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ABOUT COVER

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EDITORIAL

Epicardial adipose tissue deposition in patients with diabetes and renal impairment: Analysis of the literature

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Abstract

Diabetes mellitus (DM) is defined as a chronic disease of disordered metabolism with an ongoing increase in prevalence and incidence rates. Renal disease in patients with diabetes is associated with increased morbidity and premature mortality, particularly attributed to their very high cardiovascular risk. Since this group of patients frequently lacks specific symptomatology prior to the adverse events, a screening tool for the identification of high-risk patients is necessary. The epicardial adipose tissue (EAT) is a biologically active organ having properties similar to visceral adipose tissue and has been associated with metabolic diseases and coronary artery disease. Superior to conventional cardiovascular risk factors and anthropometric measures, including body mass index and waist circumference, the EAT can early predict the development of coronary artery disease. Assessment of EAT can be performed by two-dimensional echocardiography, magnetic resonance imaging or computer tomography. However, its role and significance in patients with DM and nephropathy has not been thoroughly evaluated. The aim of the current editorial is to evaluate all available evidence regarding EAT in patients with DM and renal impairment. Systematic search of the literature revealed that patients with DM and nephropathy have increased EAT measurements, uncontrolled underlying disease, high body mass index and raised cardiovascular risk markers. Acknowledging the practical implications of this test, EAT assessment could serve as a novel and non-invasive biomarker to identify high-risk patients for cardiovascular adverse events.

Key words: Epicardial adipose tissue; Epicardial fat; Diabetes mellitus; Renal impairment; Diabetic nephropathy; Cardiovascular risk

Core tip: The epicardial adipose tissue (EAT) is a biologically active organ and has been associated with metabolic diseases and coronary artery disease. EAT is a superior

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cardiovascular risk factor compared to conventional measures. This editorial evaluates the reported measurements of EAT in patients with diabetes mellitus and renal impairment, along with their clinical and laboratory characteristics. Patients with diabetes mellitus and nephropathy have increased EAT volume, uncontrolled disease, high body mass index and raised cardiovascular risk markers, when compared with healthy population. Based on current literature, EAT assessment could be used as a novel biomarker for the identification of patients at high risk for cardiovascular adverse events.

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INTRODUCTION

Diabetes mellitus (DM) consists a chronic multisystem disease of disordered metabolism with a worldwide prevalence reaching approximately 425 million[1]. The major complications of DM can be divided into macrovascular (cardiovascular disease) and microvascular [chronic kidney disease (CKD), diabetic retinopathy, diabetic neuropathy][2-4]. Diabetic nephropathy (DN) is a major cause of morbidity and mortality in diabetic patients, with a prevalence of 20%-40% in patients with type 1 or type 2 DM[5]. The majority of DM cases with CKD result from DN[6]. In addition, increased albuminuria and diminished renal function indicate unfavorable prognosis in terms of cardiovascular disease[7].

Epicardial adipose tissue (EAT) is a biologically active organ with properties similar to visceral adipose tissue[8,9]. EAT is defined as the adipose tissue located between the visceral pericardium and the myocardium, in the absence of a structure separating it from the myocardium and the epicardial vessels[8]. Assessment of EAT can be performed by the following imaging techniques: Two-dimensional echocardiography, magnetic resonance imaging (MRI), or computer tomography (CT)[10]. CT could concomitantly assess the presence of coronary calcification or stenosis[11]. Increased amounts of EAT have been associated with the presence of metabolic syndrome, DM and coronary artery disease[10]. EAT has also been proposed as a key mediator in the pathogenesis of cardiovascular disease in end-stage renal disease (ESRD) patients, the most common cause of death in this particular group[12,13].

