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Fully automated epicardial adipose tissue volume quantification with deep learning and relationship with CAC score and micro/macrovascular complications in people living with type 2 diabetes: the multicenter EPIDIAB study

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Abstract

Background The aim of this study (EPIDIAB) was to assess the relationship between epicardial adipose tissue (EAT) and the micro and macrovascular complications (MVC) of type 2 diabetes (T2D).

Methods EPIDIAB is a post hoc analysis from the AngioSafe T2D study, which is a multicentric study aimed at determining the safety of antihyperglycemic drugs on retina and including patients with T2D screened for diabetic retinopathy (DR) (n = 7200) and deeply phenotyped for MVC. Patients included who had undergone cardiac CT for CAC (Coronary Artery Calcium) scoring after inclusion (n = 1253) were tested with a validated deep learning segmentation pipeline for EAT volume quantification.

Results Median age of the study population was 61 [54;67], with a majority of men (57%) a median duration of the disease 11 years [5;18] and a mean HbA1c of7.8 ± 1.4%. EAT was significantly associated with all traditional CV risk factors. EAT volume significantly increased with chronic kidney disease (CKD vs no CKD: 87.8 [63.5;118.6] vs 82.7 mL [58.8;110.8], p = 0.008), coronary artery disease (CAD vs no CAD: 112.2 [82.7;133.3] vs 83.8 mL [59.4;112.1], p = 0.0004, peripheral arterial disease (PAD vs no PAD: 107 [76.2;141] vs 84.6 mL[59.2; 114], p = 0.0005 and elevated CAC score (> 100 vs < 100 AU: 96.8 mL [69.1;130] vs 77.9 mL [53.8;107.7], p < 0.0001). By contrast, EAT volume was neither associated with DR, nor with peripheral neuropathy. We further evidenced a subgroup of patients with high EAT

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volume and a null CAC score. Interestingly, this group were more likely to be composed of young women with a high BMI, a lower duration of T2D, a lower prevalence of microvascular complications, and a higher inflammatory profile.

Conclusions Fully-automated EAT volume quantification could provide useful information about the risk of both renal and macrovascular complications in T2D patients.

Article Highlights

Why did we undertake this study? What is the specific question(s) we wanted to answer?

This study addresses the unmet need to assess epicardial fat volume quantification in high-risk people living with type 2 diabetes using a fully-automated deep learning AI tool.

What did we find?

Fully automated epicardial fat volume quantification with cardiac CT performed for CAC scoring is possible and reliable in T2D.

Epicardial fat volume was associated with all cardiovascular risk factors, CKD and macrovascular complications but not with diabetic retinopathy or peripheral neuropathy.

We identified a subgroup of T2D patients with a null CAC score and high EAT volume which was characterized by a higher systemic proinflammatory profile.

What are the implications of our findings?

This study provides new insights for non-invasive deep phenotyping of patients living with type 2 diabetes with epicardial fat volume quantification using cardiac CT performed for CAC scoring, that could be used in clinical practice.

These findings set the stage for personalized medicine and prospective randomized trials testing new antihyperglycemic drugs that target inflammation.

Keywords Epicardial adipose tissue, Deep learning, Type 2 diabetes, Cardiac computed tomography, CAC score

Introduction

While it is now recognized that regional adiposity such as visceral adiposity is a stronger cardio-metabolic risk factor than overall obesity [1], the ability of the subcutaneous adipose tissue to expand with positive energy balance constitutes the main determinant of ectopic fat deposition in peripheral organs such as the heart [2, 3]. Epicardial adipose tissue (EAT) is a perivascular depot located between myocardium and the visceral pericardium [4]. EAT has unique properties that distinguish it from other depots of visceral fat, due to its unobstructed proximity to the myocardium and to the coronary arteries, allowing bidirectional paracrine or vasocrine crosstalk between adipocytes, cardiomyocytes and cells of the vascular wall [5]. An imbalance between cardioprotective and harmful adipokines secreted by epicardial fat has been linked to the development of coronary atherosclerosis in humans [6, 7].

Given its high metabolism, thermogenic capacity, unique transcriptome, secretory profile, and simply measurability, epicardial fat has drawn increasing attention in the recent years to help clinicians in evaluating individual cardiovascular risk and implementing precision medicine [8–10]. The quantity and the inflammation of this perivascular fat depot has been independently associated with major adverse cardiovascular events, incident myocardial infarction, all-cause mortality and cardiac mortality in high risk individuals [11–13]. We and others have evidenced that EAT is associated with the progression of coronary artery calcification and blunted coronary microvascular response, especially in young subjects and subjects with low coronary artery calcium (CAC) score measured by cardiac computed tomography (CCT), suggesting that EAT may promote early atherosclerosis development [14, 15]. Type 2 diabetes (T2D) has been consistently associated with an increase in EAT [11, 16]. Besides, a loss of transcriptomic brown-like fat features in EAT has been evidenced in people living with T2D [17], promoting a switch to a pro-atherogenic and a pro-arrhythmogenic profile [4, 18]. EAT is increasing being recognized as a determinant of vascular complications of metabolic diseases such as obesity or T2D [19]. However, manual quantification of EAT in clinical practice is time-consuming and requires important individual imaging data post processing treatment [20]. In this context, we developed a deep-learning-based quantification of epicardial adipose tissue volume using non-contrast CCT performed for CAC scoring [21], in a large sample of people living with T2D (n = 1253) and included in the Angiosafe T2D cohort. The aim of this study was to evaluate the relationship between EAT volume and the micro and macrovascular complications (MVC) of T2D.

