The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS)
ISSN: 2791-8033

The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS), 2022

Volume 6, Pages 57-64

ICGeHeS 2022: International Conference on General Health Sciences

The Association between Epicardial Adipose Tissue and Coronary Artery Disease in Hemodialysis Patients Using a Systematic Review

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Abstract: The role of epicardial adipose tissue (EAT) may play in the pathogenesis of coronary vascular disease CVD in patients on hemodialysis and whether imaging of EAT may hold prognostic implications for CVD events and mortality within this patient group .This systematic review investigated the association between epicardial adipose tissue and developing coronary artery diseases in patients undergoing hemodialysis. A search strategy was developed to identify primary studies published until 2 November/2019. Studies were obtained from multiple electronic databases (PubMed, HINARI, Science Direct). Searches were supplemented by hand searching and checking the reference lists of included articles. After the removal of duplicates, the search identified 89 titles, following title and abstract review twenty–three publications were considered potentially relevant, of which 6 studies were retrieved plus two studies from references list. The eight studies were included in the current review. Epicardial Adipose tissue thickness or volume is correlated significantly with coronary artery calcification in hemodialysis patients regardless its long term or incident. This systematic review suggests the significant relationship between epicardial adipose tissue and developing coronary artery disease in this special cohort of patients, hemodialysis patients. Further research should consider more the availability of using EAT as a non-invasive method to assess cardiovascular risk in HD patients.

Keywords: Epicardial adipose tissue, Coronary artery disease, Dialysis patients, Systematic review.

Introduction

Epicardial adipose tissue (EAT) is the visceral fat covering the surface of the heart and coronary artery adventitia, located below the parietal pericardium and accounts for 20% of the heart weight, and shares the same embryological origin with abdominal fat, which are strongly correlated and appear to be in brown adipose tissue originally in infants. It is an active metabolic tissue, secretes cytokines, and pro-inflammatory mediators; which believed to contribute to atherosclerosis through paracrine and vasocrine effect (Iacobellis et al., 2003; Sacks & Fain, 2007). Physiologically, (Marchington & Pond, 1990) Pathologically, Adipokines play role in myocardial inflammation as an inflamed EAT, and because of its proximity from coronary arteries, it makes vaso vasorum proliferate till they reach the intima of coronaries, promoting atherosclerotic plaques (Subbotin, 2012). The biochemical proprieties of epicardial adipose tissue suggest its possible role as a cardiovascular and metabolic risk indicator (Iacobellis et al., 2003). Cardiovascular disease (CVD) is the major cause of death in patients with end-stage renal disease (ESRD). In the general population, CVD morbidity and mortality have declined substantially over the past three decades through risk factor identification and reduction and more effective treatment of coronary artery disease (CAD) (Levey et al., 1998).

Recent studies evaluated the association between EAT and atherosclerosis in dialysis patients by measuring carotid intima thickness (Altun et al., 2014; Turan et al., 2013; Ulusal Okyay et al., 2015), arterial stiffness, and coronary artery calcification. It is well established that Insulin Resistance, dyslipidemia, hypertension, hyperglycemia, and inflammation are highly associated with the development of the atherosclerotic disease, particularly CAD. Consistent with this is the observation that epicardial adipose volume correlates strongly with coronary calcium burden and coronary atherosclerotic plaques (Toth, 2012) EAT may serve as a new predictive marker for CAD. EAT thickness and volume may be an effective way to assess severe atherosclerosis and predict CAD (Xu et al., 2012). In Hemodialysis, However, data about epicardial fat in this patient group is very limited.

Measuring EAT has various imaging modalities, the three common ways are transthoracic echocardiography, computed axial tomography scanning, and cardiac MRI whereas echo two dimensional, CT, and cardiac MRI are three dimensional. However, echo is widely available and do not subject patients to radiations, CT can measure total EAT volume and simultaneously assess coronary artery calcification (CAC) (Graham-Brown et al., 2015). Moreover, echocardiographic calculation of epicardial adipose was easily reproducible and showed excellent reliability with the MRI epicardial and visceral adipose tissue measurements. Echocardiographic assessment of visceral fat could be an easy method to indicate patients with high cardiovascular risk (Iacobellis et al., 2003). The objective of this review is to write a proposal to convince our hospital to measure EAT thickness or volume in hemodialysis patients.

