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Article

Association of Epicardial Adipose Tissue With Novel Inflammation and Heart Failure Biomarkers in Type 2 Diabetes Patients: Effect of Metabolic Control

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Abstract: Background: Type 2 diabetes (T2D patients) have a 74% increased risk of heart failure (HF) but traditional HF biomarkers lack sensitivity in early disease detection. Increased epicardial adipose tissue volume (EATv) is associated with cardiovascular risk in T2D, and novel biomarkers such as, Growth differentiation factor 15 (GDF15), Galectin-3, and soluble suppression of tumorigenicity 2 (sST2) are inflammatory biomarkers linked to HF. **Methods**: we investigated associations between EATv, and inflammation biomarkers, and the effect of metabolic control in 14 healthy controls (HC) and 36 newly diagnosed T2D patients before (PGC) and after 12-months of metabolic optimization (GGC). EATv indexed to body surface area (iEATv) was quantified by multidetector computed tomography, and biomarker levels measured by immunoassays. **Results**: PGC patients had higher iEATv (59.53±21.67 vs. 36.84±16.57 cm^3/m^2, $p=0.0017$) and elevated GDF15, Galectin-3, and sST2 (all $p<0.05$) than HC. The metabolic optimization reduced iEATv ($p=0.0232$) and sST2 ($p=0.048$), while GDF15 and Galectin-3 remained unchanged. Multivariable analysis confirmed independent associations between iEATv, GDF15 ($\beta = 0.27$, $p = 0.027$) and sST2 ($\beta = 0.29$, $p = 0.02$). **Conclusions**: these results support the link between systemic inflammation, EAT expansion, and cardiac dysfunction, and the role of adiposity in the early HF risk of T2D patients.

Keywords: epicardial adipose tissue (EAT); type 2 diabetes (T2D); cardiovascular risk; heart failure (HF); inflammatory biomarkers; GDF15; Galectin-3; sST2; metabolic control (MC)

1. Introduction

Patients with T2D exhibit a twofold increased risk of developing heart failure (HF), regardless of traditional cardiovascular risk factors [1–3]. This heightened risk is attributed to a combination of insulin resistance (IR), oxidative stress, and low-grade chronic inflammation, which contribute to vascular dysfunction, myocardial remodeling and fibrosis [4–6].

Among the metabolic alterations observed in T2D, visceral adipose tissue (VAT), particularly epicardial adipose tissue (EAT), has gained attention as a key modulator of cardiovascular risk [7–9]. EAT, located between the myocardium and pericardium, functions as an active endocrine organ, releasing inflammatory cytokines, adipokines, and profibrotic mediators that may contribute to myocardial fibrosis, diastolic dysfunction, and HF progression [10–12]. Notably, increased EAT volume (EATv) has been associated with HF with preserved ejection fraction (HFpEF), the most prevalent form of HF in T2D [13–15].

While natriuretic peptides (NPs) remain the gold standard for HF diagnosis, their predictive accuracy in HFpEF is limited [16,17]. Thus, there is an urgent need for alternative biomarkers to aid in the early identification of cardiovascular high-risk T2D patients. Growth differentiation factor 15 (GDF15), Galectin-3, and soluble suppression of tumorigenicity 2 (sST2) have emerged as potential novel HF-related biomarkers, given their roles in fibrosis, myocardial stress, and systemic inflammation [18–20].

Given the interplay between EAT, metabolic dysregulation, and inflammatory biomarkers, this study aims to investigate the association between EATv, and novel biomarkers related with inflammation and HF (GDF15, Galectin-3, and sST2) in newly diagnosed T2D patients, as well as determine the effect of metabolic optimization on this association.