Study population

The present study, named EPIDIAB study is a post-hoc analysis from AngioSafe T2D study, which is a bicentric 3-year longitudinal study (NCT02671864) aimed at determining the safety of antihyperglycemic drugs in

the retina and angiogenesis and described elsewhere [22]. The overall study plans to include 7200 people living with T2D at the Centre Universitaire du Diabète et de ses Complications, Lariboisière Hospital, APHP, Paris, or at the Endocrinology, Metabolic diseases and Nutrition department, Pole ENDO, APHM, Marseille, France and screened for diabetic retinopathy (DR) by retinal fundus photographs. The International classification of Diabetic Retinopathy [23] was used to perform DR staging. All consecutive T2D patients (≥18 years old) attending these two centers from June 2016 to March 2024 and who had undergone a non-contrast cardiac CT (=1253) performed for CAC (Coronary Artery Calcium) scoring were selected for the analysis. Exclusion criteria were pregnancy, Maturity-Onset Diabetes of the Youth (MODY), type 1 or pancreatic diabetes, dense cataract preventing DR grading, or patients with panretinal photocoagulation of a duration of 10 years or longer. All patients gave their written informed content before inclusion. The local ethics committee (Comité de protection des Personnes ILE DE FRANCE V) gave his agreement for this ancillary study (15.00261.015070-MS05), all the trial procedures were in compliance with the Declaration of Helsinki.

Data collection

Data were extracted from patients' medical records and collected in a secure health database.

Collected data included clinical characteristics (age, sex, waist circumference, body mass index, duration of diabetes), cardiovascular risk factors (hypertension, dyslipidemia, current tobacco consumption and pack-year smoking history, obesity defined as BMI≥30 kg/m^2). HbA1c (high performance liquid chromatography), total, low-density lipoprotein, and high-density lipoprotein cholesterol; triglycerides; aspartate aminotransferase (ASAT), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), urine albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease-Epidemiology Collaboration Equation), uric acid, high sensitive CRP, fibrinogen, brain natriuretic peptide (BNP) were assessed the day of inclusion.

Chronic kidney disease was defined as eGFR<60 mL/min/1.73 m^2 and/or UACR≥3 mg/mmoL). The kidney failure risk equation (KFRE) was applied to calculate the patient risk progression to kidney failure requiring dialysis or transplant at 5 years using calculator https://www.kidneyfailurerisk.co.uk/. Neuropathy was defined as any sign or symptom of polyneuropathy i.e. sensory signs (disruption of sensitivity to light touch e.g., cotton-wool and pinprick, monofilament, or to vibration with tuning fork) and/or symptoms (pain, cramps, numbness, paresthesia), and/or absence of at least one tendon reflex motor, and/or deficit or trophic disorders. The presence of macrovascular complications was defined according to the presence of a previous history of ischemic heart disease (including a history of myocardial infarction and/or coronary artery revascularization or heart failure), cerebrovascular disease (including history of stroke or transient ischemic attack (TIA)) and/or peripheral artery disease (amputation owing to ischemic disease and/or lower limb artery revascularization).

CT imaging and deep learning model automated segmentation of epicardial fat volume

CAC scores and EAT volumes were calculated using ECG-gated cardiac CT without contrast injection. CT scans were performed on several scanners (FRONTIER, REVO EVO, APEX; General Electric Healthcare, Buc, France). Coronary artery calcium score was quantified by the Agatston method on noncontrast cardiac CT scans using commercially available software (Aquarius Workstation® V.4.4.11–13, TeraRecon Inc, Foster City, CA, USA), in those patients with an indication for CAC score assessment.

For each patient, images were extracted from the picture archiving and communicating system and imported in the DICOM format on the validated post-processing software 3D Slicer (3D Slicer v4.11.20210226) [24].