Methods

Eligibility Criteria

All eligible studies for the last ten years were included if they met the predetermined inclusion and exclusion criteria detailed in the PICO model, no filters applied to the search, except for language. The search restriction was limited to the English language. The inclusion and exclusion criteria were listed below as shown in (Table 1).

Table 1. Inclusion and exclusion criteria

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult hemodialysis patients	Pediatric group
Intervention/Exposure	Epicardial adipose tissue thickness or volume	
Year of publication	2009-2019	
Outcomes	Coronary artery calcification	
Study types	Quantitative study and review	

Search Strategy and Selection

Potential studies were identified using Pubmed, HINARI, Science Direct, Cochrane for recent ten years, from 2009 until 2/11/2019. In addition, references of included articles by 2 reviewers, the search strategy included the following terms selected from medical subheadings medical subject headings (MeSH): (epicardial fat OR epicardial visceral fat OR epicardial adipose tissue OR epicardial visceral volume OR epicardial fat volume) AND(coronary artery calcification OR coronary artery disease OR coronary atherosclerosis OR coronary arteriosclerosis) AND(Hemodialysis OR peritoneal dialysis OR end-stage renal disease OR renal dialysis OR extracorporeal dialysis OR transplant kidney). This systematic review followed the PRISMA guidelines as showed in Figure (1). Two reviewers independently were assessed all retrieved articles and make the decision based on the inclusion and exclusion criteria.

Data Extraction and Quality Assessment

Two reviewers developed a template for data extraction, information extracted including, biographic details, appraisal tool score, and study design, characteristics of participants, data collection, sampling, findings, and implications on practice. Eligible articles were reviewed and relevant data was then extracted and organized as shown in table 2. The quality of studies was evaluated using the Hawkers assessment tool (Hawker et al., 2002), composed of 9 items: Abstract and title, Introduction and aims, Method and data, Sampling, Data analysis, Ethics and bias, Findings, Transferability, and Implications and usefulness. Score for each item ranged

from 1 to 4, 1 for "very poor", 2 for "poor", 3 for "Fair", 4 for "Good". The quality assessment was conducted independently by two authors and then compared as shown in Table (3). Regards the quality of studies included the score was accepted and ranged between 27-34. More half of them used Cross-sectional study and others were prospective, retrospective study and sub-analysis of RCT study.

