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Cardiac autonomic neuropathy is associated with ectopic fat distribution in autoimmune but not in type 2 diabetes

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Abstract

Background Cardiac autonomic neuropathy (CAN) is a life-threatening complication of diabetes. While obesity is a well-known risk factor of dysautonomia, the association between CAN and body fat distribution has not been fully clarified, especially in autoimmune diabetes (AD).

Aim To evaluate if the association between CAN and body fat distribution differs between AD and type 2 diabetes (T2D).

Methods Body fat distribution was evaluated by Dual X-Ray Absorptiometry in 143 people with diabetes (44 with ADand 99 with T2D) undergoing clinical screening for CAN. The association of CAN with markers of ectopic fat distribution was evaluated in multivariate regression models adjusting for confounders and testing for the interaction between diabetes type and CAN.

Results A significant interaction between CAN and diabetes type was found with respect to markers of ectopic fat distribution. Specifically, people with CAN had significantly higher amount of visceral adipose tissue (530 [376–665] g versus 251[189–360]g, p = 0.001), total fat mass (22708[20200–27845]g versus 15434[12981–21879]g, p = 0,016), and trunk-to-leg ratio (0.88 [0.75–1.04] versus 0.70 [0.56–0.78], p = 0,023) compared to those without CAN only in participants with AD, but not in T2D (p-values for interaction < 0.05 for all comparisons).

Conclusion Ectopic fat distribution is more strongly associated with CAN in AD than in T2D. This highlights the distinct role of fat distribution in the cardiometabolic health of people with AD, suggesting the need for further studies to better understand the pathophysiology and implications of overweight in this population.

Keywords Autoimmune diabetes, Type 2 diabetes, Adipose tissue distribution, Cardiac autonomic neuropathy, Obesity

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Introduction

Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes (T2D), the most frequent form of diabetes, results from a relative defect of insulin secretion on the background of insulin-resistance [1]. Conversely, autoimmune diabetes (AD) derives from the autoimmune destruction of pancreatic β cells, which makes people reliant on exogenous insulin for survival [2]. Despite their different pathogenesis, both T2D and AD are associated with long-term complications. Among these, cardiac autonomic neuropathy (CAN) is a life-threatening complication caused by damage to the autonomic nerve fibers innervating the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [3, 4]. CAN prevalence varies among people with diabetes depending on the criteria used for CAN diagnosis and on the characteristics of the population enrolled [5]. When it is clinically overt, the classical symptoms include palpitations, dizziness, presyncope, and syncope. However, the majority of patients with CAN among people with diabetes have subclinical or asymptomatic disease, rendering the diagnosis and appreciation of CAN in clinical practice rather difficult [6, 7]. This is alarming, considering that presence of symptoms characterizes the most advanced stages of CAN, which is essentially irreversible and associated with a definite increased risk of mortality [8].

Established risk factors for CAN are aging, diabetes duration, glycemic control, hypertension, dyslipidemia, smoking, and the presence of diabetic microvascular complications [9, 10]. Furthermore, evidence support that central and ectopic obesity, insulin resistance, high triglyceride and low HDL concentration play a role in the development of autonomic dysfunction [11–16]. The relationship between autonomic nervous system dysfunction and obesity seems to be bidirectional. On the one hand, fat mass excess, and in particular visceral fat accumulation, is a risk factor for abnormalities of the cardiac autonomic activation [17–19] and abnormal autonomic response [20, 21], which seems to be reversible with weight loss [22, 23]. On the other hand, autonomic nervous system itself contributes to body weight maintenance, through the regulation of satiety, energy expenditure and storage [24]. In addition, it is well known that the sympathetic nervous system strongly innervates the adipose tissue and modulates process of lipogenesis, thermogenesis, inflammation, being potentially involved also in adipose tissue distribution [25, 26].

Although AD is traditionally considered a disease of lean people, overweight and obesity are becoming increasingly more common in these people [27–31]. While obesity, when it is accompanied by visceral fat accumulation, is a well-known pathogenetic and aggravating risk factor in patients with T2D, its impact on the natural history of AD with regards to the development of complications, including CAN, has not been fully investigated.