To quantify the epicardial fat from a CCT scan, a deep learning segmentation pipeline, was first developed from low-dose computed tomography (LDCT) and validated in a cohort of 353 consecutive patients with COVID-19 and who underwent LDCT for lesions extension[21]. Then, in the EPIDIAB study, we trained and optimized the AI algorithm on cardiac CT already performed for CAC scoring in high-risk people living with type 2 diabetes and referred for diabetes care in the Assistance Publique Hôpitaux de Marseille (APHM) Endocrinology department. HRNet, the main backbone convolutional network, initially trained with 95 manually annotated patients (47,214 CCT slices), was fine-tuned with 65 additional T2D patients, randomly extracted from the Angiosafe T2D database (the target distribution), which gave a total of 160 training examples. To control model performance on the target distribution, i.e. real-world patients with T2D, a visual quality control was performed in 150 unseen CCT from the Angiosafe T2D cohort referred for CAC scoring. Finally, the deep learning pipeline was used to quantify the EAT volume of 300 unseen patients from Angiosafe Marseille and of 1000 other patients from Angiosafe Paris.

Briefly, manual segmentation had been performed slice by slice on the entire intrapericardial soft tissue volume by delineating the external border of the pericardium using thresholding, painting, and erasing methods. The superior and inferior limits of the pericardium were first identified as the top of the left atrium, and the lower

limit corresponded to the last slice in which the left ventricle was identified. Pericardial fat was excluded. The EAT tissue was then identified inside the intrapericardial volume by using the standard fat attenuation range as a threshold, from −190 Hounsfield units (HU) to −30 HU [25]. A post-processing with small connected region (<50 voxels) removal, morphological closing and median filter with a kernel size of 5, was finally applied on each slice. The obtained segmentation masks were all validated by one experienced chest radiologist (A.J., 25 years of experience).

Algorithm development was run on a Biprocessor Intel Xeon Silver 4216 2.1 GHz, RAM=96Go, 2 GPU Nvidia Quadro RTX5000, 16Go.

An example of automated machine segmentation of epicardial fat volume on anterior superior and inferior view is presented in Fig. 1.

Statistical analysis

Anthropometric and biological parameters were expressed as mean±SD or median [25th;75th percentile] according to the normality of the distribution and categorical variables as numbers (n) and percentages. The normal distribution of quantitative data was assessed using the Shapiro–Wilk normality test. Significant differences between groups "EAT volume>100 mL and CAC>100 AU" and "EAT>100 mL and CAC=0 AU" were determined using the Student's t-test or Mann–Whitney test where appropriate. The Chi-2 test was used to compare categorical variables between groups. Pearson's and/or Spearman's correlations were performed to identify the parameters associated with EAT. Multivariate analysis included all the parameters with at least 50% of data available and correlated with EAT volume in univariate analysis. In sub-group analyses, an EAT volume cut-off of 100 mL was chosen to identify patients with high EAT volume, as previously proposed [26]. Statistical analyses were performed with Prism 9 (Graphpad, MA, USA). A two-sided value of less than 0.05 was considered statistically significant. No data replacement procedure was used for missing data.

Results

EAT algorithm performance

The mean Dice coefficients for the automatic segmentation of all the pericardial and EAT volumes were 0.948±0.024 and 0.848±0.068, respectively. Mean acquisition time per patient was less than 2 min.

Study population

Among the 1300 patients living with T2D included in the Angiosafe DT2 cohort, who had had CCT for CAC scoring and who met study inclusion criteria with retinopathy grading, the validated algorithm was used. An EAT volume was obtained for 1253 patients. Their clinical

