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CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Evaluation of common carotid artery in type 1 diabetes mellitus patients through speckle tracking carotid strain ultrasonography

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PURPOSE
We aimed to evaluate the effectiveness of speckle tracking carotid strain (STCS) technique, which enables measurement of arterial stiffness and strain parameters, in the detection of early atherosclerotic findings in type 1 diabetes mellitus (T1DM).

METHODS
We prospectively enrolled 30 T1DM patients and 30 age- and sex-matched control participants with no history of cardiovascular disease. All study population underwent carotid ultrasonography. Radial and circumferential movement of the common carotid artery (CCA) in the transverse plane as the well as the radial movement of the CCA in the longitudinal plane were calculated automatically by using the STCS method. In addition, the strain (%), strain rate (per second), and peak circumferential and radial displacements (mm) were calculated. Arterial stiffness parameters, such as elastic modulus, distensibility, arterial compliance, and β-stiffness index, were calculated using the radial measurements. The mean value of the carotid intima media thickness (CIMT) was calculated semi-automatically for each CCA, in the longitudinal plane. We also analyzed the patients' overall body composition.

RESULTS
T1DM and control groups were compared in terms of strain and stiffness parameters and no statistically significant difference was found ($p > 0.05$). CIMT was higher in diabetic patients than in the control group ($p = 0.039$). In both groups, age was correlated with all arterial stiffness and strain parameters ($p < 0.05$). The duration of diabetes was also correlated with β-stiffness index, distensibility, and elastic modulus in the longitudinal plane ($p < 0.05$). In the diabetic group, abdominal fat ratio, whole body fat ratio, and fat mass were correlated with radial and circumferential displacement and strain parameters in transverse plane, and radial displacement in longitudinal plane ($p < 0.05$, for each). Diabetic patients were divided into subgroups according to the presence of nephropathy and dyslipidemia. Although no significant difference was found between the groups in terms of CIMT, patients with nephropathy had higher values for transverse and longitudinal elastic modulus, pulse-wave velocity, and longitudinal β-stiffness index, as well as lower values for longitudinal arterial compliance and distensibility, compared with patients without nephropathy ($p < 0.05$). Also, patients with dyslipidemia had higher longitudinal β-stiffness and elastic modulus values compared with patients without dyslipidemia ($p < 0.05$).

CONCLUSION
STCS ultrasonography is an effective, easy, and noninvasive method for evaluating the arterial elasticity. It may provide an early assessment of atherosclerosis in patients with T1DM, especially in the presence of nephropathy and dyslipidemia; thus, together with CIMT measurement, it may be used more frequently to detect subclinical damage and stratify atherosclerosis.

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Researchers have shown that the mortality rate in type 1 diabetes mellitus (T1DM) patients is three times higher than in the general population (1). The major cause of mortality in T1DM patients of both sexes is atherosclerosis; on average, cardiovascular events occur 10 years earlier in this population than in the general population (1, 2). Long-term nonenzymatic glycosylation of arterial wall proteins and excessive superoxide production are thought to play a role in the etiology (3). Advanced glycation end-products (AGEs) accumulate at a high rate in T1DM and form abnormal protein-protein crosslinks on the collagen molecule. AGEs-mediated crosslinks may prevent enzymatic digestion and

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slow degradation, resulting in increased overall collagen content in the arterial wall and collagen:elastin ratio (4). These factors are thought to play a role in the etiology, cause endothelial dysfunction, stiffening of the arterial wall, and consequently atherosclerotic changes (3).

Studies have shown that the atherosclerotic process typically manifest early in the carotid arteries (5). Therefore, evaluation of carotid arteries is very important in cardiovascular risk assessment. Carotid B-mode ultrasonography allows for noninvasive evaluations of atherosclerotic changes, including the measurement of carotid intima media thickness (CIMT), as well as the presence and extent of carotid plaque and arterial stiffness (6–9). The existence of carotid plaque or thickened CIMT is indicative of the morphological changes that result from the progression of atherosclerosis in the carotid artery. The local common carotid artery (CCA) stiffness parameters such as the elastic modulus, distensibility coefficient, strain, strain rate reflect the functional characteristics of atherosclerotic alterations in the carotid artery; these functional alterations manifest before structural alterations such as the intimal thickening of the artery wall and carotid plaque (10).

Applanation tonometry is the gold standard technique used to evaluate arterial wall stiffness. However, this technique is time consuming, requires dedicated equipment and is not widely used in clinical routine (11, 12). Moreover, it assumes vascular homogeneity and does not provide sufficient information about the localized deformation characteristics of the arterial wall (13).