In this study we hypothesized that the presence of CAN may be associated with variations in body fat distribution among people with diabetes. Furthermore, considering the distinct pathophysiological and clinical characteristics of autoimmune diabetes (AD) and type 2 diabetes (T2D), we hypothesize that the type of diabetes may influence this relationship. Our primary aim was to investigate the association between CAN and body fat distribution in people with diabetes, with a particular focus on determining whether this relationship varies between AD and T2D.

Methods

Study design and population

In this cross-sectional study we enrolled consecutive participants referring to the Diabetes Unit of Policlinico Umberto I General Hospital, Rome, Italy, and performing cardiovascular reflex tests (CARTs) because meeting the criteria for undergoing cardiac autonomic neuropathy screening as recommended by the Cardiac Autonomic Neuropathy Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy [5]. Eligibility criteria were: (1) diagnosis of AD and T2D according to American Diabetes Association criteria [32] (2) age ≥ 18 and ≤ 80 years old; 3) willingness to participate in the study. Participants were excluded from the study if they had a previous diagnosis of neuropathy/arrhythmia from any cause other than diabetic neuropathy or if they were affected by co-morbidities contraindicating the execution or impacting the results of cardiovascular provocative tests (i.e. endocranial hypertension, chronic obstructive pulmonary disease or respiratory insufficiency). All the participants underwent screening for micro and macrovascular complications of diabetes in accordance with current international guidelines [33]. All the participants signed informed consent. The maximum time interval between data collection, CAN assessment and DXA scan was six months.

Data collection

Data regarding diabetes history, co-morbidities, biochemistry (HbA1c, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, serum creatinine, eGFR, urine albumin) were collected from clinical records. Body mass index (BMI) was calculated as body weight in kilograms divided by height in square meters (kg/m^2). Estimated glomerular filtrate rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Microalbuminuria was defined for urine albumin levels > 30 mg/L. Diabetic retinopathy was

defined in the presence of mild non-proliferative diabetic retinopathy or more severe stages.

Commercial BioVendor ELISA kits were used to assess serum concentrations of Adiponectin (Minneapolis, USA; catalogue # DRP300) and leptin (Minneapolis, USA;catalogue # DLP00). Adiponectin to Leptin Ratio (ALR), which represents a functional biomarkers for adipose tissue inflammation [34], was assessed as the ratio between the two adipokines.

Cardiac autonomic neuropathy assessment

CAN was screened in all participants by the following CARTs repeated once: heart rate response to deep breathing (expiratory-to-inspiratory ratio), heart rate response to lying-to-stand test (30:15 ratio), orthostatic hypotension test. All tests were performed by expert clinicians. Participants were asked to discontinue any interfering drug (i.e. beta-blockers, calcium channel blockers, drugs acting on the renin–angiotensin–aldosterone system, diuretics, sympatholytic agents, benzodiazepines, tricyclic antidepressants) at least 24 h before the tests. Participants were considered to have early cardiac autonomic neuropathy if they had at least one out of three abnormal tests [8]. CARTs were performed by using the following equipments: Esaote My cardiopad ECG reader; Gamma XXL-LF Heine sphygmomanometer.

Body fat composition

Body fat composition was measured by Dual X-Ray Absorptiometry (DXA) (QDR Discovery Acclaim, Hologic Inc., Waltham, MA) in fasting patients wearing light clothing and no shoes. Total fat mass, as well as abnormal body fat distribution parameters, such Visceral Adipose Tissue (VAT) Mass Trunk Fat Mass, and Trunk to Legs Fat Mass Ratio (TLR) were collected.

Statistical analysis and sample size considerations

Continuous variables are presented as median [25th–75th percentile] and categorical variables as number and percentages with 95% CI. Shapiro–Wilk test was used to evaluate parametric distribution of continuous variables. Kruskal–Wallis test was used to evaluate differences in continuous variables between groups. Chi-squared test or Fisher's exact test was used to test differences of the distribution of categorical variables among groups, as appropriate. Multivariate general linear models were used to assess the relationship of CAN and diabetes type with body fat distribution parameters, adjusting for confounders. Specifically, we run three different models having VAT mass (the primary outcome of this analysis), trunk fat mass and TLR (secondary outcomes) as continuous dependent variables, respectively, the presence/absence of cardiac autonomic neuropathy and diabetes type (AD/T2D) as dichotomous independent variables, and sex, age, BMI,HbA1c and diabetes duration as prespecified confounders to be tested within the main models, with a conservative p-value < 0.1 as criterion for retention within the model, in order to balance inclusivity and model utility. Interactions between diabetes type and CAN diagnosis were calculated to evaluate whether the association between parameters of body mass composition and adipokines profile and CAN differ between AD and T2D. All non-parametric variables were ln-transformed before entering the regression models.