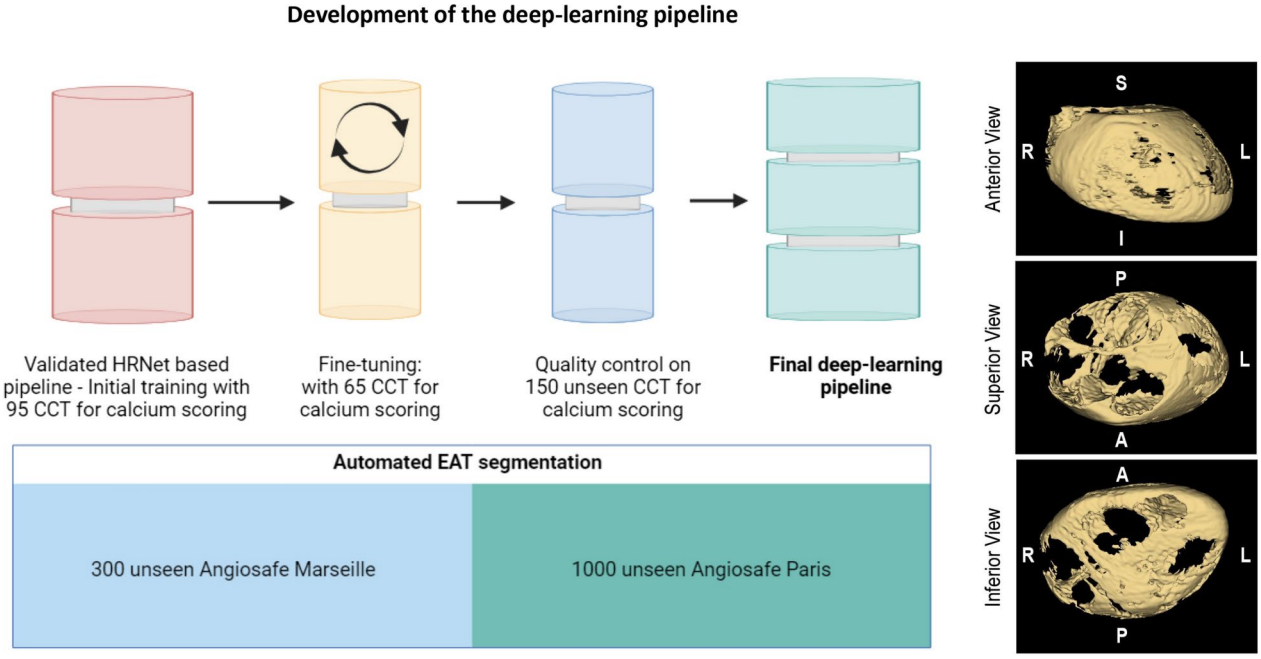

Fig. 1 Schematic representation of the scientific approach to the development of the deep-learning model Automated Segmentation of Epicardial adipose tissue within the Pericardium Schematic representation of the scientific approach to the development of the deep-learning model from LDCCT, to CCT used for CAC scoring. The development of the deep learning network model was performed through internal and external subgroups of the Angiosafe DT2 cohort, to validate a reliable application for the automated epicardial adipose tissue (EAT) volume quantification LDCCT low dose chest computed tomography CCT cardiac computed tomography

characteristics are depicted in Table 1 with n representing the number of available data.

The median age of the study population was 61 years old [54; 67], with a majority of men (57%), and a high number of people with cardiovascular risk factors: 42% lived with obesity; 63% had hypertension; 52% had dyslipidemia, 42% had ever smoked (14% of active smokers). The median duration of the disease was 11 years [5;18], with a mean HbA1c 7.8±1.4%. A majority of patients were treated with oral antihyperglycemic agents (86%), 24% were under GLP-1 receptor agonist treatment, 2% under SGLT-2 inhibitors and 34% were requiring insulin treatment.

Regarding microvascular complications, 27% had clinical symptoms of peripheral neuropathy, 35% had CKD, and 32% had DR: 201 with mild (16%), 85 with moderate (7%), 37 with severe non proliferative (3%) and 76 with proliferative DR or history of laser panphotocoagulation (6%).

Macrovascular complications were present in 11% of patients with 4% of coronary artery disease (CAD), 2% of cerebrovascular disease, and 5% of peripheral arterial disease (PAD) and were in secondary cardiovascular disease prevention. The median of CAC score was relatively low at 20 AU [0;198], with 430 patients with a CAC score at 0 AU (34%).

Table 1 Patients characteristics

Features	n	Median [25th;75th percentile] or n (%)
Epicardial adipose tissue (mL)	1253	85 [60;115]
Age (years)	1253	61 [54;67]
Sex (M, %)	1253	720 (57)
Diabetes duration (years)	1239	11 [5;18]
Hba1c (%)	1239	7.5 [6.8;8.4]
Body mass index (kg/m^2)	1215	28.7 [25.8;32.6]
Obesity (≥ 30 kg/m^2)	1215	505 (42)
Waist circumference (cm)	895	104 [95;113]
Hypertension	1252	795 (63)
Dyslipidemia	1242	652 (52)
Smoking exposure	1197	505 (42)
DT2 treatment		
- OADs	1253	1078 (86)
- GLP-1	1253	304 (24)
- i-SGLT2	1253	20 (2)
- Insulin	1253	423 (34)
Macroangiopathy	1226	108 (9)
Coronary artery disease	1224	48 (4)
Cerebrovascular disease	1249	22 (2)
Peripheral arterial occlusive disease	1094	52 (5)
Peripheral neuropathy	1108	300 (27)
Retinopathy (DR) (n,%)	1253	399 (32) ■ No DR: 854 ■ Mild NPDR: 201 ■ Moderate NPDR: 85 ■ Proliferative DR + laser: 76 ■ Severe NPDR: 37
CKD (GFR < 60 et/ou ACR > 3)	1240	429 (35)
Total Cholesterol (mg/dL)	1201	1.72 [1.49;2.02]
HDL-Chol (mg/dL)	1201	0.45 [0.38;0.53]
LDL-Chol (mg/dL)	1166	1.01 [0.79;1.22]
Triglycerides (mg/dL)	1204	1.22 [0.85;1.72]
ASAT (UI/L)	1192	25 [20;31]
ALAT (UI/L)	1197	25 [18;38]
Gamma GT (UI/L)	1196	31 [22;50]
Uric acid (µM)	1105	324.5 [273;383]
Troponin (ng/mL)	828	3 [3;4]
BNP (ng/L)	855	11.7 [10;27]
High sensitive CRP (mg/L)	862	2.1 [0.9;4.7]
Fibrinogen (g/L)	861	3.5 [3.0;4.0]
Coronary artery calcium score (CAC)	1247	20 [0;198]
Creatininemia (µM)	1169	70 [57.9;85]
Albuminuria (mg/L)	1211	12 [5;36]
Proteinuria (g/L)	1080	0.09 [0.07;0.15]
Creatininuria (mmol/L)	896	9.59 [5.78;14.00]
Albumin/creatinin ratio (ACR) (mg/mmol)	976	1.00 [0.53;2.82]
Protein/creatinin ratio (g/mmol)	698	0.010 [0.006;0.016]