Main points

- In type 1 diabetes mellitus (T1DM) group, abdominal fat ratio, whole-body fat ratio, and fat mass were negatively correlated with radial and circumferential displacement and the strain parameters in the transverse plane, as well as radial displacement in the longitudinal plane.
- STCS ultrasonography is an effective, easy, and noninvasive method for evaluating the elastic properties of the arterial wall. STCS technique may provide an early assessment of atherosclerosis in patients with T1DM, particularly those with nephropathy and dyslipidemia.
- Duration of diabetes was correlated with β-stiffness index, distensibility, and elastic modulus in the longitudinal plane.

Another approach to evaluate arterial wall stiffness is the speckle tracking carotid strain (STCS) method, which enables both morphological and functional analysis of the CCA by providing arterial stiffness measurements and CIMT measurements, and which leads to earlier detection of cardiovascular disease, especially for at-risk populations (14). Studies have shown that the STCS method can be an alternative to applanation tonometry in the evaluation of arterial wall stiffness (15, 16). The feasibility of STCS method has been validated by *in vitro*, *in silico*, and *in vivo* studies (15, 17–22). Arterial analysis software using an ultrasound-based STCS method provides the measurement of changes in arterial diameter created by each pulse pressure. From the diameter and pressure measurement, variables concerning arterial wall stiffness such as distensibility, compliance, elastic modulus index, β-stiffness index, and pulse wave velocity (PWV) and variables concerning arterial strain such as displacement, strain and strain rate can be calculated. Studies have shown that subclinical signs of arterial wall stiffening due to increased cardiovascular risk can be detected by the STCS method (10, 15, 17, 18, 23–25). Moreover, it has been proposed that the STCS method allows determination of the vulnerability of atherosclerotic