Based on our preliminary data [35] we calculated that a sample size of at least 40 patients with AD, with an expected prevalence of CAN in this group of 25–40% [11], was required to provide the study with 80% power (alpha level: 0.05) in order to detect differences in VAT Mass by CAN diagnosis. In order to evaluate whether differences in the primary outcome by CAN were consistent also in T2D, we also enrolled a group of people with T2D at an enrolment ratio AD:T2D of 1:2. Two-sided tests at the 0.05 level of significance were used for all statistical comparisons. Stata/IC 12.1 software used for data analysis and Prism 8.4 Software for graphical representations.

Ethics

The study was performed in accordance with the Declaration of Helsinki, and the study procedures were approved by the Umberto I 'Policlinico' General hospital ethics committee [Prot 1027/19]. All participants signed written informed consent.

Results

Population features

A total of one hundred forty-three participants with diabetes were enrolled in the study. The study population was composed by 44 patients with AD (30.9%) and 99 with T2D (69.1%). Characteristics of population by diabetes type are summarized in Supplementary Table 1S. Women were 53 (37.1%), mean age was 67 (61–70) years old and mean BMI was 27.3 (24.3–30.7) kg/m^2.

Fifty patients (34.9%) out of one-hundred forty-three, fifteen with AD and thirty-five with T2D, had $\geq 1/3$ abnormal CARTs. Among these, only eleven participants had $\geq 2/3$ abnormal CARTs (2 out of 44 with AD and 9 out of 99 with T2D). Clinical and biochemical features of participants by presence of CAN are summarized in Supplementary Table 2S. Except for the more frequent positive history of cardiovascular disease observed among people with CAN, no other significant clinical differences were found.

Body fat and CAN

After controlling for confounders, a significant interaction between presence of CAN and diabetes type was found with respect to VAT mass, (p-value for interaction:

0.017), trunk fat mass (p-value for interaction: 0.030), TLR (p-value for interaction: 0.032) (Fig. 1A–C). Specifically, among participants affected by AD, those with CAN, compared to those without CAN, showed higher VAT mass (530 [376–665] g versus 251 [189—360] g, p = 0.001), total fat mass (22,708 [20,200–27845] g versus 15,434 [12,981–21879] g, p = 0,016), and TLR (0.88 [0.75–1.04] versus 0.70 [0.56–0.78], p = 0,023) (Table 1), independently from BMI, age, sex, HbA1c and diabetes duration. Such differences were not found among participants with T2D. Other parameters differing between people with and without CAN among those with AD were sex, BMI, triglycerides, total fat mass and percentage of people showing microalbuminuria (Table 1). Also in this case, such differences were not found among people with T2D (Table 2). ALR was not found to differ among study groups after correction for confounders (Fig. 1D).

Discussion

This study showed that ectopic fat distribution is associated with the presence of CAN in participants with AD but not in T2D. More specifically, we found that a visceral body fat accumulation phenotype in participants with CAN compared to those without CAN among people with AD, with greater total fat mass, trunk fat mass, VAT mass and TLR in the group of participants affected by CAN. Overall, our study corroborates the existing literature