Quantitative parameters associated with epicardial fat volume

EAT volume was positively associated with age, BMI, waist circumference, fasting plasma triglycerides, ALAT, GGT, uric acid, BNP, high sensitive CRP, fibrinogen, CAC score, serum creatinine, albuminuria, proteinuria and KFRE. It was negatively correlated with HDL, LDL cholesterol and GFR (CKD epi) (Supplementary Table 1).

EAT volume and CV risk factors in T2D

EAT volume was associated with all CV risk factors and was significantly higher in men than women (median 87.9 mL [62.4; 121.7] versus 78.7 mL [54.3; 107.4], respectively $p<0.0001$), in people living with obesity than without (97 mL [70.9; 126.8] 75.9 mL [53.7; 106], respectively, $p<0.0001$, hypertension (HTA) ("with HTA" 87.8 mL [62.6; 118.6] vs "without HTA" 76.6 mL [53.2; 105.1], smoking ("active smoking + past smoking < 3 years" 95.4 mL [68.6; 128.8], versus "non smokers and past smokers > 3 years" 77.6 mL [53.6; 105.4], $p<0.0001$), and higher in patients with dyslipidemia than without 88.0 mL [63.0; 116.7], versus 80.6 [55.8; 111.3], respectively $p=0.0011$ (Fig. 2A).

EAT volume and T2D complications

EAT volume was significantly higher in patients with CKD (yes 87.8 [63.5; 118.6]; no 82.7 mL [58.8; 110.8],

Table 1 (continued)

Features	n	Median [25th;75th percentile] or n (%)
GFR CKD epi (mL/min/1,73 m^2)	1199	93 [77.9;102.6]
KFRE (%)	964	0.003 [0.001;0.020]

OADs oral antidiabetic drugs; GLP-1 glucagon like peptide 1; i-SGLT2 sodium-glucose transporter 2 inhibitor; DR diabetic retinopathy; CKD chronic kidney disease; CAC Coronary artery calcium score; ACR Albumin/creatinin ratio; GFR glomerular filtration rate; CKD epi Chronic Kidney Disease Epidemiology Collaboration equation; KFRE kidney failure risk equation

p=0.008), with CAD (yes 112.2 [82.7; 133.3] vs no 83.8 [59.4; 112.1], p=0.0004), with PAD (yes 107 [76.2; 141] vs no 84.6 mL [59.2; 114], p=0.0005) and with high CAC score (CAC score>100 AU: 96.8 mL [69.1; 130] vs CAC score<100 AU: 77.9 mL [53.8; 107.7], p<0.0001) (Fig. 2).

By contrast, EAT volume was neither associated with DR status, nor with peripheral neuropathy (Fig. 2).

In multivariate analysis, EAT volume remained significantly associated with age, sex, waist circumference (but not BMI), ALAT, BNP, and fibrinogen (supplementary Table 1).

Characteristics of T2D patients with null CAC score and a relatively high EAT volume > 100 mL

Remarkably, we evidenced 48 T2D patients a high volume of EAT (median of the cohort 85 mL [60; 115] (Table 1) and a null CAC score. Interestingly, this group of T2D patients were more likely to be young women with a high BMI, a lower duration of the disease, a lower rate of microvascular complications (CKD and DR) and with a higher "low-grade" inflammatory profile, (ie. higher high-sensitive CRP and fibrinogen (Table 2).

Discussion

This study provides evidence in a large cohort of patients living with T2D and screened for diabetic retinopathy, that deep-learning fully-automated segmentation of epicardial fat volume is achievable, robust and reliable on cardiac CT performed for CAC scoring. Mean acquisition time was less than 2 min, with expert manual quantification high agreement, and a respectable Dice similarity coefficient compared to other studies [27, 28]. Second, we showed that epicardial adipose tissue volume increased with all CV risk factors, and with T2D micro and macrovascular complications (MCV) such as CAD, and PAD, but also CKD. However, EAT volume was not significantly associated with diabetic retinopathy and did not increase with the severity of DR. Finally, we report for the first time a group of patients living with T2D and with a null CAC score, who have significant epicardial fat accumulation associated with a low-grade inflammatory profile, but less microvascular complications. These findings could potentially indicate that these patients might be at risk of CV events independently of their subclinical coronary atherosclerosis, and could take benefit from treatments that target inflammation, to improve cardiovascular prognosis. In the ORFAN study including more than 40 000 individuals (18.2% living with diabetes), EAT inflammation quantification using artificial intelligence risk model has been recently shown to exceed traditional risk factor-based risk calculators to predict major adverse cardiac events (MACE) and cardiac mortality in patients without obstructive CAD, suggesting that this parameter could be a critical point to take into account in clinical practice to better phenotype patients living with T2D [13].

