of diet was more on EEAT and visceral fat as measured on CT 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 has been noted that preferential visceral fat reduction is seen only in those patients presenting with higher levels of visceral fat at baseline. The amount of diet induced weight loss and epicardial fat loss needed to induce favorable metabolic changes is also not known.

Effect of Statins on EEATT

Park et al compared the effects of Atorvastatin and Simvastatin/Ezetimibe on EEATT in patients who underwent Percutaneous Coronary Intervention (PCI) as part of a retrospective cohort. This study demonstrated that atorvastatin was associated with significant reduction in the EEATT compared to Simvastatin, although the degree of cholesterol reduction and HSCRP changes were similar in both the groups. In this study, the effect of statins was observed on lipids, HSCRP and EEATT without any change in the BMI following PCI [16].

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. Further research is needed to study the effects of various types of statins on EEATT through prospective randomized controlled trials and also its use in asymptomatic high risk individuals.

Effect of Growth Hormone Replacement Therapy on EEATT

EEATT was found to be increased in untreated Growth Hormone Deficiency (GHD) adolescents when compared to those treated with GHD and healthy controls. Ferrante et al demonstrated a 29 % reduction in EEATT after 6-months of rhGH replacement therapy and 40% reduction from baseline after 12 months of Growth Hormone Replacement Therapy (rhGH). There were no significant changes observed in BMI or waist circumference after 6 or 12 months of rhGH therapy [17].

EEATT has been found to be a valuable marker of visceral fat changes during rhGH replacement treatment in patients with GHD. The positive effects of rhGH therapy may help in preventing the future risk of cardiovascular diseases in young age. Further research can be focused on long term implications of visceral fat changes associated with rhGH therapy

Effect of Bariatric Surgery on EEATT

Howard et al demonstrated that bariatric surgery induced weight loss was associated with reduction in EATT measured in follow up echocardiograms in 23 severely obese subjects. The preferential effect on visceral abdominal fat was observed in the phase of rapid weight loss after laparoscopic bariatric surgery. However, this preferential visceral fat reduction occurred only in patients presenting with higher levels of visceral fat deposition at baseline and higher levels of weight loss. The amount of reduction of excess weight in relation to the ideal body weight was more than the EEATT reduction. . It was also observed to have variable individual response of epicardial fat thickness to weight loss following bariatric surgery [18].

The studies on bariatric surgery induced weight loss effects on subcutaneous, epicardial and abdominal compartments are limited. Further research is required to learn the positive effects of epicardial fat reduction, possible role in prevention of cardiac diseases and associated changes in the cardiac functions following bariatric surgery.

Effect of Aerobic Exercise on EEATT

Available literature on effects of exercise on EEATT is limited. Only two studies have examined the effect of aerobic exercise on EEATT. Kim et al studied the effect of 12 weeks of supervised aerobic exercise program with isocaloric diet on EEATT in 24 obese middle-aged Japanese men. The percent change in epicardial fat thickness was twice as high compared with those of the waist, BMI, and body weight after exercise training. The change in EEATT also correlated well with changes in blood pressure, quantitative insulin sensitivity check index and abdominal fat measured by CT 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 [19]

The mortality rate due to cardiovascular diseases is very high in chronic kidney disease patients. Kenneth et al evaluated the efficacy of endurance exercise training in 17 haemodialysis patients on EEATT, a novel risk factor for cardiovascular diseases. The patients were randomized to either an exercise training (cycling) group or a non-exercising control group with a follow up period of 4 months. EEATT reduced by 11% in exercise training group while there was no change in control group, suggesting that endurance training during hemodialysis in chronic kidney disease patients may reduce the risk of future cardiovascular disease risks. The EEATT reduction was associated with reductions in novel risk factors including serum oxidative stress and serum alkaline phosphatase. This study supports the adoption of aerobic exercise as an important component of management of chronic kidney disease patients on haemodialysis. [20]

The EEATT reduction with minimal or no change in body mass with increased physical activity levels might be explained by promotion of fat catabolism and muscle anabolism. The effect of exercise parameters such as intensity, duration or dose-response relationship is not established. Till date, there is no literature on effects of resistance training and combined effects of aerobic and resistance training on EEATT.

DISCUSSIONS

EEATT has been identified as a reliable marker of cardiovascular disease and also an effective therapeutic target. It has been proved that EEATT is modifiable and regresses even without significant weight loss [14-21]. Echocardiography measures EAT linearly at a single location and it may not reflect the total epicardial fat volume. However, echocardiographic examination is relatively accurate, easier and more accessible for cardio-metabolic risk stratification than the MRI or computerized tomography scanning [23]. 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 proved to have good reproducibility. [22, 23]

Iacobellis et al suggested that EEATT is best measured at end-systole [5]. However, majority of the studies measured it at end-diastole. The correlation between end-systole and end-diastole measurements and validation with the other imaging methods may be necessary to establish in future research. Also, the possibility of measurement error is high using echocardiography as the examiner has to discriminate one or low millimeter using commercially available echocardiography machine. The varying methodologies used to measure EEATT might have influenced the magnitude of effect of the therapeutic interventions. The clinical use of EEATT as a therapeutic target remains questionable unless a consensus is arrived on its correct method of measurement and application. 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 [25, 26]. EEATT changes correlated well with the post intervention visceral fat changes measured by computer tomography [19] changes in lipid profile and certain inflammatory markers [15-21] 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.