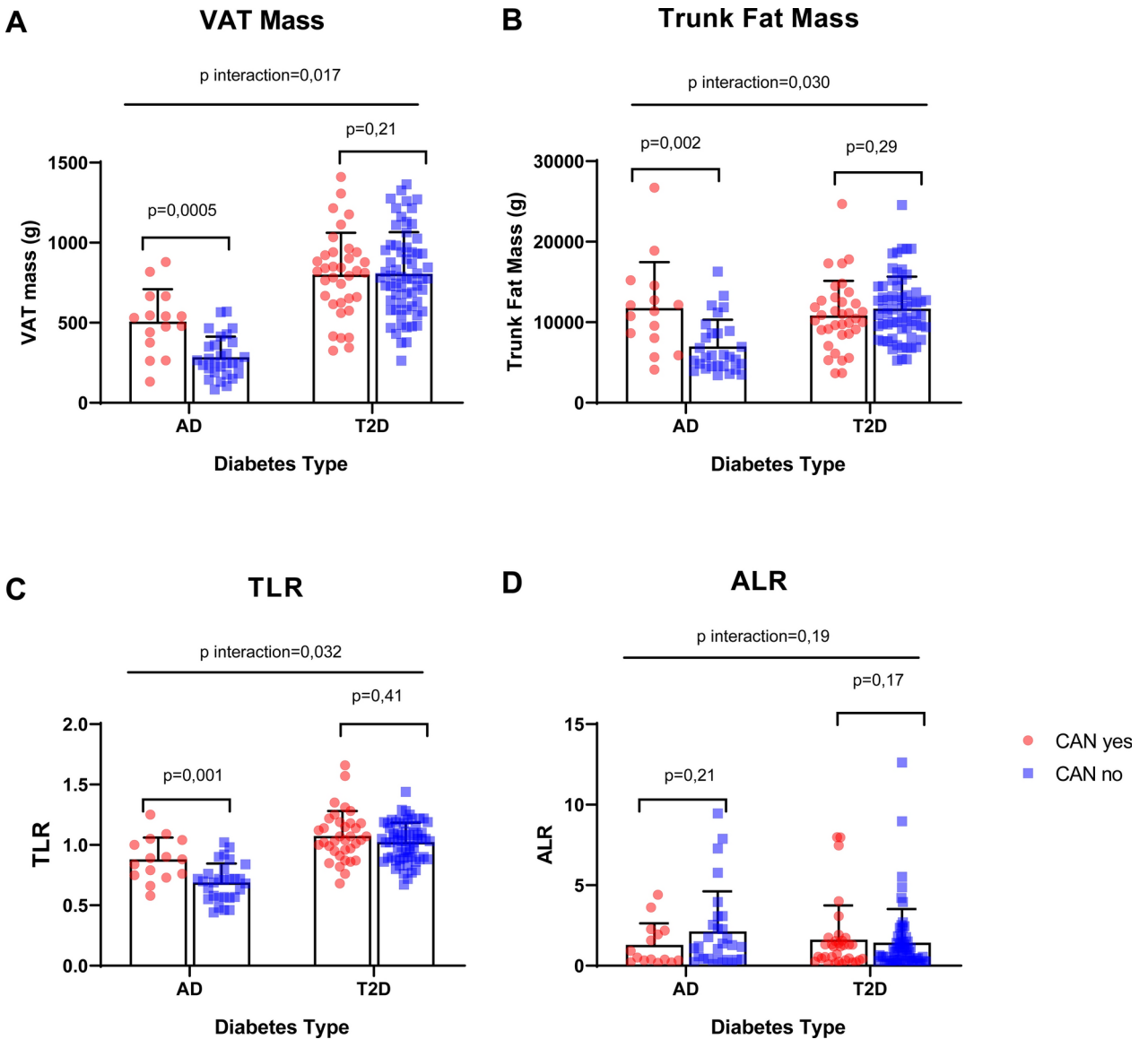

Fig. 1 **A**–**D** Differences in VAT mass **A**, Trunk Fat Mass **B**, and TLR **C**, ALR **D** in people with (red dots) and without (blu squares) CAN by diabetes type. Model was adjusted by confounders (sex, age, BMI, HbA1c% and diabetes duration). *VAT* Visceral Adipose tissue, *ALR* Adiponectin to Leptin Ratio, *TLR* Trunk to Legs Fat Mass Ratio, *AD* Autoimmune diabetes, *T2D* Type 2 diabetes