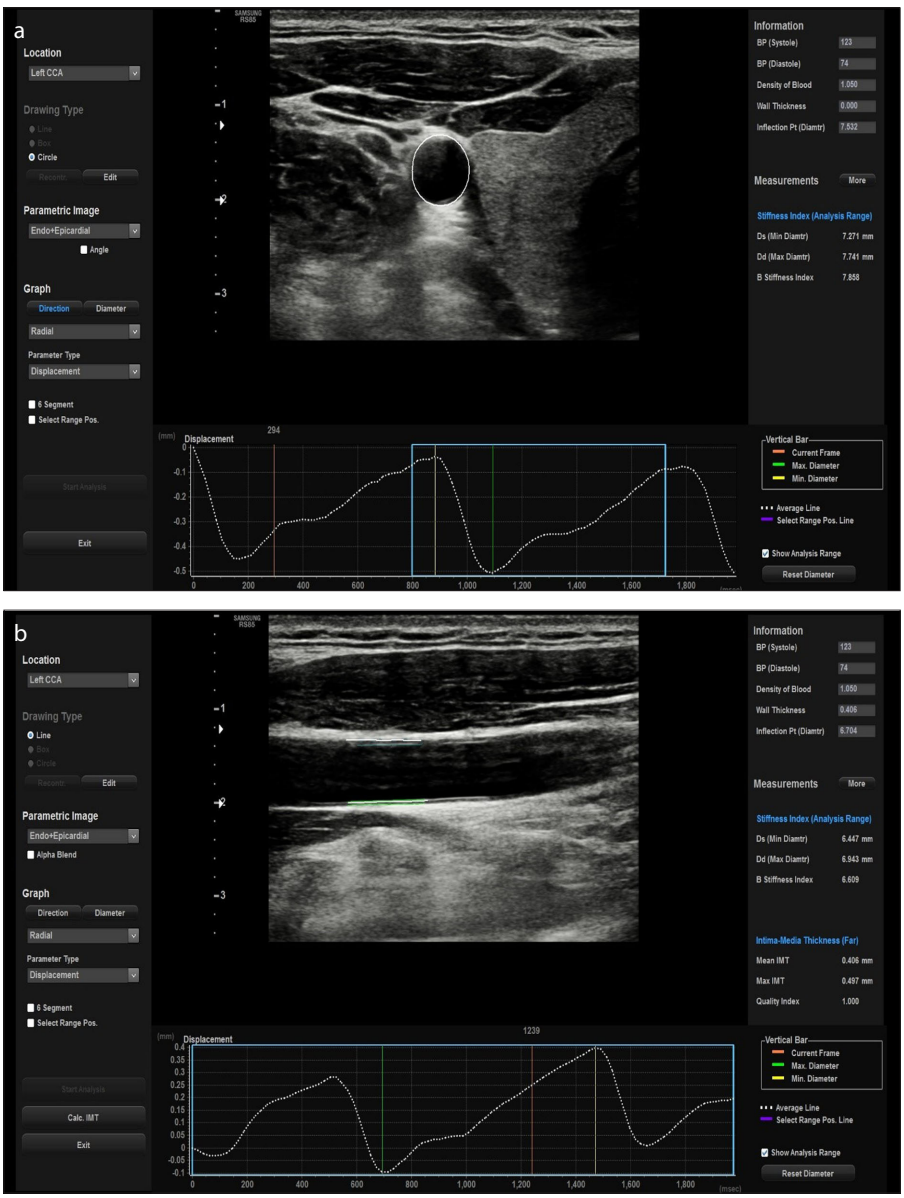

Figure 1. a, b. Evaluation of the strain parameters of CCA in **(a)** transverse and **(b)** longitudinal planes using the STCS method in carotid B-mode US.

plaques (26). Also, in another study, STCS imaging-based measurements have been shown to allow early assessment of potential effects of statins on vascular function (27). This suggests that early determination of arterial stiffness has the potential to be a valuable tool in the prevention of cardiovascular events. In several studies, the STCS method has been used to identify cardiovascular risk in many different patient populations such as atherothrombotic stroke, end-stage renal disease, rheumatoid arthritis, obstructive sleep apnea, and hypertension (28–32). This method promises to be beneficial, noninvasive, quick, and easily applicable, especially in the evaluation of the CCA (11, 32).

Arterial stiffness has been defined as an early marker of atherosclerosis in T1DM patients (3, 33). However, to the best of our knowledge, no prior study evaluated the effectiveness of the STCS method and arterial analysis software in the detection of early atherosclerotic signs in adult T1DM patients.

We aimed to evaluate the effectiveness of STCS technique, which enables measuring arterial stiffness and strain parameters in the detection of early atherosclerotic findings in T1DM.

Table 1. Terminology of arterial analysis software

Parameter	Definition	Formula
Arterial compliance	Absolute change in vessel diameter according to change in applied pressure	Difference between diastolic and systolic diameter (ΔD)/ difference between systolic and diastolic blood pressure (ΔP)
Arterial distensibility	The relative change in vessel diameter according to change in applied pressure	ΔD/(ΔP × vessel diameter in the diastolic phase (D)) in mm Hg
Elastic modulus index	Alteration of pressure necessary for theoretical stretch from resting vessel diameter	(ΔPxD)/ΔD in mm Hg
β-stiffness index	The ratio of the natural logarithm of systolic/diastolic pressure to relative change in diameter	log (SBP/DBP)/(ΔD/D)
Pulse wave velocity (PWV)	The speed of the pulse wave extends through the length of the vessel	Stiffness index × diastolic blood pressure/(2 × blood density) When the blood density is assumed to be 1.050 g/cm^3.

Methods

Study population

The Institutional Review Board (24074710-604.01.01-08) approved this prospective study. Written informed consent was obtained from all patients. The sample consisted of 30 T1DM and 30 nondiabetic individuals (control group) with no history of cardiovascular disease. The two groups were matched according to age, sex and body mass index (BMI). Individuals (in diabetic and control group) with visible atherosclerotic plaques in the carotid arteries were not included in the study. The mean duration of diabetes in the diabetic group was 18±9.8 years. Overall, 13 (43%) of the 30 diabetic patients and 7 (23%) of the 30 individuals of the control group were smokers. All diabetic patients were using insulin and any other medications were not being taken. Individuals in the control group were not using any medication. For the diabetic group, carotid artery analysis was performed in the morning before the rapid-acting analogue insulin injection.

Blood samples were taken from all participants (following a 10-hour fast) for biochemical evaluation, early in the morning, just before the carotid ultrasonography examination. Age, sex, heart rate (/min), central systolic and diastolic blood pressure (mmHg), BMI (kg/m^2), total cholesterol (mg/dL), LDL, HDL, apo B, triglycerides (mg/dL), smoking status, fasting blood sugar, HgA1c, visceral fat (kg), abdominal fat ratio (%), whole-body fat ratio (%), fat mass (kg), fat-free mass (kg), total blood weight (kg), creatinin (mg/dL) values were recorded for all patients on the day of carotid ultrasound. Non-HDL cholesterol level was calculated as [total cholesterol - HDL cholesterol]. The recommended level of non-HDL cholesterol is <130 mg/dL in diabetic patients without cardiovascular disease (34).

Microalbuminuria is considered to be a finding of diabetic nephropathy in our T1DM patients. Patients who have one of the following findings such as impairment of pain, light touch, and temperature or loss of vibratory sensation and altered proprioception reflect, were considered to have diabetic polyneuropathy. The presence of diabetic retinopathy was evaluated by an ophthalmologist.