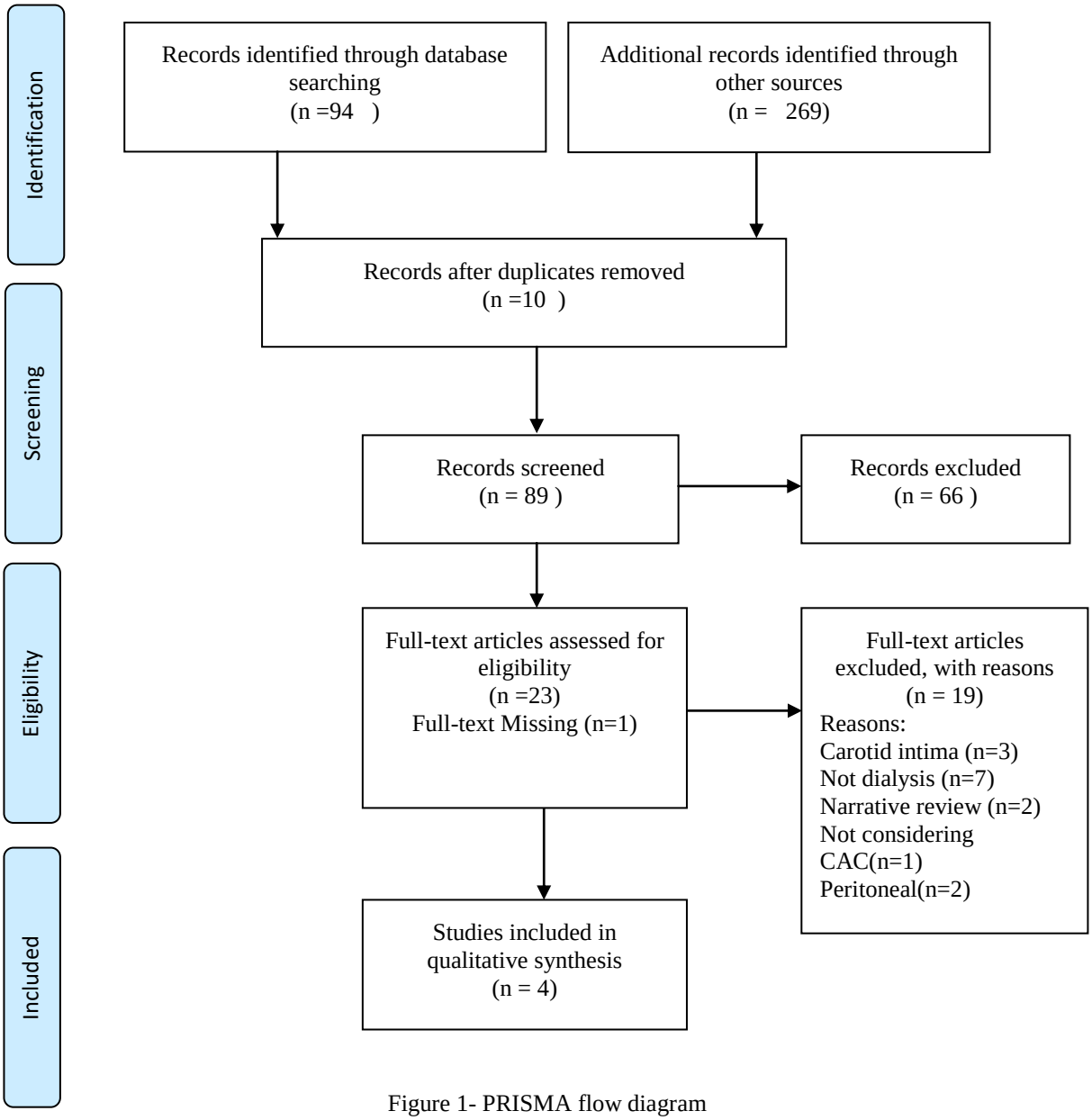

Figure 1- PRISMA flow diagram

Results

This systematic review was able to identify the association between epicardial adipose tissue thickness and coronary artery calcification. After title and abstract screening, the search resulted in 94 articles of which 23 were eligible for full text screening. The authors excluded 19 articles for one of the following reasons: not dialysis patients, carotid, peritoneal dialysis, renal transplant, pericardial adipose tissue, and narrative reviews. Thus 6 Articles were included in this review, plus 2 were included also from references, so the total of included studies were 8 studies, 5 of them were cross sectional studies (Abdallah et al., 2017; Atakan et al., 2014; Karatas et al., 2018; Macunluoglu et al., 2014; Ozcicek et al., 2017), two were cohort (Barros et al., 2016; Gaubeta et al., 2014) and one was a sub-analysis (D'Marco et al., 2013). Four articles of them were done in Turkey (Atakan et al., 2014; Karatas et al., 2018; Macunluoglu et al., 2014; Ozcicek et al., 2017); two in Germany (Barros et al., 2016; Gaubeta et al., 2014); one in USA (D'Marco et al., 2013) and one in Egypt (Abdallah et al., 2017).

General Specifications of Studies

The number of participants in a single study was ranged from 73 to 136, the mean age of participant varied between 44 and 64.1 years, male gender was predominant in four studies (Abdallah et al., 2017; Barros et al., 2016; D'Marco et al., 2013; Gaubeta et al., 2014) meanwhile, female gender was predominant in the other three (Atakan et al., 2014; Macunluoglu et al., 2014; Ozcicek et al., 2017) and Karats et al (Karatas et al., 2018) did not report the gender. Five studies measured EAT by transthoracic echocardiography (Abdallah et al., 2017; Atakan et al., 2014; Karatas et al., 2018; Macunluoglu et al., 2014; Ozcicek et al., 2017) while the other three used computed tomography (Barros et al., 2016; D'Marco et al., 2013; Gaubeta et al., 2014). All studies assessed the relationship between EAT and coronary artery calcification, five studies found a significant correlation. While, Gaubta et al (Gaubeta et al., 2014) reported that it was significant in 46 patients, who are younger than 55 years meanwhile, Abdullah et al (Abdallah et al., 2017) and Karatas et al (Karatas et al., 2018) did not assess it, but rather assessed other parameters contributes to CAD, EAT thickness and volume.