Table 1 Characteristics of population with AD by presence of CAN

	Cardiac autonomic neuropathy		P value
	Yes (n = 15)	No (n = 29)	
Female sex, n (%)	9 (60)	12 (40)	0.008
Smokers, %	26.6	21.4	0.71
Age, years	57 (51–64)	51 (41.5–58.5)	0.07
BMI, kg/m^2	27.9 (25.7–31.6)	23.9 (22.4–26.1)	0.001
SBP, mmHg	120 (130–140)	120 (112.5–131)	0.17
DBP, mmHg	75 (70–80)	80 (75–90)	0.09
HR, beats/min	72 (68–82)	72 (68–77)	0.98
TIDD/kg	0.44 (0.34–0.71)	0.33 (0.24–0.49)	0.07
CSII, n (%)	3 (20)	4 (14)	0.99
Metformin, (%)	8 (53)	15 (52)	0.54
SGLT2i, n (%)	0	0	> 0.99
GLP1RAs, n (%)	3 (20)	3 (10)	0.39
DPP4i, n (%)	0	1 (4)	0.99
Sulfonylureas, n (%)	0	0	> 0.99
Glycaemia, mmol/L	9.2 (6.8–11.7)	8.6 (7.3–12)	0.97
HbA1c, mmol/mol	56 (53–66)	65 (56–70)	0.14
Total cholesterol, mmol/L	4.3 (3.9–5.5)	4.6 (3.9–4.9)	0.80
HDL cholesterol, mmol/L	1.6 (1.2–1.9)	1.5 (1.3–1.9)	0.81
LDL cholesterol, mmol/L	1.8 (2.5–3.2)	2.5 (2–2.8)	0.53
Triglycerides, mmol/L	1 (0.8–1.1)	1.7 (0.5–0.9)	0.02
eGFR, ml/min/1.73m^2	90 (79–104)	97.1 (84.9–110.8)	0.23
Total fat mass, g	22,708(20,200–27845)	15,434(12,981–21,879)	0.016
Total fat mass, %	30.4 (24.9–36.6)	25.9 (21.6–30.3)	0.04
Vat mass, g	530 (376–665)	251 (189–360)	0.001
Trunk fat mass, g	11,381(8043–14562)	5703(4504–8768)	0.0023
TLR	0.88(0.75–1.04)	0.7(0.56–0.78)	0.023
Adiponectin, ng/mL	6302 (4738–14,082)	7992 (5380–11978)	0.61
Leptin, pg/mL	8589(4156–16,302)	6564 (2213–14,350)	0.34
ALR	1.3 (0.2–1.9)	0.2 (0.4–3.1)	0.21
Diabetes duration, yrs	13 (2.3–18)	6.4 (3–16)	0.74
Retinopathy, n (%)	2 (13.3)	4 (13.8)	0.98
Non-proliferative, n (%)	2 (13.3)	4 (13.8)	
Proliferative, n (%)	0	0	
Microalbuminuria, n (%)	2 (13.3)	0	0.05
Established CVD, n (%)	1 (6.7)	0	0.22

Continuous variables are presented as median [25th–75th percentile] and categorical variables as percentage.*AD* Autoimmune diabetes, *T2D* Type 2 diabetes, *CAN* Cardiac autonomic neuropathy, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HR* Heart rate, *TIDD/Kg* Total insulin daily dose pro kg, *CSII* Continuous subcutaneous insulin infusion, *SGLT2i* Sodium-glucose co-transporter 2 inhibitors, *GLP1Ras* Glucagon-like peptide 1 receptor agonists, *DPP4i* Dipeptidyl peptidase 4 inhibitors, *e GFR* Estimated glomerular filtration rate, *HbA1c* Glycated haemoglobin, *TLR* Trunk to Legs Fat Mass Ratio, *ALR* Adiponectin to Leptin Ratio, *CVD* Cardiovascular disease