Epicardial adipose tissue is a unique ectopic fat depot located in direct contact with myocardium and coronary arteries, with a distinctive transcriptome, proteome and immune cells such as innate lymphoid cells (ILCs), essential effectors of innate immunity via the rapid production of both proinflammatory and regulatory cytokines that infiltrate epicardial adipocytes and could modulate its inflammatory/beiging phenotype [8, 29] compared to other adipose tissues. We recently evidenced a positive correlation between the T helper cell subtype Th2 immune pathway and browning genes in human EAT versus thoracic subcutaneous adipose tissue [29]. Gene expression phenotyping confirmed specific upregulation of Th2 pathway and browning genes (IL-33 and uncoupling protein 1 [UCP-1]) in EAT, whereas ILC1was the most prevalent type of ILCs in all adipose tissues [29]. Accumulation of adipose ILC1s can trigger an increase local inflammation and systemic insulin resistance and is strongly associated with glucose homeostasis in humans, such as glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), homoeostasis model assessment for insulin resistance (HOMA-IR), adipose tissue insulin resistance index (Adipo-IR) and serum free fatty acids (FFAs) [30]. An imbalance between proinflammatory/beiging phenotype has been observed in patients with T2D and multivessel disease with a decrease of PGC1α, and UCP1 mRNA expression in EAT of patients with CAD compared to patients non diabetics with CAD or with patients with no CAD disease [17].

Recent research in the field of cardiometabolic diseases shows that scientists and clinicians should take a step back from BMI-centric, to organ-specific adiposity and that EAT could become a therapeutic target for drugs inducing significant weight-loss, decreasing inflammation and providing cardiovascular or renal benefits [4, 19]. A recent real-world study using multi-organ quantitative multiparametric MRI from Diamond et al., demonstrated a high burden of combined steatosis and fibro-inflammation, within the liver, pancreas and kidneys associated with visceral adiposity and poor vascular health in patients with T2D [31]. Unfortunately, EAT was not evaluated in this study. But this highlights