EAT Measurement

Five studies (Abdallah et al., 2017; Atakan et al., 2014; Karatas et al., 2018; Macunluoglu et al., 2014; Ozcicek et al., 2017) measured EAT using Transthoracic echocardiography, two of them performed it with a VIVID 7 (GE, General Electrics,Waukesha, WI, USA) while Ozcicek et al (Ozcicek et al., 2017) used GE-Vivid S5. The average value measured from three cardiac cycles in (Atakan et al., 2014; Gaubeta et al., 2014; Macunluoglu et al., 2014), while Karatas et al did not report it(Karatas et al., 2018), Abdullah et al used the average of five cardiac cycles (Abdallah et al., 2017). EFT was measured on the free wall of the right ventricle from the parasternal long-axis view. Epicardial fat tissue was defined as an echo-free space between pericardial layers on the two-dimensional echocardiography. Epicardial adipose tissue was measured perpendicularly on the free wall of right ventricle at end diastole for three cardiac cycles, reported thickness in (mm). Meanwhile, for the other studies, used Computed tomography each study put different definitions for CAC. Barros et al study (Barros et al., 2016) defined it as an area of more than 2 connected voxels with attenuation of more than 130 HU, while Gaubeta et al study (Gaubeta et al., 2014) determined a threshold of 130 HU in at least 2 consecutive pixels to identify a calcified lesion and D`Marco et al study (D'Marco et al., 2013) considered coronary artery calcification coronary artery calcification (CAC) present if three or more contiguous pixels with an attenuation of 130 HU. The CAC score was calculated according to the Agatston methodology. According to a systematic review, Betraso et al reported that EA thicknesses > 5 mm , or a volume > 125 mL or 68 mL/m² might be considered abnormal (Bertaso et al., 2013).

Predictors of Epicardial Adipose Tissue in Hemodialysis Patients

All studies reported older age as significantly a predictor of EAT in HD patients except Ozizcek et al (Ozcicek et al., 2017). Six studies reported higher BMI significantly correlated in the prediction of EFT thickness/volume while Ozizcek et al found no significance, and Karats et al did not report it. Total cholesterol was assessed in four studies, three of them reported that is significantly correlated with EAT (Abdallah et al., 2017; Atakan et al., 2014; Macunluoglu et al., 2014). The relation between EAT and duration of dialysis was found not significant in Guabta et al (Gaubeta et al., 2014) and Abdullah et al (Abdallah et al., 2017). C-reactive protein (CRP) was found to be not significant in Ozizcek et al (Ozcicek et al., 2017), while Marco et al (D'Marco et al., 2013) found that race, gender and total aortic calcification are correlated with EAT, Barros et al (Barros et al., 2016) found aortic valve calcification correlate to EAT , Karatas et al (Karatas et al., 2018) and Ozizcek et al (Ozcicek et al., 2017) found EAT positively correlated to Ferritin, Atakan et al (Atakan et al., 2014) found that coronary reserve flow (CRF)inversely correlated with EAT thickness, macunuglo et al (Macunluoglu et al., 2014) demonstrated that there is significant inverse correlation between EAT thickness and plasma Co-Q10 levels in HD patients, Abdullah et al found Paraoxonase-1 PON-1 activity inversely correlated with EAT thickness, Karatas et al demonstrated that ischemic modified albumin (IMA) and myeloperoxidase (MPO) statistically significant.