2. Materials and Methods

2.1. Study Population

A longitudinal prospective single-center observational cohort study was conducted with 36 newly diagnosed type 2 diabetes (T2D) and 14 age- and sex- matched healthy control participants (HC). . Patients were recruited between 2017 and 2020 and controlled at the Endocrinology and Nutrition Department of Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). . The inclusion criteria included: patients older than 18 years, without previous hypoglycemic, lipid-lowering, anti-inflammatory pharmacology treatment, estimated glomerular filtration rate (eGFR) > 60mL/min/1.73m^2) and heart function. The HC group were normolipidemic and normoglycemic individuals, without major risk factors of CVD, and no family history of premature coronary or inflammatory disease. The patients with T2D were studied at diagnosis (poor glycemic control group-PGC-) and after 12 months of metabolic optimization (good glycemic control-GGC-). All patients received a structured program of lifestyle changing, physical activity and pharmacology therapy based on clinical guidelines recommendations The initial pharmacological therapy included metformin, dipeptidyl peptidase inhibitors (DPP4i) and basal insulin in 90% of patients. Basal insulin was suspended after 2 weeks, and non-insulin pharmaceutical treatment was modified based on individualized characteristics of the patients. Neither of the patients was under heart failure-specific therapy. Anthropometric and clinical characteristics, hypoglycemic treatment and biochemical profile of all subjects at baseline and 12 months after follow-up are shown in Supplementary Table 1. At study completion, 30 T2D patients were treated with metformin and 33 with empagliflozin. Additionally, 4 patients were on DPP-4i and 2 received GLP-1 receptor agonists (GLP1-RA), in accordance with current diabetes management guidelines. Notably, no participants received statins or antiplatelet therapy during the study period. These clinical and biochemical data for this cohort were published at Rives et al. [21]. The study was approved by the Ethics Committee of the Hospital de

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Sant Pau (IIBSP-REL-2017-27). Written informed consent was obtained from all participants. This study was performed in full compliance with the Declaration of Helsinki.

2.2. Laboratory Analysis

Blood samples were collected using Vacutainer™ tubes (Becton Dickinson, NJ, USA) with serum and plasma processed in additive-free or EDTA-containing tubes. Serum and plasma were obtained by centrifugation for 15 min at 1500 g at room temperature. A complete profile, included glucose, glycated hemoglobin A1c (HbA1c), C-peptide, total bilirubin, liver function (gamma glutamyl transferase [GGT], aspartate aminotransferase [AST], alanine transaminase [ALT], and alkaline phosphatase [ALP]), high sensitivity C-reactive protein (hsCRP), and lipid profile (cholesterol, triglycerides, VLDLc, LDLc, HDLc, and Lp(a)), was performed on all individuals, as previously described [21]. As specific markers related with the presence of HF, high-sensitive troponin T (hsTnT), N-terminal pro B-type natriuretic (NT-proBNP), GDF15, Gal-3 and sST2 levels were determined. hsTnT, NT-proBNP and GDF15 were quantified by electrochemiluminescence immunoassays in a Cobas e601 autoanalyzer (Roche Diagnostics, Basel, Switzerland). Galectin-3 was determined by chemiluminescence immunoassay in an Alinity Ci autoanalyzer (Abbott, Chicago, IL, USA). sST2 was measured by immunoturbidimetry (Critical Diagnostics, San Diego, CA, USA) in a Cobas e601 autoanalyzer (Roche Diagnostics). Inflammatory biomarkers, which included IL6, TNFα, IL1β, leptin, adiponectin and resistin, were measured using a Luminex system with xMAP® technology (MILLIPLEX® MAP multiplexed assay kit, Millipore).