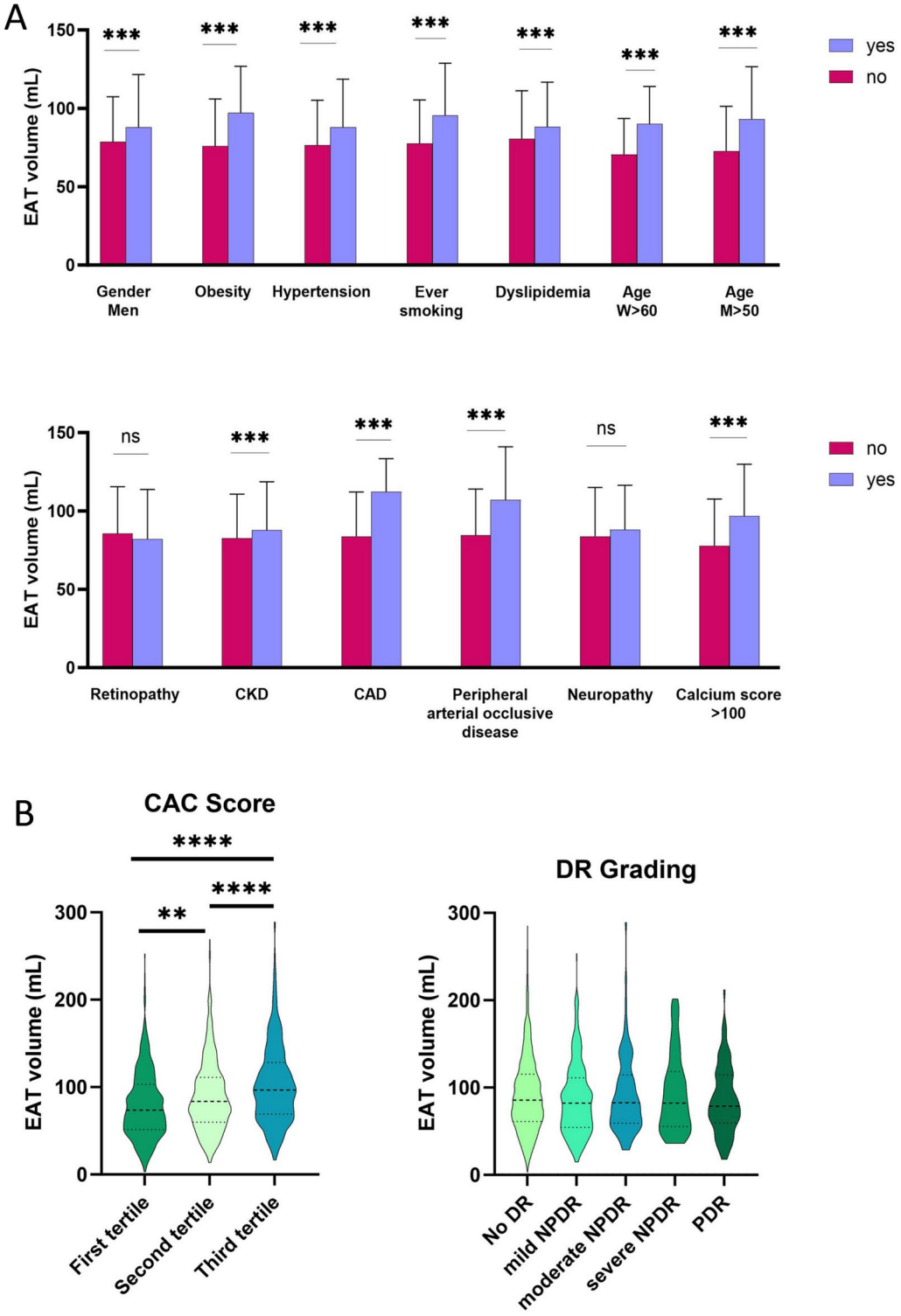

Fig. 2 **A** Association deep-learning model Automated Segmentation of EAT volume with cardiovascular risk factors. W: women M: men ***$p < 0.0001$. **B** EAT volume relationship with CAC score represented by tertiles and diabetic retinopathy status assessed by retinophotography. DR diabetic retinopathy; NPDR non proliferative diabetic retinopathy; PDR proliferative diabetic retinopathy

Table 2 Comparison of clinical and biological characteristics of T2D patients with null CAC score and a relatively high EAT volume > 100 mL and patients with EAT > 100 mL and CAC > 100

Features	EAT volume > 100 and CAC > 100 (n = 233)	EAT > 100 and CAC = 0 (n = 112)	p value
Gender (M, n, %)	159 (68)	54 (48)	**0.0004**
Age (years)	64.8 ± 8.2	57.5 ± 9.5	**< 0.0001**
Diabetes duration (years)	16 [10;22]	8.5 [4.3;12.8]	**< 0.0001**
HbA1c (%)	7.7 [7;8.4]	7.2 [6.5;8.3]	**0.0298**
Insulin treatment	92 (39)	32 (29)	0.0553
Dyslipidemia	153 (66)	46 (41)	**< 0.0001**
Body mass index	28 [24.9;30.5]	31.6 [27.6;34.9]	**< 0.0001**
Hypertension	176 (76)	65 (58)	**0.0011**
Ever smokers	104 (45)	46 (41)	0.5632
Total Cholesterol	1.66 [1.44;1.99]	1.72 [1.49;1.99]	0.2025
HDL-Chol (g/L)	0.43 [0.36;0.50]	0.45 [0.37;0.51]	0.6517
LDL-Chol (g/L)	0.93 [0.75;1.17]	1.01 [0.79;1.18]	0.2709
Triglycerides (g/L)	1.25 [0.84;1.72]	1.33 [0.44;1.93]	0.0574
ASAT (UI/L)	25 [21;31]	24 [19;30]	0.2071
ALAT (UI/L)	24 [17;37]	25 [19;42]	0.8426
Gamma GT (UI/L)	31 [21;47]	33 [22;52]	0.2556
hs CRP (mg/L)	1.63 [0.75;3.40]	3.2 [1.47;6.41]	**< 0.0001**
Fibrinogen (g/L)	3.41 [3.00;4.03]	3.59 [3.13;4.21]	**0.04**
Creatininemia (µM)	73 [62;89]	65.8 [55;78]	**0.0001**
Macroangiopathy	23 (10)	10 (9)	0.8473
Coronary artery disease	14 (6)	2 (2)	0.1024
Peripheral arterial occlusive disease	7 (3)	6 (5)	0.3650
CKD (GFR < 60 ou ACR > 3)	71 (30)	14 (13)	**0.0003**
Diabetic retinopathy	97 (42)	16 (14)	**< 0.0001**