Table 2 Characteristics of population with T2D by presence of CAN

	Cardiac autonomic neuropathy		P value
	Yes (n = 35)	No (n = 64)	
Female sex, %	7 (20)	20 (31)	0.21
Smokers, %	48.6	46.8	0.99
Age, years	68 (66–71)	69 (66.5–72)	0.17
BMI, kg/m^2	27.4 (25.9–30.1)	27.9 (25.8–31.7)	0.58
SBP, mmHg	130 (120–140)	125 (120–137.5)	0.44
DBP, mmHg	80 (70–80)	75 (70–80)	0.18
HR, beats/min	82 (65–92)	75 (62–88)	0.43
Metformin user, n (%)	31 (88.6)	61 su 64 (95.3)	0.24
SGLT2i, n (%)	5 (14.2)	21 (32.8)	0.06
GLP1-RA, n (%)	18 (51.4)	29 (45.3)	0.67
DPP4i, n (%)	4 (11.4)	4 (6.3)	0.99
Sulfonylureas, n (%)	0	1 (1.6)	0.99
Any insulin therapy, n (%)	10 (28.6)	14 (21.9)	0.99
Glycaemia, mmol/L	6.7 (6.1–7.4)	6.6 (5.6–7.8)	0.86
HbA1c, mmol/mol	46 (43–57)	48 (42–55)	0.64
Total cholesterol, mmol/L	4 (3–4.7)	4 (3.4–4.6)	0.27
HDL cholesterol, mmo/L	1.1 (0.9–1.3)	1.2 (1.1–1.4)	0.47
LDL cholesterol, mmo/L	2.1 (1.3–2.6)	2.1 (1.6–2.8)	0.40
Triglycerides, mmo/L	1.1 (0.9–1.7)	1.4 (0.9–1.8)	0.49
eGFR, ml/min/1.73m^2	79 (67–102)	81 (68.5–98)	0.97
Total fat mass, g	19,932(16,684–25,027)	18,936(16,779–25,955)	0.69
Total fat mass, %	24.2 (22.3–29.6)	25.9 (23.2–31.0)	0.11
Vat mass, g	820 (624–940)	775.5 (608–966)	0.89
Trunk fat mass, g	10,458(8562–12,691)	11,358(9208–13619)	0.27
TLR	1.04(0.95–1.18)	1.03(0.89–1.16)	0.53
Adiponectin, ng/mL	6544 (4272–9088)	5865 (3712–7714)	0.17
Leptin, pg/mL	5733 (3612–11,933)	5633 (3589–14,189)	0.52
ALR	1.2 (0.5–1.8)	0.7 (0.30–1.5)	0.29
Diabetes duration, years	10 (4–13)	8 (5–12)	0.74
Retinopathy, n (%)	3 (9.0)	10 (15.6)	0.74
Non-proliferative, n (%)	2 (5.7)	8 (12.7)	
Proliferative, n (%)	1 (2.9)	2 (3.2)	
Microalbuminuria, n (%)	3 (8.8)	7 (11.5)	0.78
Established CVD, n (%)	6 (17.1)	4 (6.4)	0.09

Continuous variables are presented as median [25th–75th percentile] and categorical variables as percentage. *AD* Autoimmune diabetes, *T2D* Type 2 diabetes, *CAN* Cardiac autonomic neuropathy, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure; HR, heart rate, *SGLT2i* Sodium-glucose co-transporter 2 inhibitors, *GLP1-RAs* Glucagon-like peptide 1 receptor agonists, *DPP4i* Dipeptidyl peptidase 4 inhibitors, *e GFR* Estimated glomerular filtration rate, *HbA1c* Glycated haemoglobin, *TLR* Trunk to Legs Fat Mass Ratio, *ALR* Adiponectin to Leptin Ratio, *CVD* Cardiovascular disease

suggesting a relationship between central obesity and autonomic dysfunction [12, 13, 17–21, 24]. However, to the best of our knowledge, this is the first study providing an in-depth evaluation of body fat distribution in relation to CAN in people with AD, also providing a comparison with people with T2D. Before us, Voulgari and colleagues found that waist circumference was higher among people with CAN in both in AD and T2D [14]. Also in this case, the relationship was stronger in AD than in T2D [14]. Our results expand this knowledge by providing a more detailed evaluation of body fat distribution through DXA

method, rather than limiting only to waist circumference, also including estimates of VAT, trunk fat and adipokines. Since overweight and obesity are becoming much more common among people with AD [27–31], there is a need for studies like this, elucidating the relationship between adiposity and the clinical course of AD. Some evidence suggest that obesity is associated with poorer glycemic control, higher total insulin daily dose and increased risk for atherosclerotic CVD in patients with AD [27, 29], all factor potentially associated with CAN. However, in our study the relationship between adiposity and CAN was independent from confounders such as age, BMI, sex and HbA1c%, diabetes duration.