THE NECESSITY OF A NEW SCREENING TOOL

EAT has been currently identified as a marker of cardiovascular risk[8,9]. Patients with DM and renal impairment have a high prevalence of cardiovascular adverse events, frequently lacking warning symptoms such as chest pain, usually due to either diabetic autonomic neuropathy, uremic neuropathy, or impaired exercise capacity[14,15]. This high-risk group of patients requires regular follow-up, since cardiovascular disease consists the single leading cause of morbidity and mortality in patients with CKD in all stages[6]. In light of these considerations, this editorial will focus on the value of EAT assessment in patients with DM and renal disease.

AVAILABLE EVIDENCE

Two online databases (PubMed and Scopus) were systematically searched for articles published from inception up to December 2019. The search term applied consisted of the following key words: ("diabetes mellitus" OR "diabetic" OR "diabetes") AND ("epicardial fat" OR "epicardial adipose" OR "subepicardial fat" OR "subepicardial adipose"), in order to identify all published articles reporting data on patients with DM and renal impairment who were assessed for EAT measurements. Reference lists of full articles were also reviewed.

Articles with the following requirements were included: (1) Primary research papers (*e.g.*, case reports, case series, observational studies, randomized control trials);

(2) Studies describing patients (adults ≥ 18 years) with type 1 or type 2 DM and renal impairment who had undergone measurement of EAT deposition; and (3) Studies published in English.

Studies containing at least one of the following items were excluded: (1) Studies published in other than English language; (2) Experimental studies on animals; (3) Cases not diagnosed with DM; (4) Studies including exclusively patients with gestational DM; (5) Secondary research papers; (6) Editorials and papers not reporting results of primary research; and (7) Studies not referring to patients with DM, renal impairment and epicardial fat deposition measurements.

Study outcomes were to evaluate all available evidence regarding EAT measurements in patients with DM and renal impairment; to record all clinical and laboratory characteristics and comorbid conditions; and to identify possible risk factors that could contribute to epicardial fat tissue deposition in these patients.

ANALYSIS OF CURRENT LITERATURE

A total of eight studies referring to patients with DM and renal impairment with EAT assessment were incorporated in the analysis[16-22]. Table 1 summarizes the characteristics of the 8 included studies and the 452 patients that were analyzed. All were cross-sectional, except one case-report. According to data available in 368 patients, mean age was 59 years of age (range: 49-71) and 140 (31%) patients were female[16,17,19,21,23].

Epicardial adipose tissue characteristics

The EAT was quantified in all eight studies. Investigators used either transthoracic echocardiography[16,17] or multi-detector CT (MDCT)[18-22] to assess epicardial fat. Transthoracic echocardiography was used to measure EAT thickness in three studies: mean 3.2 ± 1.6 mm[17], median 4.5 mm (range: 2-9 mm) and 5.3 mm (range: 4.4-9 mm) in the micro- and macro-albuminuric group respectively[16], and mean 6.5 ± 1.4 mm[23]. According to previous studies, the mean thickness value in systole described by Iacobellis *et al*[24] during the investigation of cardiovascular risk, was 6.8 mm (range: 1.1-22.6). The mean value in diastole introduced by Jeong *et al*[25] in more than 200 patients admitted for coronary angiography, was 6.4 mm (range: 1.1-16.6). Although there is no consensus for EAT thickness cut-off values, measurements higher than 5 mm indicate increased EAT, especially in low risk populations[8].

MDCT was used to assess EAT volume in cm^3 or mm^3 units. In one study, EAT was expressed as single slice epicardial fat volume or as single slice epicardial fat area[20]. A previous study determined that single slice epicardial fat area measured at the level of left main coronary artery provides a reliable estimate of total epicardial fat volume[26]. Most of the studies using MDCT included the range of -190 to -30 of Hounsfield units regarding determination of fat. The mean EAT volume of the four studies was 258.4 cm^3 (range: 0.01-487)[18-20,22]. One study reported the median EAT volume of 17 patients which equaled 215.5 cm^3 (range: 126.5-271.2)[21]. The value of 0.01 cm^3, reported in one study, could be attributed to the different range of Hounsfield units used for determination of fat density[18]. In comparison, the mean volume of EAT ranged from 68 ± 34 cm^3 to 124 ± 50 cm^3 in previous population-based studies[27,28]. A cohort study derived from Framingham Heart Study, found a mean EAT volume of 110 ± 41 cm^3 in women and 137 ± 53 cm^3 in men[11]. Based on current literature, a cut-off EAT volume of more than 125 cm^3 can be considered as abnormal[8]. Hence, patients with DM and renal impairment seem to have an increased EAT volume compared to healthy populations.