Carotid ultrasonography

Carotid B-mode ultrasonography was applied with a high-resolution B-mode device (Samsung Medison RS85) using a L3-12A (Samsung Medison Co., Ltd.) linear probe. The frame rate was 32 fps during the examination. The evaluations included both carotid arteries in the head midline and hyperextension positions. Both CCAs were evaluated using recordings at ≥2 consecutive beats.

Speckle tracking strain analysis of the carotid artery

Arterial Analysis software (Samsung Medison Co., Ltd.), which was inherent to US device, was used to quantify CCA strain and stiffness parameters. Vascular wall displacement was automatically calculated by software to evaluate the functional capabilities of vascular structures. For the analysis, ≥5 mm of the CCA below the origin of the carotid bulb was used. The user-defined control points in the vessel wall were set to follow the optical flow algorithm in a determined frame automatically. The control points were limited to maintain the round shape of the vascular structure and move within a certain focal range. The suitability of tracking was confirmed through two trials.

Radial and circumferential movement of the CCA in the transverse plane, as well as the radial movement of the CCA in the longitudinal plane, were calculated automatically by using the STCS method. In addition, the strain (%), strain rate (per second), and peak circumferential and radial displacements (mm) were calculated. The displacement of the carotid wall is shown in Fig. 1a (the transverse plane) and Fig. 1b (the longitudinal plane).

Calculation of arterial stiffness parameters

Arterial stiffness parameters, such as elastic modulus, arterial distensibility, arterial compliance and β-stiffness index, were calculated using the radial measurements and arterial analysis software. In order to calculate the arterial stiffness parameters,

Table 2. Baseline descriptive features and laboratory results of T1DM and control groups

	T1DM (n=30)	Control (n=30)	*p*
Age (years)	34.27±9.12	34.23±8.58	0.988
Men, n (%)	11 (36.6)	13 (43.3)	0.598
Heart rate (/min)	86.13±10.89	79.83±10.44	0.026
Central systolic blood pressure (mmHg)	123.13±12.96	125.3±11.21	0.410
Central diastolic blood pressure (mmHg)	80.53±9.75	78.43±9.07	0.392
Body mass index (kg/m^2)	23.7±3.06	25.3±3.45	0.916
Total cholesterol (mg/dL)	187 (138–293)	188 (138–266)	0.968
Apo B	111±26.8	97.6±24.6	0.077
LDL (mg/dL)	117.84±31.04	115.72±26.86	0.781
HDL (mg/dL)	59.57±12.32	53.03±11.00	0.036
Non-HDL cholesterol (mg/dL)	133.96±35.97	137.48±32.69	0.702
Triglycerides (mg/dL)	82 (33–211)	90 (35–352)	0.212
Smoking, n (%)	13 (43)	7 (23)	0.100
Fasting blood glucose (mg/dL)	179 (28–384)	83 (72–117)	<0.001
HbA1c (%)	8.2 (6.3–12)	5.1 (4–5.7)	<0.001
Visceral fat (kg)	7.05±3.85	9.05±5.39	0.113
Abdominal fat ratio (%)	29.69±8.55	33.59±7.19	0.065
Whole-body fat ratio (%)	22.86±8.03	25.94±6.87	0.123
Fat mass (kg)	14.9 (4–28.2)	18.4 (7.9–38.8)	0.012
Fat-free mass (kg)	49 (37.4–68.9)	48.2 (39.9–81.2)	0.316
Total blood weight (kg)	35.8 (27.4–50.5)	35.3 (29.2–59.4)	0.312
Creatinine (mg/dL)	0.79±0.16	0.74±0.13	0.275

Data are expressed as n (%), mean ± standard deviation (for normal distributions) or median (min-max) (for non-normalized variables).

the systolic and diastolic blood pressure was measured by a trained, experienced technician with pulse wave analysis of the brachial artery using an ERKA sphygmomanometer (ERKA, D- 83646 Perfect Aneroid). Blood pressure measurements were performed on the elbow after the patients had rested in the supine position for 5 minutes. The measured systolic and diastolic blood pressure was entered into the software, and all arterial stiffness parameters were then automatically calculated by the software with respect to the pre-defined formula for each parameter. The definition and formula of each arterial stiffness parameter are presented in Table 1. An increase in elastic modulus, β-stiffness indices and PWV indicates an increase in arterial stiffness, whereas an increase in arterial distensibility and arterial compliance indicates a greater extent of arterial distension per unit of pressure.