2.3. Image Analysis

EAT volume was measured by unenhanced scan acquired with a 256-slice multidetector computed tomography (MDCT) scanner (Brilliance iCT 256-slice, Philips Healthcare). This scan was triggered at 75% of the RR interval using from 100 to 120 kV (120 kV in patients with a body mass index > 30 kg/m2). After that, MDCT studies were analyzed in an off-line workstation. The methodology to calculate EAT was done with dedicated software (OsiriX MD, v 6.5, FDA cleared, Pixmeo) as follows: first, the upper and lower slice limits of pericardium were manually defined using axial views. Then, EAT was marked in each slice by drawing regions of interest with voxel density between −150 to −30 Hounsfield units (corresponding to adipose tissue). After that, a contiguous 3-dimensional volume render (showing EAT volume) was performed and quantified in cubic centimeters (cm^3) as well as indexed to body surface area (iEAT, cm^3/m^2). To ensure measurement accuracy, inter-rater variability, and measurements were independently analyzed by experienced cardiologist. Cardiac MRI, used to assess LVEF, was performed as described [16,21].

2.4. Statistical analysis

The descriptive statistics were used to represent the study populations, and data were expressed as the mean ± SD or median ± IQR for continuous variables and as frequencies (percentages) for categorical variables. The normality of numerical data distribution was verified using the Shapiro-Wilk test. A bivariate analysis was used for paired data, the analysis was validated using a non-parametric approach. Relationships between HF and inflammatory biomarkers, and iEATv were assessed using Spearman correlation analysis. Significant variables associated with iEAT in the correlation analysis were included in the forward stepwise multivariable linear regression analysis. Regression models were adjusted for potential confounders, including age, BMI, renal function, and glycemic control. Collinearity among independent variables was assessed using the variance inflation factor (VIF) < 5 (Table 2). A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software packages IBM-SPSS 27.0, and GraphPad Prism Software 9.

3. Results

3.1. Clinical Characteristics

This is the same cohort studied in Ribes et al, [21] and clinical characteristics and biochemical profile can be found in that study. However, to facilitate the reading of this study, we have included this same data as a Supplementary Table 1. Briefly, compared with HC, T2D diabetic patients at diagnosis (poor glycemic control group-PGC-) had greater BMI, higher levels of the parameters of hepatic function and systemic inflammation (hsCRP), and marked alterations in the lipid profile. After a 12-month follow-up, HbA1c decreased from 11.7 ± 2.1 to 6.1 (0.77) % (p= <0.05) and BMI from 33.53 ± 7.27 to 31.87 ± 5.59 kg/m^2 (p=<0.05) in T2D patients with good glycemic control group (GGC). This improvement in metabolic optimization, although improved, did not normalize most parameters compared with HC.

3.2. iEAT Volume and Left Ventricular Function

A significant difference in iEATv was observed between the groups. iEATv in the PGC group was higher than in HC (59.53 ± 21.67 vs 36.84 ± 16.57 cm/m^2; p = 0.0017). In TD2 group, iEATv decreased after metabolic optimization (59.53 ± 21.67 vs 54.59 ± 18.76 cm/m2; p = 0.0232), but remains higher than in the HC group (54.59 ±18.76 vs 36.84 ± 16.57 cm/m^2; p = 0.007). Although LVEF was within the normal range in T2D patients in PGC (58.80 ± 4.45%) and did not differ from that of HCs (61.39 ± 5.53%), there was a slight improvement in LEVF in T2D after metabolic optimization (65.61 ± 6.18%; p = 0.0257). As we mentioned before, these results have been previously published [21]. Furthermore, PGC group had significantly higher end-systolic volume (ESV) compared to those with GGC (36.16 ± 19.27 mL/m^2 vs. 29.80 ± 16.83 mL/m^2, p= 0.024), while end-diastolic volume (EDV) did not differ significantly (81.21 ± 22.80 vs. 74.87 ± 20.46 mL/m^2, p= ns).

3.3. Biomarkers of Inflammation

Plasma levels of inflammation-related biomarkers, including IL6, TNFα adiponectin and resistin, are altered in the PGC group compared with HC group. The improvement of metabolic control significantly decreased IL1β, IL6 and resistin levels, but remained higher than in controls (Figure 1).