Diabetes mellitus characteristics

Type of DM was reported in 359 patients[16-18], of which 350 (96.8%) had type 2 DM[16,17,23] and 9 (3.2%) had type 1 DM[18]. Duration of DM was reported in 350 patients and ranged from 0 to 30 years[16,17,23]. The HbA1c levels, reported in 350 patients, ranged from 6% to 14.5%, with an approximate mean value of 8.7%[16,17,23]. Among 291 patients with available data on treatment of diabetes, 223 (76.6%) patients were being treated with oral antidiabetics and/or 180 (80.7%) patients were being treated with either insulin injections or insulin infusion pump[16,17,23]. Average body mass index (BMI), estimated in 368 patients, was 32.3 kg/m^2 (range: 28.5-34.4)[16,17,19,21,23]. The characteristics of DM are reported in Table 2.

BMI is an anthropometric measure widely used to assess visceral adipose tissue deposition[29]. Excess visceral adipose tissue is a marker of patients with high risk for cardiovascular disease[30,31]. This finding is in line with the current literature suggesting that visceral adipose tissue has a strong correlation with EAT[30,32].

Table 1 Study and patient characteristics

Ref.	Study design	Age group	Number of patients with diabetes and renal impairment	Age, mean in years (range)	Gender, female, *n* (%)
Akbas *et al*[16], 2014, Turkey	Cross-sectional	Adults	68	Micro-albuminuric patients: 60 ± 11 Macro-albuminuric patients: 59 ± 9.6	34 (50)
Christensen *et al*[17], 2017, Denmark	Cross-sectional	Adults	200	59 (50-68)	48 (24)
Darabian *et al*[18], 2016, United States	Cross-sectional	Adults	9	NR	NR
Do *et al*[19], 2009, Korea	Case-report	Adult	1	59	1 (100)
Kerr *et al*[20], 2013, Canada	Cross-sectional	Adults	36	NR	NR
Tonbul *et al*[21], 2011, Turkey	Cross-sectional	Adults	17	58 (45-71)	8 (47)
Turan *et al*[22], 2013, Turkey	Cross-sectional	Adults	39	NR	NR
Turan *et al*[23], 2019, Turkey	Cross-sectional	Adults	82	59.4 ± 7.6	49 (59.7)

NR: Not reported.

Renal impairment characteristics

Patients from all different CKD stages were included. Albuminuria was used as an early and sensitive marker of renal impairment in three studies[16,17,23]. One study included patients with both macroalbuminuria and ESRD[18]. Albuminuria was estimated in 350 patients[16,17,23], among which 274 patients had microalbuminuria (30-299 mg/g Cr) and 76 patients had macroalbuminuria (> 300 mg/g Cr)[16,17,23]. Three studies revealed that albuminuria was a significant predictor of greater EAT[16,18,20]. Mean eGFR and mean creatinine, assessed in 350 patients, were 82 mL/min/1.73/m^2 (range: 20-123)[16,17,23] and 1.0 mg/dL (range: 0.4-3.5), respectively[16,17,23]. Patients with ESRD were reported in 57 patients in three studies[19,21,22]. Renal impairment characteristics are depicted in Table 2.

Albuminuria is a marker of diffuse endothelial dysfunction associated with hypertension, smoking, DM, obesity and dyslipidemia[33,34]. Albuminuria consists a risk factor for cardiovascular disease and is associated with increased abdominal adiposity[35]. The ADVANCE Study showed that albuminuria and reduced GFR were independently and additively associated with increased cardiovascular and renal events in patients with type 2 DM[36].