Measurement of carotid intima media thickness

Arterial Analysis software was used to measure CIMT. The mean value of the CIMT was calculated semi-automatically for each CCA, in the longitudinal plane, at a location where the nontortuous region is a minimum of 5 mm below the beginning of the CCA bulbus. Both the anterior and posterior

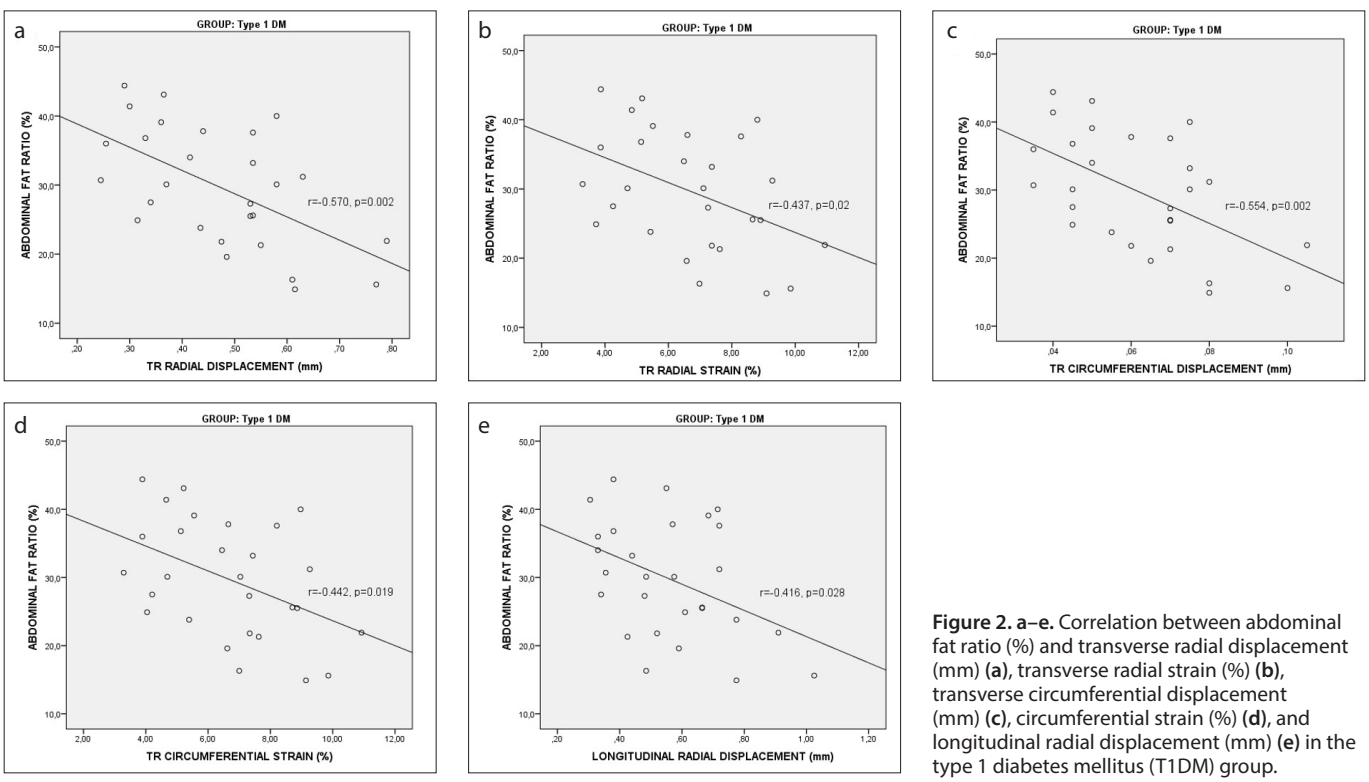

Figure 2. a–e. Correlation between abdominal fat ratio (%) and transverse radial displacement (mm) **(a)**, transverse radial strain (%) **(b)**, transverse circumferential displacement (mm) **(c)**, circumferential strain (%) **(d)**, and longitudinal radial displacement (mm) **(e)** in the type 1 diabetes mellitus (T1DM) group.

Table 3. Comparison of parameters in the transverse and longitudinal plane between groups