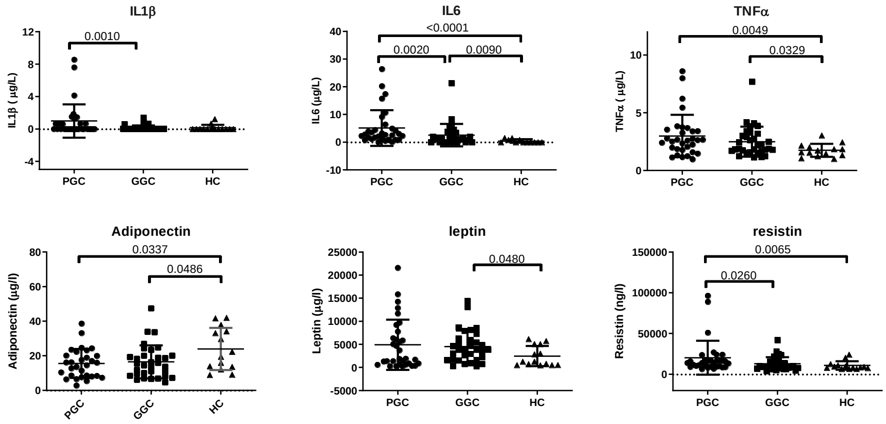

Figure 1. Scatter plots of inflammatory markers. Inflammatory parameters were determined using a Luminex system with xMAP® technology, as described in the Methods section. HC: healthy controls; PGC: T2D patients with poor glycemic control; GGC: T2D patients with good glycemic control. The horizontal bar indicates statistically significant differences. Data are expressed as mean ± SD.

The most relevant correlations of inflammatory biomarkers are shown in Table 1. As a summary, inflammation markers correlated with weight-related, glycemia-related, HDLc and liver function parameters, but only TNFα showed correlations with iEATv and cardiac function (LVEF).

Table 1. Statistically significant correlations of inflammation markers with clinical and laboratory parameters using the Spearman's rank correlation coefficient**.**

Spearman's rank correlation coefficient test			
		r	p
IL1β	HbA1c	0.295	0.006
	hsCRP	0.259	0.013
	AST	0.272	0.010
	LVEF	-0.293	0.029
	Tg	-0.250	0.016
IL6	BMI	0.247	0.015
	AW	0.252	0.016
	HbA1c	0.339	0.002
	hsCRP	0.563	< 0.001
	AST	0.304	0.004
	HDL-c	- 0.235	0.022
TNFα	AW	0.208	0.038
	HbA1c	0.268	0.012
	hsCRP	0.342	0.002
	AST	0.261	0.013
	ALT	0.232	0.023
	ALP	0.258	0.013
	iEATv	0.242	0.021
	LVEF	-0.263	0.025
	HDL-c	-0.373	<0.001
Adiponectin	Age	0.192	0.046
	ALT	-0.439	<0.001
	GGT	-0.333	0.002
	Tg	-0.259	0.013
	HDL-c	0.328	0.002
	VLDL-c	-0.241	0.020
Leptin	Weight	0.468	<0.001
	BMI	0.653	< 0.001
	AW	0.553	< 0.001
	ALT	0.243	0.018
	hsCRP	0.310	0.004
Resistin	BMI	0.258	0.012
	AW	0.251	0.016
	HbA1c	0.268	0.012
	hsCRP	0.298	0.005

3.4. Multivariate Analysis of EAT and Inflammatory Biomarkers

Given these significant correlations, we conducted a multivariate analysis to determine whether EAT were independently associated to inflammatory biomarker levels. However, after adjusting for metabolic and cardiovascular variables, no independent associations were found (data not shown).

3.5. Novel HF-Related Biomarkers

Traditional markers for the diagnosis of HF such as LVEF, NT-proBNP and hsTnT were not significantly different between groups. These data have been previously published [21] and indicate that there was no evidence of overt HF in these patients.

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Regarding novel inflammation and HF-related biomarkers, increased plasma levels were observed in T2D patients, compared to HC, in both PGC and GCG groups (Figure 2). Metabolic optimization significantly reduced plasma sST2 levels.