EAT is a biologically active organ having properties similar to the visceral adipose tissue, secreting proatherogenic hormones and cytokines such as leptin and resistin[8]. The absence of a specific fascial layer or aponeurosis between the epicardial vessels and the myocardium surrounding the adventitia of coronary arteries and their branches, allows for a shared micro-circulation and the subsequent development of coronary artery disease[8,37]. The protective effect of adiponectin which acts by increasing insulin sensitivity is found to be reduced in patients with increased deposits of EAT[38,39]. CKD involves chronic inflammation, characterized by the presence of increased inflammatory markers, including C-reactive protein, IL-6, and TNF-α[12]. C-reactive protein is also associated with the prevalence of metabolic syndrome, hypertension and DM in United States adults[40]. Atherosclerosis is greatly enhanced under higher inflammation status or increased oxidative stress[12]. Microvascular complications of DM, including DN, are promoted under the influence of inflammation and oxidative stress by the metabolism of hyperglycemia and dyslipidemia[16,41-46].

Conclusively, the presence of albuminuria along with endothelial dysfunction and increased abdominal adiposity, the secretion of proatherogenic hormones and cytokines by EAT in combination with the loss of protective effect of adiponectin, the pronounced inflammation and oxidative stress in CKD patients, all contribute to the development of coronary artery disease in patients with DM and renal impairment.

Coronary artery calcium score

Total coronary artery calcium score (CACS) was evaluated in 217 patients[17,21]. Left

Table 2 Diabetes and renal disease characteristics

Ref. (number of patients)	Diabetes type	Diabetes duration, median (IQR) or mean ± SD in years	Criteria for renal impairment diagnosis	eGFR,mean ± SD (mL/min/1.73 m^2)	Albuminuria, median (IQR) (units)	Creatinine, median (IQR) or mean ± SD (mg/dL)	Other related measurements
Akbas *et al*[16] (*n* = 68)	Type 2	Micro-albuminuric patients: 9 (0-30); Macro-albuminuric patients: 8.5 (1-29)	Presence of albuminuria (> 30 mg/g Cr)	Micro-albuminuric patients: 94 ± 29; Macro-albuminuric patients: 64 ± 44	Micro-albuminuric patients: 74 (33-294) (mg/g Cr); Macro-albuminuric patients: 716 (312-1985) (mg/g Cr)	Micro-albuminuric patients: 0.75 (0.5-2); Macro-albuminuric patients: 1.4 (0.4-3.5)	BMI (kg/m^2): 30; Waist circumference (cm): 102; SBP (mmHg): 135 (90-210); DBP (mmHg): 78 (40-110)
Christensen *et al*[17] (*n* = 200)	Type 2	13 ± 7	Presence of albuminuria (> 30 mg/g Cr)	89 ± 17	102 (39-229) (mg/24 h)	0.86 ± 0.2	BMI (kg/m^2): 32.6; SBP (mmHg): 130 ± 16; Cholesterol (mg/dL): 151; LDL (mg/dL): 73.4; HDL (mg/dL): 46.4
Darabian *et al*[18] (*n* = 9)	Type 1	NR	Presence of albuminuria (> 30 mg/g Cr) or ESRD	NR	NR	NR	NR
Do *et al*[19] (*n* = 1)	NR	NR	ESRD (peritoneal dialysis)	(End-stage renal failure)	NR	9.13	BMI (kg/m^2): 29.6
Kerr *et al*[20] (*n* = 36)	NR	NR	CKD diagnosis according to National Kidney Foundation Criteria	NR	NR	NR	NR
Tonbul *et al*[21] (*n* = 17)	NR	NR	ESRD (hemodialysis or peritoneal dialysis)	(End-stage renal failure)	NR	NR	BMI (kg/m^2): 28.5; SBP (mmHg): 135 ± 27; DBP (mmHg): 80 ± 16; LDL (mg/dL): 120; HDL (mg/dL): 37; Triglycerides (mg/dL): 127
Turan *et al*[22] (*n* = 39)	NR	NR	ESRD (hemodialysis)	(End-stage renal failure)	NR	NR	NR
Turan *et al*[23] (*n* = 82)	Type 2	12.7 ± 6.7	Presence of micro-albuminuria (30-300 mg/g)	80 ± 20	134 ± 83 (mg/g)	0.91 ± 0.2	BMI (kg/m^2): 34.4 ± 6.2; SBP (mmHg): 135 ± 16; DBP (mmHg): 80.5 ± 11; LDL (mg/dL): 123 ± 35; HDL (mg/dL): 44 ± 10.6; Triglycerides (mg/dL): 211