Discussion

This systematic review focused on the association between epicardial adipose tissue and coronary artery calcification in hemodialysis patients, as EAT has emerged to be a strong marker of cardiovascular risk and independent of traditional cardiovascular risk factors in the contributing in fatal and nonfatal coronary events in

the general population (Mahabadi et al., 2013) . The included eight studies and all of them found that epicardial adipose tissue volume was significantly higher in HD patients as compared to healthy controls (Abdallah et al., 2017; Atakan et al., 2014; Barros et al., 2016; Karatas et al., 2018; Macunluoglu et al., 2014; Ozcicek et al., 2017), or to the general population (D'Marco et al., 2013; Gaubeta et al., 2014) indicating that the metabolism of visceral fat is disturbed in HD patients as Barros et al (Barros et al., 2016) suggested. While all of them demonstrate the significant difference in EAT thickness/ volume, this review found just five studies assessed coronary artery calcification meanwhile Abdullah et al focused on assessing the relationship between PON-1 as it is an HDL-associated antioxidant enzyme and it will prevent LDL peroxidation and EAT as a marker of atherosclerosis, they demonstrated the inverse correlation, the rational of this that inflammation and oxidative stress are participating in developing CVD also in mortality and morbidity (Nusair et al., 2012). Atakan et al (Atakan et al., 2014) evaluated coronary reserve flow (CRF) as an early indicator of endothelial dysfunction in HD patients, this study could determine the relation between EAT and endothelial dysfunction as indicated by CRF which they reported that it can be used at the very beginning of the uremic state for assessing the atherosclerotic load. It is obviously clear that the study of Macunluoglu et al (Macunluoglu et al., 2014) focusing at the same principle of Atakan of oxidative stress and it is linkage to the development of CAD as they investigated plasma Co-enzyme Q10 levels which is an effective physiologic anti-oxidant. Ozizcek et al (Ozcicek et al., 2017) assessed neutrophil to lymphocyte ratio (NLR)as an inflammation parameter in HD patients and researchers divided HD group into two subgroups according to their NL ratio (NLR < 3.07, n=21, NLR ≥ 3.07, n= 22) and they reported a significant difference in EAT, CRP, Albumin and ferritin between these subgroups contributing this to the higher status of inflammation, but as predictors for EAT they assessed NLR, CRP, Albumin and body mass index (BMI) and only NLR was found to be an independent predictor of EAT , authors of this study stated that two dimensional echocardiography measurements may were not sufficient to assess the total epicardial adipose volume. Barros et al stated that EAT remained stable over 2 years as they follow up their HD patients, they reported only a modest , insignificant longitudinal increase, adding to that they report a subgroup in whom EAT volume decreased, who had higher baseline EAT levels, this observation was controversial as to what is already known regarding ESRD patients , the more at the baseline the more the increase in progression rate, they assessed a cohort of 59 HD patient, followed them for 23+- 4.7 months and reported a significant increase in CAC and aortic valve calcification, one more interesting finding that as 32 patients died during follow up, there was no association between EAT and all–cause mortality but a hazard ratio of 1.04 per 10 cm^3 increase in baseline EAT was reported.

This review found that seven studies assessed BMI correlation to EAT, one reported that BMI cannot be considered as a predictor for EAT (Ozcicek et al., 2017) furthermore, Ozizcek et al (2017) did not establish any differences in means of age, BMI, and gender between HD patients and healthy groups. Willens et al., (2007) reported in their study that, EAT thickness decreases in severely obese patients who undergone weight loss after bariatric surgery, and Measuring EAT using echocardiography may be useful to monitor visceral fat loss with weight reduction therapies (Willens et al., 2007). Reviewed showed that significant weight loss can be associated with significant reduction in the epicardial adipose thickness, marker of visceral adiposity in severely obese subjects. Another study described that during weight loss, Epicardial fat changes are significantly associated with obesity-related cardiac morphological and functional changes, and thus measuring may provide a better understanding of the metabolic risk associated with difference in fat distribution (Iacobellis et al., 2008).

One study reported no significance correlation between EAT and CAC, contributing this result to different mechanisms happen in HD patients, and it could be age as they demonstrated a significant correlation in a sub-group of 46 patients who are younger than 55 between EAT and CAC but they reported two interesting associations, first that there is no association between duration dialysis and EAT and this consistent with the follow up results of Barros et al but it was significantly correlated with age and diabetes mellitus type 2 as a cardiovascular risk factor.