	Transverse plane			Longitudinal plane		
	T1DM (n=30)	Control (n=30)	*p*	T1DM (n=30)	Control (n=30)	*p*
CIMT (mm)				0.47±0.11	0.42±0.05	0.039
Minimum diameter (mm)	6.8 (5.8–8.5)	6.8 (5.8–7.8)	0.657	5.91±0.59	5.98±0.52	0.650
Maximum diameter (mm)	7.34±0.70	7.26±0.55	0.641	6.4 (5.4–7.9)	6.4 (5.6–7.7)	0.749
Stiffness parameters						
β-stiffness index	5.7 (3.1–16.2)	5.9 (2.4–14.9)	0.824	4.3 (2.5–10.4)	5.3 (1.7–10.3)	0.160
Arterial compliance (mm/kPa)	0.98±0.34	0.99±0.413	0.947	1.02±0.42	0.96±0.49	0.642
Arterial distensibility (/kPa)	0.01 (0.01–0.03)	0.01 (0.01–0.03)	0.826	0.02 (0.01–0.04)	0.02 (0.01–1.01)	0.489
Elastic modulus (kPa)	78.4 (37.7–220)	84.8 (31.6–193)	0.965	58.6 (30.8–141)	68.2 (22.6–133.5)	0.308
Pulse wave velocity (m/s)	5.80±1.27	5.72±1.19	0.789	5.10± 1.05	5.17± 1.02	0.771
Strain parameters (radial)						
Displacement (mm)	0.48±0.15	0.47±0.15	0.889	0.55±0.18	0.52± 0.19	0.590
Strain (%)	6.81±2.14	6.70±2.26	0.852	8.86±2.80	8.18±2.84	0.355
Strain rate (1/s)	0.72 (0.39–1.34)	0.77 (0.3–1.35)	0.929	0.84 (0.55–1.46)	0.77 (0.43–1.13)	0.165
Strain parameters (circumferential)						
Displacement (mm)	0.06 (0.04–0.11)	0.06 (0.03–0.11)	0.953			
Strain (%)	6.82±2.13	6.82±2.19	0.990			
Strain rate (1/s)	0.72 (0.38–1.33)	0.75 (0.29–1.34)	0.965			

T1DM, type 1 diabetes mellitus; CIMT, carotid intima media thickness.
Data are expressed as mean±standard deviation for normal distributions or median (min–max) for non-normalized variables.

Table 4. Comparison of stiffness parameters in T1DM patients with non-HDL cholesterol value >130 mg/dL and ≤ 130 mg/dL

	Non-HDL>130 mg/dL (n=15)	Non-HDL≤130 mg/dL (n=15)	*p*
Longitudinal plane			
CIMT (mm)	0.47±0.12	0.48±0.12	0.748
β-stiffness index	4.83 (3.4–10.4)	3.66 (2.5–8.96)	0.049
Elastic modulus (kPa)	62.18 (39–141)	48.78 (30.8–119)	0.049

T1DM, type 1 diabetes mellitus; HDL, high-density lipoprotein; CIMT, carotid intima media thickness.
Data are expressed as mean±standart deviation if normally distributed or median (min-max) if non-normally distributed.

wall interfaces that define the blood-intima boundaries in the carotid artery (at least 4 spots in all) were marked on a still image, then the movement of the marked points was automatically monitored by the software. The average of the right and left carotid artery CIMT values were used in the study analysis (Fig. 1).

Other physiological measurements

TANITA Body Composition Analyzer (BC-418 MA, Tanita Corp.) was used for anthropometric and body composition measurements and Tanita AB-140 ViScan (Tanita Corp.) was used for abdominal fat ratio measurement.

Statistical analysis

Categorical variables were presented as n (%), non-normally distributed continuous variables were shown as "median (min-max)", and normally distributed variables were shown as "mean ± standard deviation". The normality of data distribution in groups and subgroups was evaluated with the Kolmogorov-Smirnov test and Shapiro Wilks test, respectively. Pearson's chi-square test was used to compare the categorical variables; the Mann-Whitney U test (for non-normal distribution) or Student's t test (for normal distribution) was used to compare the continuous variables. In the diabetic group, the impact of age, duration of diabetes, CIMT, fat mass, and whole-body fat ratio on the parameters of carotid artery strain and arterial stiffness were assessed using Pearson and Spearman correlation coefficient (two-tailed) for data with normal and non-normal distribution, respectively. Significance level was set at $\alpha = 0.05$. We performed all the statistical analyses using SPSS (Version 22.0, IBM). When the prevalence of T1DM was accepted as 0.08%, the power of our study was 98.3% according to the power analysis performed in the epi info program by taking the alpha value 0.05, within the 95% confidence interval (35).

Results

As shown in Table 2, T1DM and control groups were similar in terms of age, sex, central systolic and diastolic blood pressure, BMI, total cholesterol, Apo B, LDL, non-HDL cholesterol, triglycerides, smoking, visceral fat, abdominal fat ratio, whole-body fat ratio, fat-free mass, total blood weight and creatinine. In the T1DM group, the heart rate, HDL, fasting blood glucose, and HbA1c were higher than in the control group ($p = 0.026$, $p = 0.036$, $p < 0.001$, $p < 0.001$, respectively). In the control group, the fat mass was higher than in the diabetic group ($p = 0.012$). In the T1DM group, nephropathy or neuropathy was present in