Visceral fat is presently considered as an important component of the metabolic syndrome more than the waist circumference [24]. Although, visceral fat reduction is associated with improvement of the cardiometabolic profile, the amount of visceral adipose tissue loss needed to induce favorable 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 favorable changes in the cardiovascular risk remains to be studied. Epicardial fat decrease was found to be proportionally higher than overall adiposity decrease in most of the interventional studies [14-20] from the limited data available. Epicardial fat loss was also substantially high compared to loss in other body fat compartments [15], suggesting the favorable changes in visceral fat and cardiovascular risk profile with the therapeutic interventions. It was also interesting to find that epicardial fat reduction may also occur without a change in the body mass and anthropometrics following pharmacological interventions [16, 17]. However, 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% 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.

The studies on measurement of EAT and its relationship with cardiovascular disease risks has been mostly limited to European-Caucasian subjects [24]. 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 multiethnic studies. The association between regression of EEAT with interventions and risk of coronary events remains to be demonstrated in long term follow up studies.

CONCLUSIONS

Echocardiographic epicardial adipose tissue has been found to be a reliable marker of visceral adiposity and also a potential therapeutic target in cardiovascular and metabolic disorders. The pharmacological and non-pharmacological interventions directed to reduce the body weight and fat were associated with a 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 prevention of cardiovascular and metabolic disorders

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APPENDICES

Title of the Study	Authors, Year	Subjects	Intervention	Change in BMI and Amount of Weight Loss	Change in EEATT
Aerobic exercise training reduces epicardial fat in obese men	Kim etal	Twenty-four obese healthy men	12 weeks aerobic exercise training	4.3% reduction in Mean BMI (30.7 ± 3.3 to 29.3±2.9) 4.4% reduction of Waist circumference (103.0±7.8 to 98.4±.6.9cms) 4.3 % reduction of Body mass in kg (87.7±11.2 to 84.1±10.2)	8.61% reduction in EEATT (8.11 ±1.64 vs. 7.39 ±1.54 mm) after exercise training
Intradialytic exercise training reduces oxidative stress and epicardial fat: a pilot study	Kenneth etal	Seventeen patients on maintenance haemodialysis (Nine females, Eight males)	4-Months Intradialytic endurance exercise cycling	2.4 % reduction in BMI in exercise group (29.0±2.0 to 28.3± 1.8 in exercise group vs. 30.1±2.4to 30.3±2.5 in control group)	9.8% reduction in EEATT (6.1 to 5.5 mm) in intervention group No change in control group

Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography	Howard etal	23 patients with severe obesity who Underwent bariatric surgery	Follow up study after Bariatric surgery EEATT recorded before and 8.3±3.7 months after undergoing bariatric surgery	26% reduction in BMI (54± 12 to 40±10)	24% reduction in EEATT (5.3 ±2.4 to 4.0 ±1.6 mm)
Epicardial fat thickness significantly decreases after short-term growth hormone (GH) replacement therapy in adults with GH deficiency	Ferrante et al	Ten GHD adolescents on GH treatment, 12 untreated GHD adolescents,	6-months of rhGH replacement therapy	No significant change in BMI	29% reduction in EATT after 6 months (9.8 ± 2.8 to 7.0 ± 2.3 mm) 40% reduction after 12 months 7.0 ± 2.3 to 5.9 ± 3.1 mm,
Comparison of epicardial, abdominal and regional fat compartments in response to weight loss	Tanka etal	27 moderately obese men	12 Week low calorie diet	11% reduction in BMI 29.8% reduction in abdominal fat	17.2% reduction in EEATT
Substantial changes in epicardial fat thickness after weight loss in severely obese subjects	Iacobellisetal	Twenty white severely obese	6-month very low calorie diet	20% reduction in body weight BMI reduced by 19% waist circumference decreased by 23%	32% reduction in EATT (12.3±1.8 to 8.3±1 mm)
Effects of statins on the epicardial fat thickness in patients with coronary artery stenosis underwent percutaneous coronary intervention: comparison of atorvastatin with simvastatin/ezetimibe	Park etal	Retrospective analysis of 145 patients (58 females and 87 males). who underwent successful PCI	82 received 20 mg of torvastatin 63 received 10 mg of simvastatin with10 mg of ezetimibe and six to eight-months follow-up coronary angiography	BMI unchanged	EEATT reduced by 10.0 ± 15.0% in atorvastatin group and 3.1 ± 13.3% reduction in simvastatin/ezetimibe group