Epicardial fat accumulation, cardiometabolic profile and cardiovascular events in patients with chronic kidney disease stage 3-5

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Background

Epicardial adipose tissue (EAT), i.e. the visceral adipose tissue surrounding the heart, is a particularly active tissue. This fat depot covers 80% of the midcardiac circumference and is situated predominantly on the right-ventricular free wall and the left-ventricular apex, accounting for approximately 20% of total heart weight.

It has been hypothesized that EAT exerts pathogenic effects on cardiac structures. However, its role in non-dialyzed CKD patients is poorly understood and whether EAT enlargement confers an increased risk of cardiovascular events in these patients is unknown.

Objective

We aimed to evaluate clinical correlates and the prognostic significance of EAT in non-dialysis dependent stage 3-5 CKD patients.

Methods

In a cross-sectional study, 277 non-dialyzed stage 3–5 CKD patients (61 [53-68] years; 63% men) underwent assessments of EAT, abdominal visceral adipose tissue (VAT) and coronary artery calcium score (CACs) by computed tomography, myocardial scintigraphy and echocardiography. Patients were followed for 32 (20–39) months and the composite of fatal and non-fatal CV events was recorded.

Results

✓ General characteristics of the studied population as well as patient's characteristics according to quartiles of EAT distribution (with the two middle quartiles combined) are summarized in **Table 1**. Across increasing quartiles, patients were older, had a higher GFR and were more often receiving ACEI/ARB, acetylsalicylic acid, and statins; and, regarding body composition parameters, across increasing quartiles, patients expectedly had a higher BMI, a larger waist circumference, as well as enlarged abdominal VAT. Whereas hemoglobin, triglycerides, albumin, CRP and leptin concentration were increased, total cholesterol, HDL cholesterol, 25-OH vitamin D and 1,25-OH vitamin D were incrementally reduced across increasing EAT quartiles. Coronary artery calcification, as well as the prevalence of left ventricular hypertrophy and myocardial ischemia increased significantly with the increments on EAT.

✓ The multivariate correlates of EAT (logarithm transformed) are shown in **Table 2.** Age, hemoglobin, BMI, abdominal VAT and 25-OH vitamin D levels emerged as independent associates.

✓ During a median follow-up of 32 (IQR 20–39) months, there were 58 CV events (fatal and nonfatal) Cox proportional hazards models explored the aetiological association between EAT (as a continuous or categorical variable) and CV events (Table 3). Increased EAT was associated with higher risks of CV events in both crude and adjusted models which included, amongst other variables, abdominal VAT. Cox proportional models further explored the prognostic value of EAT, VAT or both to predict CV events over and above a basic set of risk factors (Table 4). Although the prognostic gain of adding EAT was slightly better than that of adding VAT, the overall discrimination power did not differ substantially from the basic models.

Results

Table 1. Demographics and clinical characteristics[1] of 277 non-dialysis dependent patients with CKD stages 3 - 5 patients, and according to the quartiles of epicardial fat distribution.