Table 5. Comparison of strain and stiffness parameters in T1DM patients with and without nephropathy, neuropathy, and retinopathy

Transverse plane	Nephropathy (+) (n=12)	Nephropathy (-) (n=18)	*p*	Neuropathy (+) (n=12)	Neuropathy (-) (n=18)	*p*	Retinopathy (+) (n=8)	Retinopathy (-) (n=22)	*p*
Elastic modulus (kPa)	98.12 (37.7–220)	72.35 (37.7–219)	0.039	80.79 (48.7–174.4)	75.95 (37.7–219.8)	0.553	77.05 (71.5–174.4)	80.57 (37.7–219.8)	0.574
Pulse wave velocity (m/s)	5.98 (5.07–8.73)	5.26 (3.92–8.9)	0.031	5.79 (4.51–7.79)	5.55 (3.92–8.9)	0.374	5.44 (5.1–7.8)	5.57 (3.92–8.9)	0.439
Longitudinal plane									
Elastic modulus	84.1 (48.8–140.5)	55.5 (30.8–116.7)	0.016	60.0 (97–359)	56.9 (30.8–140.5)	0.735	70.8 (48.8–124.6)	56.9 (30.8–140.5)	0.302
β-stiffness index	5.61 (3.4–10.4)	4.03 (2.5–8.4)	0.047	4.37 (2.54–10.3)	4.27 (2.50–10.4)	0.866	4.65 (3.35–10.2)	4.2 (2.5–10.4)	0.453
Arterial compliance (mm/kPa)	0.83 (0.32–1.63)	1.15 (0.46–1.94)	0.042	1.03 (0.32–1.94)	0.99 (0.41–1.85)	0.687	0.87 (0.42–1.63)	1.09 (0.32–1.94)	0.398
Distensibility (/kPa)	0.0100 (0.01–0.03)	0.015 (0.01–0.04)	0.026	0.02 (0.01–0.03)	0.02 (0.01–0.04)	0.965	0.02 (0.01–0.03)	0.02 (0.01–0.04)	0.243
Pulse wave velocity (m/s)	5.58 (4.31–7.05)	4.5 (3.54–6.53)	0.038	5.04 (3.81–6.8)	4.71 (3.54–7.05)	0.268	5.29 (4.31–6.58)	4.74 (3.54–7.05)	0.464
CIMT (mm)	0.50 (0.35–0.65)	0.46 (0.28–0.76)	0.362	0.51 (0.34–0.65)	0.44 (0.28–0.76)	0.138	0.50 (0.40–0.65)	0.46 (0.28–0.76)	0.241

CIMT, carotid intima media thickness.
Data are expressed as mean±standart deviation if normally distributed or median (min-max) if non-normally distributed.

Table 6. Correlation of age and arterial analysis parameters in T1DM group

	Longitudinal plane		Transverse plane	
	r	*p*	r	*p*
CIMT	0.624	<0.001		
β-stiffness index	0.687	<0.001	0.715	<0.001
Arterial distensibility	- 0.670	<0.001	-0.712	<0.001
Arterial compliance	- 0.633	<0.001	-0.616	<0.001
Elastic modulus	0.738	<0.001	0.734	<0.001
Pulse wave velocity	0.753	<0.001	0.753	<0.001
Radial displacement	- 0.498	0.005	-0.418	0.021
Radial strain	0.542	0.002	- 0.565	0.001
Radial strain rate	- 0.308	0.308	0.704	<0.001
Circumferential displacement		-0.412	0.024	
Circumferential strain		-0.568	0.001	
Circumferential strain rate		-0.714	<0.001	

CIMT, carotid intima media thickness.

12 of 30 patients (40%), and retinopathy was present in 8 of 30 patients (27%).

The T1DM group had higher CIMT than the control group (CIMT: 0.47±0.11 mm vs. 0.42±0.05 mm, for diabetic group vs. control group, respectively; $p = 0.039$).

All CCA stiffness and strain data in T1DM and control groups were presented in Table 3. There were no significant differences between diabetic and control groups in terms of arterial stiffness indices, such as β-stiffness index, arterial compliance, arterial distensibility, elastic modulus and PWV, evaluated in the longitudinal plane and transverse plane (Table 3).

There were no significant differences between the T1DM and control groups in terms of CCA strain parameters such as radial displacement, radial strain, radial strain rate, circumferential displacement, circumferential strain, circumferential strain rate evaluated in the transverse plane and longitudinal plane (Table 3).

Diabetic patients were subdivided according to the non-HDL cholesterol values >130 mg/dL (n=15) or ≤130 mg/dL (n=15). CIMT, arterial stiffness indices, and strain parameters of the patients in these subgroups were presented in Table 4. CIMT was not significantly different between the subgroups. Patients with high non-HDL cholesterol had higher β-stiffness and elastic modulus values in the longitudinal plane compared with patients with normal non-HDL cholesterol ($p = 0.049$, $p = 0.049$, respectively).