One study considered assessing CRP and they reported no significant correlation with EAT, in CANTOS trial (Ridker et al., 2017) as they could significantly decrease CRP targeting it by Canakinomab and in light of the inflammation hypothesis and thus establishing CRP as a clinical risk marker for the cardiovascular marker. Ferritin was assessed and found to be an independent predictor of EAT in (Karatas et al., 2018; Ozcicek et al., 2017). Serum ferritin is an acute-phase reactant and marker of acute and chronic inflammation, and is nonspecifically increased in a wide range of inflammatory conditions, including chronic kidney disease (CKD)(Kalantar-Zadeh et al., 2006). It is noted also in light of inflammation hypothesis, Karatas et al in their study proposing, ischemia-modified albumin, myeloperoxidase and EAT as a follow up parameter in CKD patients. Introduction of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) level measurements and the discovery of a positive association between LDL-C level and Chronic heart disease CHD risk, and a negative association between HDL-C level and CHD risk were of major

importance for CVD prevention as established by Framingham study (Rosito et al., 2008), in our review, four studies assessed total cholesterol (Abdallah et al., 2017; Atakan et al., 2014; D'Marco et al., 2013; Macunluoglu et al., 2014), one found it is not significant (D'Marco et al., 2013), three studies(Abdallah et al., 2017; D'Marco et al., 2013; Karatas et al., 2018) found HDL significantly correlated to EAT furthermore, Abdullah reported that LDL and triglycerides (TAG) are independent predictors of EAT.

MESA study (Ding et al., 2009) support the idea that pericardial fat is a better predictor of incident coronary heart disease than are more general measures of adiposity in community-based adults without a history of cardiovascular disease. If the hypothesis is confirmed, pericardial fat may serve as a more specific and sensitive marker of coronary heart disease risk than other fat measures.

None of the studies compared the imaging modalities or justify using one way over the another, but according to literature, MRI is the gold standard for measuring EAT, but it is high cost, less availability, and contraindications in patients with pacemakers and implants, and none of the studies used it ,while CT provides better EAT assessment with the highest specificity and sensitivity (Aeddula et al., 2019). Computed tomography (CT) and magnetic resonance imaging (MRI) have been traditionally used as adjuvants to echocardiography, but their role is increasing due to high spatial resolution and the possibility of volumetric assessment (Bertaso et al., 2013) while we see all studies used diastole to measure EAT it is a controversial point in the literature as Betrosa et al reported. Inconsistencies in the nomenclature and measurement methods are limitations to its implementation according to systematic review of Betraso et al (Bertaso et al., 2013). All studies reported that small size samples and the observational study designs as limitations for their work.

Limitations

The limitations of this systematic review were the accessibility for databases, and the geographical distribution of the studies as they were limited to Turkey (Atakan et al., 2014; Macunluoglu et al., 2014; Ozcicek et al., 2017), Germany (Barros et al., 2016; Gaubeta et al., 2014), Egypt (Abdallah et al., 2017) and USA (D'Marco et al., 2013) and thus more insights are needed to cover other regions. Another limitation was the restriction to English langue search.

Conclusions

In conclusion, the results of this systematic review suggest the significant relationship between epicardial adipose tissue and developing coronary artery disease in this special cohort of patients, hemodialysis patients as its metabolically active tissue, beside suggesting other less invasive, more available parameters, which significantly correlate with EAT thickness/volume and reflect the inflammatory progression in these patients, so guiding clinicians to assess coronary artery disease more efficiently and seriously. Further research should consider more the availability of using EAT as a non-invasive method to assess cardiovascular risk in HD patients. Therapeutic target either non-pharmacological or pharmacological methods. The current review suggests the need to do more detailed prospective study.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Acknowledgements or Notes

* This article was presented as an oral presentation at the International Conference on General Health Sciences (www.icgehes.net) held in Istanbul/Turkey on August 25-28, 2022

* The data used to support the finding of this study are included within the review, and any supporting literature has been referenced within the reference list. Authors declare that no conflict of interest. I would like to thank An Najah National University. Systematic reviewers typically do not have direct access to participants of primary research studies included in their review. This work was not funded by any persons or institutions

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To cite this article:

Alshawish, E., Ghanem, A. F. A. & Shellah, D. (2022). The association between epicardial adipose tissue and coronary artery disease in hemodialysis patients using a systematic review. *The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS), 6*, 57-64.