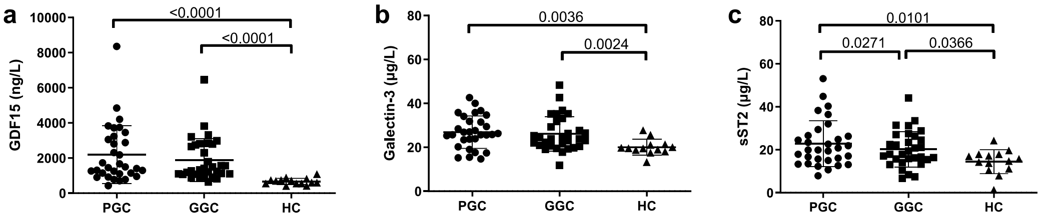

Figure 2. Scatter plots of HF-related markers. a) GDF15, b) Galectin-3, and c) sST2. Markers were determined by commercial methods in autoanalyzer, as described in the Methods section. HC: healthy controls; PGC: T2D patients with poor glycemic control; GGC: T2D patients with good glycemic control. The horizontal bar indicates statistically significant differences. Data are expressed as mean ± SD.

Spearman's rank correlation analysis revealed that GDF15, Galectin-3, and sST2 were positively correlated with age, HbA1c, AW, and BMI. In addition, iEATv showed positive correlations with GDF15, sST2, and TNFα. GDF15 and Galectin-3 were also positively correlated with IL6 and hsCRP. All three novel biomarkers correlated positively with liver function tests. Conversely, GDF15 demonstrated negative correlations with HDL-c, LDL-c, and TC, while sST2 was negatively correlated with LVEF. The correlations between all parameters are shown in the Table 2.

Table 2. Statistically significant correlations of GDF15, Galectin-3 and sST2 with clinical and laboratory parameters using the Spearman's rank correlation coefficient**.**

Spearman's rank correlation coefficient test							
		GDF15		Galectin-3		sST2	
		r	p	r	p	r	p
Clinical	Age	0.56	<0.0001	0.26	0.022	1	1
	BMI	0.23	0.04	0.27	0.02	0.28	0.015
	Weight	0.18	0.10	0.09	0.41	0.35	0.002
	AW	0.27	0.028	0.25	0.034	0.31	0.009
Biochemical	HbA1c	0.35	0.002	0.27	0.026	0.26	0.029
	Glucose	0.31	0.006	0.23	0.053	0.37	0.001
	ALP	0.29	0.010	0.25	0.033	0.14	0.22
	GGT	0.27	0.020	-0.92	0.44	0.24	0.04
	HDL-c	-0.46	<0.001	-0.19	0.11	-0.19	0.10
	LDL-c	-0.28	0.016	-0.24	0.84	-0.50	0.67
Inflammation	hsCRP	0.31	0.008	0.27	0.02	0.09	0.42
	TNFα	0.37	<0.001	0.052	0.66	0.097	0.40
	IL6	0.25	0.02	0.27	0.02	-0.058	0.61
Cardiac Parameters	iEAT	0.52	<0.001	0.19	0.11	0.37	<0.001
	LVEF	0.055	0.68	0.19	0.16	-0.30	0.025

3.6. EAT and Novel HF-Related Biomarkers

Beyond traditional inflammatory markers, we explored the relationship between EAT and novel HF-related biomarkers. To determine the parameters independently associated with GDF15,

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Galectin-3, and sST2, we performed a *stepwise multivariable analysis*, adjusting for hypoglycemic therapy. Classical variables included in the model were age, BMI, AW, sex, HbA1c, and NT-ProBNP. Additionally, iEAT and inflammation-related parameters that showed significant correlations with each biomarker were sequentially added. This analysis showed that iEATv is independently associated with GDF15 and sST2 levels. In addition, age was associated with the GDF15. On the other hand, hsCRP was the only variable associated with the values of Galectin-3. To summarize, this analysis showed that GDF15 and sST2 are closely related with iEAT, that is with visceral adiposity, whereas Galectin-3 depends mainly on hsCRP, that is with systemic inflammation (Table 3).