		Epicardial fat amount			
	All Patients (n = 277)	*Low Quartile* (n = 69)	*Middle Quartiles* (n = 139)	*High Quartile* (n =69)	*P for trend*
Epicardial fat (cm^3)	140 (80 – 210)	60 (50 – 70)	140 (110 – 180)	280 (240 – 340)	-----
Age (years)	61 (53 – 68)	53 (46 – 64)	62 (56 – 69)	64 (58 – 72)	***<0.001***
Men (n, %)	174 (63%)	38 (55%)	88 (63%)	48 (70%)	0.079
Diabetes mellitus (n, %)	138 (50%)	37 (54%)	69 (50%)	32 (46%)	0.395
Ischemic heart disease (n, %)	93 (34%)	18 (26%)	49 (35%)	26 (38%)	0.150
Glomerular filtration rate (ml/min)	22 (14– 34)	15 (11 – 24)	24 (16 – 38)	26 (19 – 36)	***<0.001***
Systolic BP (mmHg)	150 (133 – 171)	160 (134 – 184)	149 (133 – 165)	149 (131 – 168)	0.065
Diastolic BP (mmHg)	79 (71 – 90)	85 (72 – 100)	78 (70 – 86)	80 (70 – 92)	0.063
ACE inhibitors / ARBs (n, %)	167 (60%)	34 (49%)	86 (62%)	47 (68%)	***0.024***
Calcium channel blockers (n, %)	182 (66%)	46 (67%)	94 (68%)	42 (61%)	0.474
β-blockers (n, %)	178 (64%)	39 (57%)	89 (64%)	50 (73%)	0.051
Diuretics (n, %)	238 (86%)	58 (84%)	126 (91%)	54 (78%)	0.328
Acetylsalicylic acid (n, %)	177 (64%)	33 (48%)	97 (70%)	47 (68%)	***0.013***
Statin (n, %)	178 (64%)	33 (48%)	94 (68%)	51 (74%)	***0.001***
Insulin (n, %)	85 (31%)	25 (36%)	45 (32%)	15 (22%)	0.065
Body mass index (kg/m^2)	29.2 ± 5.9	25.2 ± 4.5	30.2 ± 5.7	31.1 ± 5.8	***<0.001***
Waist circumference (cm)	96 (88 – 106)	86 (79 – 92)	100 (91 – 108)	103 (94 – 108)	***<0.001***
Abdominal visceral adipose tissue (cm^2)	156 (99 – 223)	80 (34 – 111)	185 (131 – 247)	185 (139 – 234)	***<0.001***
Hemoglobin (g/dL)	12.2 ± 2.2	11.1 ± 2.1	12.4 ± 2.1	12.9 ± 2.1	***<0.001***
HOMA-IR[2]	1.7 (1.0 – 3.0)	1.1 (0.6 – 2.1)	2.0 (1.2 – 3.4)	2.1 (1.2 – 3.5)	***<0.001***
Total cholesterol (mg/dL)	174 (150 – 225)	201 (162 – 242)	172 (150 – 216)	161 (138 – 199)	***0.002***
HDL cholesterol (mg/dL)	41 (35 – 50)	46 (39 – 55)	40 (35 – 49)	39 (33 – 51)	***0.020***
Triglycerides (mg/dL)	152 (115 – 210)	123 (87 – 181)	161 (125 – 210)	156 (111 – 220)	***0.010***
Ionized calcium (mmol/L)	1.14 (1.08 – 1.21)	1.17 (1.08 – 1.22)	1.14 (1.08 – 1.20)	1.15 (1.09 – 1.21)	0.429
Phosphorus (mg/dL)	4.3 (3.5 – 4.8)	4.4 (3.9 – 5.1)	4.0 (3.5 – 4.7)	4.1 (3.5 – 4.6)	***0.005***
Parathyroid hormone (pg/mL)	157 (100 – 333)	231 (119 – 406)	156 (101 – 303)	127 (86 – 247)	***0.001***
25-OH vitamin D (ng/mL)	41 (26 – 60)	49 (34 – 66)	44 (28 – 64)	26 (17 – 42)	***<0.001***
1,25-OH vitamin D (pg/mL)	26 (21 – 38)	27 (22 – 39)	27 (22 – 39)	22 (13 – 32)	***0.002***
Albumin (mg/dL)	3.9 (3.6 – 4.2)	3.8 (3.4 – 4.0)	3.9 (3.6 – 4.2)	4.1 (3.7 – 4.3)	***<0.001***
C-Reactive protein (mg/L)	3.6 (1.4 – 8.0)	2.2 (0.9 – 6.7)	3.6 (1.4 – 8.0)	6.0 (1.7 – 10.4)	***0.007***
Leptin (ng/mL)	18.7 (7.2 – 36.4)	9.9 (3.5 – 28.3)	20.8 (9.5 – 42.5)	21.0 (11.7 – 36.6)	***0.001***
Left ventricular hypertrophy (n, %)[3]	235 (88%)	54 (82%)	118 (89%)	63 (94%)	***0.029***
Coronary artery calcium score (Agatston)[4]	139 (1 – 509)	16 (0 – 281)	155 (7 – 428)	356 (8 – 961)	***<0.001***
Myocardial ischemia (n, %)[5]	45 (22%)	4 (8%)	27 (26%)	14 (26%)	***0.027***