In people with T2D, Jang et al. observed that higher CT-scan derived VAT level was associated with poorer heart rate response to Valsalva maneuver [21]. Also, an association between CT-scan derived VAT levels and signs of CAN, evaluated with 123 I-MIBG scintigraphy, was found in an even smaller population of 24 Japanese people with T2D [15]. Differently from previous studies, we used three cardiovascular autonomic reflex tests among those recommended for the clinical diagnosis of CAN, providing a more robust evaluation of clinically relevant CAN, which was not associated with ectopic fat distribution in people with T2D, but only in AD. This crucial difference in the diagnostic evaluation of CAN, as well as the different populations enrolled, might explain the contrasting results with regards to the relationship between body fat and CAN in T2D.

The mechanisms underlying the stronger association between ectopic fat distribution and CAN observed in AD compared to T2D remain to be addressed. On the one hand, CAN might be a consequence of fat mass excess and abnormal distribution [12, 13, 17–21, 24]. However, in this case, worse autonomic dysfunction should have been found in people with greater amount of fat and VAT mass, such as those with T2D. On the other hand, preclinical and clinical models showed that sympathetic and parasympathetic systems regulate body fat storage and distribution [24] and modulate processes of lipogenesis, thermogenesis and inflammation [25, 26], suggesting that the dysautonomia observed in patients diagnosed with CAN might itself exert a detrimental effects on AD distribution and function. Based on our results, we could speculate that such detrimental effects could be observed in a population with a lower amount of fat and without the metabolic derangements classically observed in T2D, while they could have been blunted in people with an already higher amount of ectopic fat due to other causes.

Our study should be read in the light of some limitations. First, CARTs strictly depends on participants' compliance and might miss very early stages of autonomic impairment; however, they have been broadly recommended as a screening tool for CAN in patients at risk [8].In addition, CAN was assessed only by three reflex tests (heart rate response to deep breathing, heart rate response to lying-to-standing test, orthostatic hypotension test). Since cardiovascular autonomic reflex tests are time-consuming, a clinical rather than research-focused CAN assessment without resting heart rate variability measures was performed.

In this regard, a simplified battery encompassing a reduced number of tests is suggested, and having one positive heart rate test out of two or three is an internationally recognized sufficient criterion for early CAN diagnosis [8]. Furthermore, according to a recent study by Pafili et al., heart rate response to deep breathing has the highest sensitivity and sensibility for CAN diagnosis, emerging as the most useful diagnostic test alone for accurate screening [36]. In addition, although we are aware that the presence of abnormalities in more than one test on several occasions is preferable for CAN diagnosis [5], we performed CARTs only once due to clinical practice limitations. To note, current guidelines suggest that a single abnormal result among the two or three heart rate tests represent a sufficient criterion for CAN diagnosis [5]. Finally, since this is a cross-sectional study, we cannot draw conclusions about any cause-effect relationship between CAN and abnormal body fat distribution.

On the other hand, we recognize that our work has the significant strength of being the first study evaluating the relationship between adiposity distribution and CAN in a population composed of both AD and T2D. Moreover, we focused not only on fat mass excess, but also on body fat distribution parameters, including estimates of VAT and trunk fat and adipokines. In fact, it is widely recognized that ectopic fat deposition, more than parameters of absolute adiposity, is associated with unhealthy metabolic profile and cardiometabolic complications [37].

In conclusion, our findings suggest that ectopic fat distribution is more strongly associated with CAN in people with AD than in those with T2D. While the causative relationship between CAN and ectopic fat deposition cannot be established, our study highlights the significance of abnormal adipose tissue expansion in the cardiometabolic risk profile of people with AD. These findings emphasize the need for further research to clarify the impact of overweight and obesity on cardiometabolic health in AD.

Abbreviations

CAN	Cardiac autonomic neuropathy
AD	Autoimmune diabetes
T2D	Type 2 diabetes
AT	Adipose tissue
VAT	Visceral adipose tissue
TLR	Trunk to legs fat mass ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02635-6.

Supplementary file 1.

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Author contributions
RR and RA participated in the design of the study, interpreted results and drafted the first version of manuscript. VF, AB, ALP, LC, DL, DM, MW and LD contributed to data acquisition. RB and LG critically reviewed the manuscript. EM conceptualized the research plan, analyzed data, contributed to interpretation of results and critically reviewed the manuscript. All the authors have approved the submitted version of the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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