Table 3. Multivariable lineal regression analysis (stepwise) for GDF15, Galectin-3 and sST2 with clinical and laboratory parameters.

Multivariable lineal regression analysis (stepwise)										
Model		Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
GDF15										
1	(Constant)	-2623.37	1039.69		-2.52	0.014	-4701.70	-545.05		
	Age	80.60	18.40	0.48	4.38	0.001	43.82	117.38	1.00	1.00
2	(Constant)	-2520.87	1007.47		-2.50	0,015	-4535.44	-506.31	0.79	1.25
	Age	60.03	19.98	0.36	3	0,004	20.08	99.98	0.79	1.25
	iEAT	19.41	8.54	0.27	2.27	0,027	2.32	36.51		
Galectin-3										
1	(Constant)	20.57	2.36		8.70	0,001	15.85	25.30		
	HbA1c	0.64	0.26	0.297	2.42	0.01	0.11	1.17	1.00	1.00
2	(Constant)	20.90	2.25		9,.7	0.001	16.40	25.41		
	HbA1c	0.32	0.28	0.14	1,.5	0.25	-0.23	0.88	0.81	1.22
	hsCRP	0.44	0.16	0.34	2.69	0.009	0.11	0.77	0.81	1.22
sST2										
1	(Constant)	12.91	3.61		3.57	<0.01	5.67	20.14		
	HbA1c	0.90	0.40	0.28	2.21	0.031	0.08	1.72	1.00	1.00
2	(Constant)	-7.06	9.27		-0.76	0.44	-25.64	11.50		
	HbA1c	0.74	0.40	0.23	1.84	0.07	-0.063	1.54	0.96	1.03
	AW	0.19	0.08	0.28	2.32	0.024	0.027	0.37	0.96	1.03
3	(Constant)	-5.27	8.99		-0.58	0.56	-23.29	12.74		
	HbA1c	0.56	0.39	0.17	1.42	0.16	-0.22	1.35	0.92	1.07
	AW	0.12	0.08	0.18	1.43	0.15	-0.05	0.30	0.84	1.18
	iEAT	0.14	0.06	0.29	2.24	0.02	0.01	0.26	0.81	1.22
Non-significant variables from the model were: age, sex, AW, BMI, Hba1c and NT-ProBNP										

4. Discussion

In the present study, we found that newly diagnosed T2D patients had significantly higher EATv compared to controls, and that the improvement of glycemic control and weight loss allowed a significant reduction of iEATv. On the other hand, GDF15, Galectin-3, and sST2 were elevated in T2D, even in the absence of significant differences in LVEF, NT-proBNP, and hsTnT levels, which are classical markers of overt HF, and in a multivariate regression analysis iEATv was independently associated with GDF15 and sST2. These results support the potential role of adiposity in the early HF risk of T2D patients T2D patients have a 74% increased risk of HF, with HFpEF being the most underdiagnosed form [1,8]. In Spain, the DIABET-IC study reported a 39.2% prevalence of HF in T2D patients, with 30.6% attributed to HFpEF [15]. Therefore, identify a risk marker that could be used in both clinical and nonclinical settings to early risk identification of cardiovascular and HF risk of T2D patients is critical. In our study, in absence of significant alterations in LVEF, EDV, and classical markers of HF, improvement of glycemic control and weight loss increased LVEF and reduced ESV but did not significantly reduce EDV. These findings suggest that systolic function, as reflected by ESV and LVEF, may be more responsive to metabolic optimization than diastolic function, which are often more resistant to short-term interventions [22,23]. Identifying biomarkers and early metabolic disturbances associated with the development of HF may be critical for preventing and treating HF early in the type 2 diabetes population.