BMI: Body mass index; CKD: Chronic kidney disease; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; HDL: High density lipoprotein; IQR: Interquartile range; LDL: Low density lipoprotein; NR: Not reported; SD: Standard deviation; SBP: Systolic blood pressure.

anterior descending coronary artery, circumflex coronary artery and right coronary artery were added to calculate the CACS according to the protocol by Agatston *et al*[47], for quantification of CACS using ultrafast CT. The mean CACS was 192.5, with a normal range between 1 and 10.

CACS is an index that assesses the severity of atherosclerotic vascular disease and predicts the risk of future adverse cardiovascular events[48]. CACS equal to 192.5 is classified as moderate risk (relative risk: 4.3) of having a cardiovascular event according to Agatston *et al*[47]. According to previous studies, individuals with DN had a significantly higher prevalence and severity of CACS score when compared to normoalbuminuric diabetic patients[49]. Also, the progression of CACS in patients with

DM and CKD is more prevalent in those with albuminuria when compared with normoalbuminuric patient controls[50]. Increased EAT volume was also correlated with CACS in ESRD patients[21]. Two studies included measurements of inflammatory markers[16,17], which were found to be associated with increased albuminuria[16] and with EAT[17,51]. Based on the aforementioned results and according to the literature, EAT volume is associated with the malnutrition, inflammation and atherosclerosis/calcification syndrome in ESRD patients, which is associated with increased morbidity and mortality.

CRITICAL APPRAISAL OF THE LITERATURE

The above findings should be considered in relation to the fact that most available evidence is derived from observational cross-sectional studies with relatively small sample sizes. Several determinants of EAT including obesity, age and ethnicity, which may set different normal ranges, were not reported in all patients[24,52-56]. Additionally, several characteristics of DM and renal disease were not reported in all patients. MDCT protocol and definitions used varied among studies. Although MRI is considered the standard of reference for EAT quantification[57], no studies that utilized MRI were available.

FUTURE DIRECTIONS

According to current literature, EAT can be supported as a superior cardiovascular risk factor compared to conventional anthropometric measures, indicating that localized fat depositions predict more accurately the future adverse coronary events[10]. EAT was particularly increased in non-calcified and mixed plaques, the most commonly implicated in cardiovascular events, in comparison with purely calcified plaques[53,58]. At this point, there is evident need to establish cut-off points for EAT volume and thickness in high-risk patient groups such as patients with DM and DN; to that end, future studies should prefer to opt for EAT volume over thickness assessment, using standardized MDCT or MRI protocols. In addition, future studies should report more detailed data on patients, including DM and DN characteristics and somatometric data. Although not within the scope of the current review, studies have also focused on the reduction of EAT through conservative, pharmacological or surgical means, yielding various results[9,59-65]. Future studies should assess the safety and long-term effects of EAT reduction. This way, EAT could concomitantly be used as a screening tool and as a follow-up marker.

CONCLUSION

Available evidence shows that patients with DM and renal impairment have uncontrolled disease, with raised cardiovascular risk markers, high BMI and increased EAT measurements, when compared with healthy populations. Although specific cut-off limits need to be developed and acknowledging the practical issues concerning this test, EAT assessment could be used as a novel practical and inexpensive biomarker for identification of patients at high risk for cardiovascular adverse events.

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