Bold in p value for statistical significance p<0.05

the renewing interest in multi-parametric non-invasive imaging and the importance of taking into account organ specific adiposity in evaluating the risk of lipotoxic organ dysfunction. In our study, we quantified both CAC score and EAT and showed that some patients with a null CAC score could have increased EAT, implicating that EAT is not only a surrogate of atherosclerosis. Furthermore, these patients had a systemic low grade inflammation profile with a two-fold higher hs CRP than patients with a CAC score and EAT > 100. Some researchers make the hypothesis that key features of T2D such as insulin resistance, decreased insulin secretion and glycosuria are primarily mechanisms that could protect against overnutrition by preventing the accumulation and overloading of tissues with cell nutrients [32]. If these mechanisms are exceeded, damaging innate immune activation occurs, resulting in the mounting of the proinflammatory cytokine network [32]. Recent large outcome studies such as CANTOS trial showed that newly developed IL-1β- blocking antibodies can reduce cardiovascular complications in patients with metabolic syndrome and high CRP levels [33]. Besides, statins have been shown to reduce EAT volume and EAT Hounsfield units [HUs] attenuation on computed tomography which is considered as a marker/proxy of pericoronary inflammation, as evidenced by Raggi et al., in a cohort of 420 postmenopausal women, randomized to either 80 mg of atorvastatine or 40 mg pravastatin daily, and rescanned after one year [34]. Remarkably, this EAT HU decrease was independent of lipid lowering and change in LDL cholesterol, suggesting a possible pleiotropic effect of this lipid-lowering drug [34].

The paracrine effects of EAT, particularly on vascular tone and vascular inflammation, are significantly altered in metabolic diseases such as T2D. With weight gain, EAT loses its ability to affect insulin-induced vasodilatation and to antagonize sympathetic tone, predominately due to impaired adiponectin secretion [35]. The aortic perivascular adipose tissue EAT, under diabetic conditions, shifts towards a pro-inflammatory (increment in CRP, chemokine (C–C motif) ligand 2, CD36), pro-oxidant (increased aldose reductase and reduced anti-oxidant deference enzymes), and vasoconstriction state [36]. Targeting EAT inflammatory phenotype using new radiotranscriptomics analysis such as the fat attenuation index could represent in the next future, a way to personalize antidiabetic medications and decrease the CV and renal risk [19].

In our study, we found that EAT volume was not associated with diabetic retinopathy (DR). Cosson et al., reported a lower EAT volume in patients living with diabetes complicated with diabetic retinopathy compared to patients without DR and who had a CCT with EAT volume and CAC score quantification using the automated software package AW VolumeShare7 [37, 38]. One explanation regarding these discrepancy results could be that this study included also type 1 diabetic patients, and patients with another type of diabetes, who have less ectopic fat deposition and prevalence of obesity than patients living with T2D. One strength of our study is that we evaluated all the stages of DR, and we observed that patients with severe non proliferative or with proliferative DR, EAT volume was not different from patients with less severe stages of DR, suggesting that ectopic fat in the heart is not associated with retinal microvascular damage. But further longitudinal studies are warranted to determine whether epicardial fat could participate in the appearance or in the progression of DR and longitudinal follow-up of Angiosafe-DT2 at 3 years will probably help to answer this still open question.

Our study has several limitations. First, its observational design prevented us from being able to draw definite conclusions about causal relationships between EAT

volume and T2D micro or macrovascular complications. Second, we included patients screened for DR and who had a cardiac CT for CAC scoring, only 4% had CAD disease. Therefore, our results may not be representative of all diabetic patients, such as type 1 diabetic patients, or for patients in secondary CV prevention. Third we explored global but not regional EAT, and EAT volume but not its density, which could have provided more information on EAT inflammatory phenotype [8, 39–42]. However, Christensen et al. has already evidenced in 1030 patients with T2D that a high level of EAT measured with echocardiography was associated with the composite endpoint of incident cardiovascular disease and mortality, even after adjusting for CV risk factors and particularly in men [43]. Finally, radiation exposure was one of the limitation of EAT volume quantification with CT compared to cardiac transthoracic echography and/or MRI. However, no additional radiation was done for the EPIDIAB study, as the EAT volume quantification was performed on cardiac CT already performed for CAC scoring as part of the clinical care of patients.

Conclusion

We showed in a well phenotyped cohort of patients living with T2D that fully automated segmentation of epicardial fat volume is achievable, robust and reliable on cardiac CT performed for CAC scoring with a short acquisition time. This non-invasive multi-parametric imaging could be used in clinical practice to quantify ectopic fat in the heart and contribute to personalized medicine. Besides, EAT volume was significantly associated with all CV risk factors, and increased with CAC score and diabetes complications such as CAD, PAD, and CKD. EAT volume was not associated with DR and peripheral neuropathy. We identified a group of patients with a null CAC score and a high EAT volume with a high systemic inflammatory profile which could benefit from treatments targeting immune system or decreasing inflammation.

Supplementary Information

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Supplementary material 1

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Author contributions

BG, JBJ, AD, AJ, JFG contributed to the conception; BG, PA, PD, NR participated in the design of the work; BG, JBJ, AS, CD, AL, MH, PG, MR, FM, LP, JFG, AD, PD, FM participated in the inclusion of patients; JBJ, PA, MH, NV, LP, JFG, NR contributed to the acquisition, analysis or interpretation of data; JF, BGh, AB and AJ created the AI software used in the work; BG and PA drafted the work and prepared figures; JBJ, NV, JFG,LP,NR, AJ, FM substantively revised it AND all the authors have approved the submitted version.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Data access and responsibility

BG is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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