Currently, NT-ProBNP and BNP are the recommended biomarkers for HF diagnosis, but they have limitations in detecting early HF, particularly in obese patients [16,17]. As a result, novel biomarkers have been proposed for HF risk stratification [17]. GDF15, Galectin-3, and sST2 play distinct roles in HF pathophysiology. Galectin-3 promotes fibrosis and myocardial remodeling, correlating with HFpEF severity and cardiovascular mortality [19,24]. sST2, a soluble receptor for interleukin-33 (IL-33), is secreted in response to myocardial stress, promoting remodeling and apoptosis [17,25,26]. GDF15, secreted in response to ischemic and inflammatory stress, has been linked to poor prognosis in acute and chronic HF [27] . In our study, these biomarkers remained elevated despite metabolic optimization, suggesting ongoing inflammatory and fibrotic activity in T2D, which could predispose to an early development of CVD, including HF. sST2 was the only biomarker significantly reduced with metabolic optimization, supporting its role as a potential marker of metabolic intervention efficacy [25,26]. Galectin-3 levels negatively correlated with both EDV and ESV in patients with diabetes and emphasizes the potential utility of Galectin-3 as an early biomarker to identify diabetic patients at higher cardiovascular risk despite apparently normal volumetric parameters.

EAT plays a key role in early atherosclerosis and HF progression [28]. While EAT typically accounts for ~20% of the total heart weight (~100g) [13,29], it can exceed 400g in obesity and T2D 30. Due to its proximity to the myocardium and coronary arteries, excessive EAT may promote ventricular stiffness and diastolic dysfunction [13,30,31]. Additionally, EAT acts as an endocrine and paracrine organ, altering cardiomyocyte metabolism, shifting energy utilization toward free fatty acid uptake, and activating inflammation and oxidative stress pathways [12,32,33]. These mechanisms contribute to remodeling, fibrosis, and ultimately HF [12,31,34,35]. The observed relationship between EAT expansion and increased GDF15 and sST2 levels, as well as the reduction of iEATv after glycemic optimization and weight loss, supports the effect of EAT to the inflammatory and fibrotic processes leading to CVD and HF in this population, and reinforce the potential impact of these interventions in modulating cardiometabolic risk.

We also observed elevated inflammatory markers (hsCRP, IL1β, IL6, and TNFα) in T2D patients, suggesting a systemic inflammatory state rather than an isolated effect of adipose tissue, because adipose tissue-specific adipokines such as, adiponectin or leptin, were not increased in T2D. IL1β correlated with LVEF, and TNFα correlated with HbA1c, hsCRP, and iEATv, implying a potential link between systemic inflammation, EAT expansion, and cardiac dysfunction. However, after multivariable analysis, no direct association between inflammatory markers and iEATv or LVEF remained, indicating that these mediators may contribute indirectly to HF progression.

Limitations

A key limitation of our study is the small sample size, which was constrained by recruitment challenges during the COVID-19 pandemic. Also, the lack of longitudinal outcome data restricts the ability to assess the long-term prognostic value of these biomarkers. Although statistical associations between iEATv and biomarkers such as GDF15 and sST2 were observed, the cross-sectional nature of the baseline/follow-up design limits causal inference Nonetheless, our findings provide valuable preliminary insights into the interplay between EAT, metabolic control, and cardiovascular biomarkers in early T2D. Future studies with larger, more diverse cohorts are needed to validate these findings, explore long-term outcomes, and assess the impact of EAT-targeted interventions. Additionally, sex-based differences in HFpEF prevalence and biomarker expression were not explicitly examined, due to the sample size.