[1] Data are presented as median (25^{th} – 75^{th} percentiles), mean ± standard deviation or absolute (n) plus relative (%) values. [2]HOMA-IR was reported in non-diabetics only. Number of non-diabetic patients across tertiles: 32/70/37. [3] Echocardiography was available in 266 patients (66/133/67). [4]Coronary artery calcium score was available in 254 patients (64/128/62) .[5]Myocardial scintigraphy was available in 208 patients (51/103/54)

Table 2 *Factors associated[a] with an increased amount of epicardial fat (logarithm transformed) in backward linear regression analyses[b] amongst patients with stages 3–5 chronic kidney disease (n = 277)*

Covariates	Nonstandardized coefficient	95% confidence interval	*P*
Intercept	–	–	***<0.001***
Age (years)	0.013	0.007 to 0.019	***<0.001***
Body mass index ($kg\ m^{-2}$)	0.030	0.016 to 0.043	***<0.001***
Abdominal visceral adipose tissue (per SD increase)	0.130	0.044 to 0.216	***0.003***
Haemoglobin ($g\ dL^{-1}$)	0.057	0.026 to 0.088	***<0.001***
25-OH vitamin D ($ng\ mL^{-1}$)	−0.007	−0.010 to −0.004	***<0.001***

[a]The adjusted R2 for the model was 0.38. [b]Excluded variables: gender, albumin, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, use of aspirin, use of statins and logarithm transformed values of glomerular filtration rate, total cholesterol, triglycerides, parathyroid hormone, C-reactive protein and leptin. 25-OH vitamin D, 25-hydroxy-vitamin D.

Table 3 *Aetiological Cox model presenting hazard ratios (95% confidence intervals) for cardiovascular events (n = 58) as a function of an increased amount of epicardial adipose tissue (EAT) in patients with stages 3–5 chronic kidney disease (n = 277)*

Model	Variables	EAT (per 1-SD increase)	Highest EAT quartile versus the rest
1	Crude model	1.41 (1.12–1.78)	2.03 (1.16–3.54)
2	Model 1 + age and sex	1.37 (1.07–1.74)	1.88 (1.06–3.32)
3	Model 2 + glomerular filtration rate	1.44 (1.13–1.85)	2.03 (1.15–3.61)
4	Model 3 + Charlson comorbidity index	1.51 (1.17–1.94)	2.08 (1.17–3.69)
5	Model 4 + abdominal visceral fat	1.55 (1.21–1.99)	2.16 (1.20–3.88)

Table 4 *Prognostic value of epicardial adipose tissue (EAT), abdominal visceral adipose tissue (VAT) or both in the prediction of cardiovascular events over and above a basic set of traditional and uraemia-related risk factors in patients with stages 3–5 chronic kidney disease*

	Basic model[a]	+ EAT	+ VAT	+ EAT and VAT
Pseudo r^2	0.16	0.19	0.19	0.23
AUC	0.73 (0.64–0.82)	0.75 (0.66–0.83)	0.73 (0.65–0.82)	0.75 (0.67–0.83)
–2LL	466.8	459.2	406.8	397.6

AUC, area under the curve; –2LL, –2 log likelihood. [a]Because coronary artery calcium score and left ventricular mass index were not available in a small subset of individuals, the basic model included 232 patients and evaluated 42 events. Variables considered in the model were: age, glomerular filtration rate, serum levels of haemoglobin, albumin and phosphorus, albuminuria, coronary artery calcium score and left ventricular mass index.

Conclusion

Epicardial adipose tissue accumulation in patients with CKD increases the risk of CV events independent of general adiposity. This is consistent with the notion of a local pathogenic effect of EAT on the heart or heart vessels, or both. However, EAT adds negligible explanatory power to standard CV disease risk factors.

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