5. Conclusions

In newly diagnosed T2D patients, we observed increased iEATv and elevated levels of GDF15, Galectin-3, and sST2, all of which have been implicated in inflammation and HF risk. While weight loss and glycemic optimization led to reductions in iEATv and sST2, GDF15 and Galectin-3 remained persistently elevated, indicating possible ongoing inflammatory activity. Multivariable analysis confirmed independent associations between iEATv and both GDF15 and sST2, supporting the role of visceral adiposity in modulating inflammatory and metabolic pathways that may contribute to cardiovascular complications. Future studies are needed to confirm these findings and define the usefulness of new biomarkers.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, supplementary Table 1.

Author Contributions: Conceptualization: AP, JLS-Q. Formal analysis, Investigation, and Methodology: Laboratory analysis: PG-M, JR, AG-O, MG-A, NP, SB. Patients recruitment and follow-up: PG-M, IG, IM, AP. Image analysis: DV. Statistical analysis: IG and PG-M. Analysis and interpretation of data: PG-M, JR, DV, IG, IM, AP, JLS-Q, Writing – original draft: P.G-M. Writing – review and editing: PG.-M, JR, DV, IG, JJ, AP, JLS-Q, S.B; Funding acquisition: AP, JLS-Q.

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Institutional Review Board Statement: The study was approved by the Ethics Committee of the Hospital de Sant Pau (IIBSP-REL-2017-27). Written informed consent was obtained from all participants. This study was performed in full compliance with the Declaration of Helsinki.

Informed Consent Statement: All subjects gave written informed consent before participating in the study. Written informed consent to participate in the study and publish results in medical journals was obtained from patients.

Data Availability Statement: All the information of this study is available upon reasonable request by contacting with the corresponding author.

Conflicts of Interest: These authors declare that no conflict of interest exists.

Abbreviations

- AGEs – Advanced Glycation End Products
- ALP – Alkaline Phosphatase
- ALT – Alanine Transaminase
- AST – Aspartate Aminotransferase
- AW – Abdominal Waist
- BMI – Body Mass Index
- BNP – B-type Natriuretic Peptide
- CVD – Cardiovascular Disease
- DPP4i – Dipeptidyl Peptidase-4 Inhibitors
- EAT – Epicardial Adipose Tissue
- EATv – Epicardial Adipose Tissue Volume
- EDV- end-diastolic volume left ventricular
- eGFR – Estimated Glomerular Filtration Rate
- ESV- end-systolic volume left ventricular
- FFAs – Free Fatty Acids
- GDF15 – Growth Differentiation Factor 15
- GGC – Good Glycemic Control
- GGT – Gamma-Glutamyl Transferase
- GLP1-ar – Glucagon-Like Peptide 1 Agonist Receptor
- HC – Healthy Controls
- HDLc – High-Density Lipoprotein Cholesterol
- HF – Heart Failure
- HFpEF – Heart Failure with Preserved Ejection Fraction
- HFrEF – Heart Failure with Reduced Ejection Fraction
- hsCRP – High-Sensitivity C-Reactive Protein
- hsTnT – High-Sensitivity Troponin T
- iEAT – Indexed Epicardial Adipose Tissue
- IL – Interleukin
- IR – Insulin Resistance
- LDLc – Low-Density Lipoprotein Cholesterol
- LVEF – Left Ventricular Ejection Fraction
- MDCT – Multidetector Computed Tomography
- MRI – Magnetic Resonance Imaging
- NPs – Natriuretic Peptides
- NT-proBNP – N-terminal pro-B-type Natriuretic Peptide
- PGC – Poor Glycemic Control
- ROS – Reactive Oxygen Species
- sHF – Subclinical Heart Failure
- sST2 – Soluble Suppression of Tumorigenicity 2

- T1D – Type 1 Diabetes
- T2D – Type 2 Diabetes
- TC – Total Cholesterol
- Tg – Triglycerides
- TNFα – Tumor Necrosis Factor Alpha
- VAT – Visceral Adipose Tissue
- VIF – Variance Inflation Factor
- VLDLc – Very Low-Density Lipoprotein Cholesterol

following abbreviations are used in this manuscript:

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