Diabetic patients were also subdivided according to the presence of nephropathy, retinopathy and neuropathy complications. Arterial stiffness indices and strain parameters of the patients in the subgroups were presented in Table 5. In terms of CIMT, there were no significant differences between patients with nephropathy, retinopathy or neuropathy and patients without those conditions. Patients with nephropathy had higher PWV values in the transverse and longitudinal planes compared with patients without nephropathy ($p = 0.031$, $p = 0.038$, respectively). Patients with nephropathy had higher elastic modulus values in the transverse and longitudinal planes compared with patients without nephropathy ($p = 0.039$, $p = 0.016$, respectively). Patients with nephropathy had

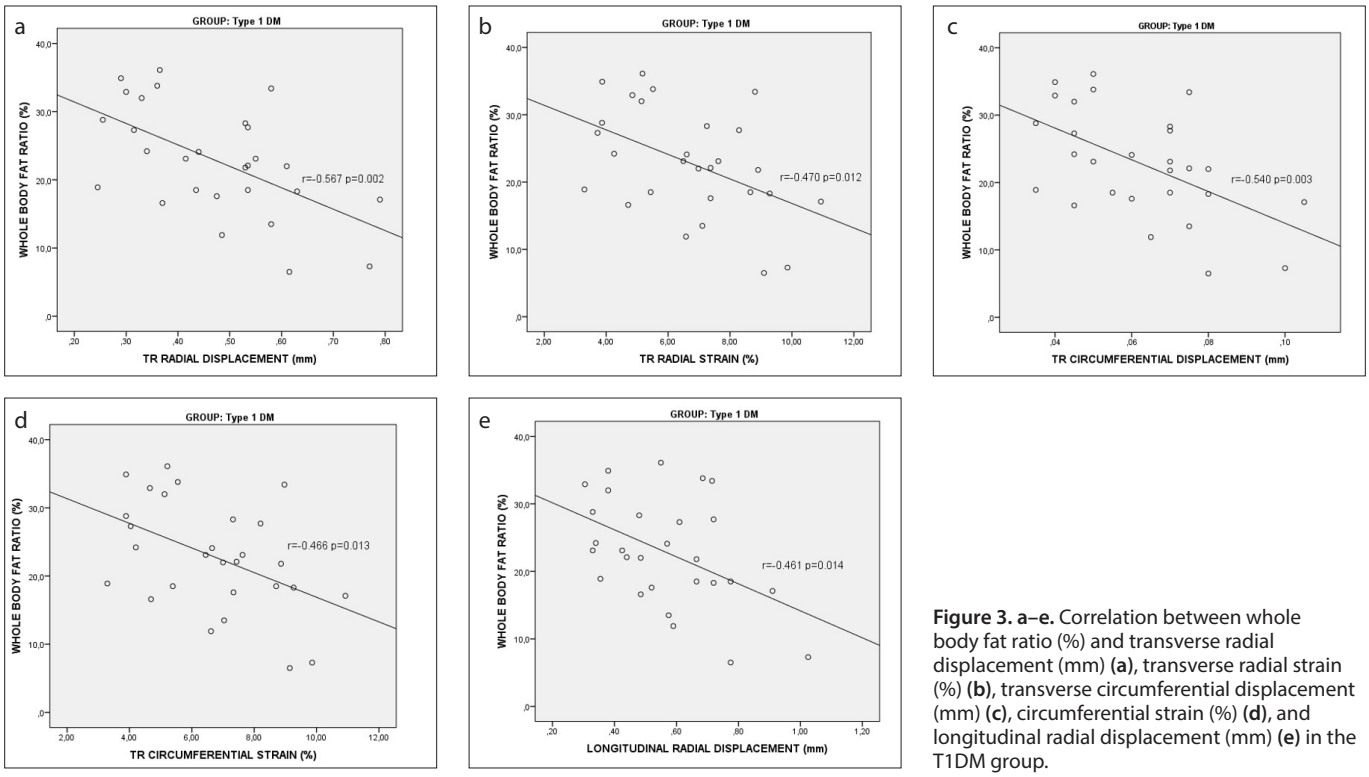

Figure 3. a–e. Correlation between whole body fat ratio (%) and transverse radial displacement (mm) **(a)**, transverse radial strain (%) **(b)**, transverse circumferential displacement (mm) **(c)**, circumferential strain (%) **(d)**, and longitudinal radial displacement (mm) **(e)** in the T1DM group.

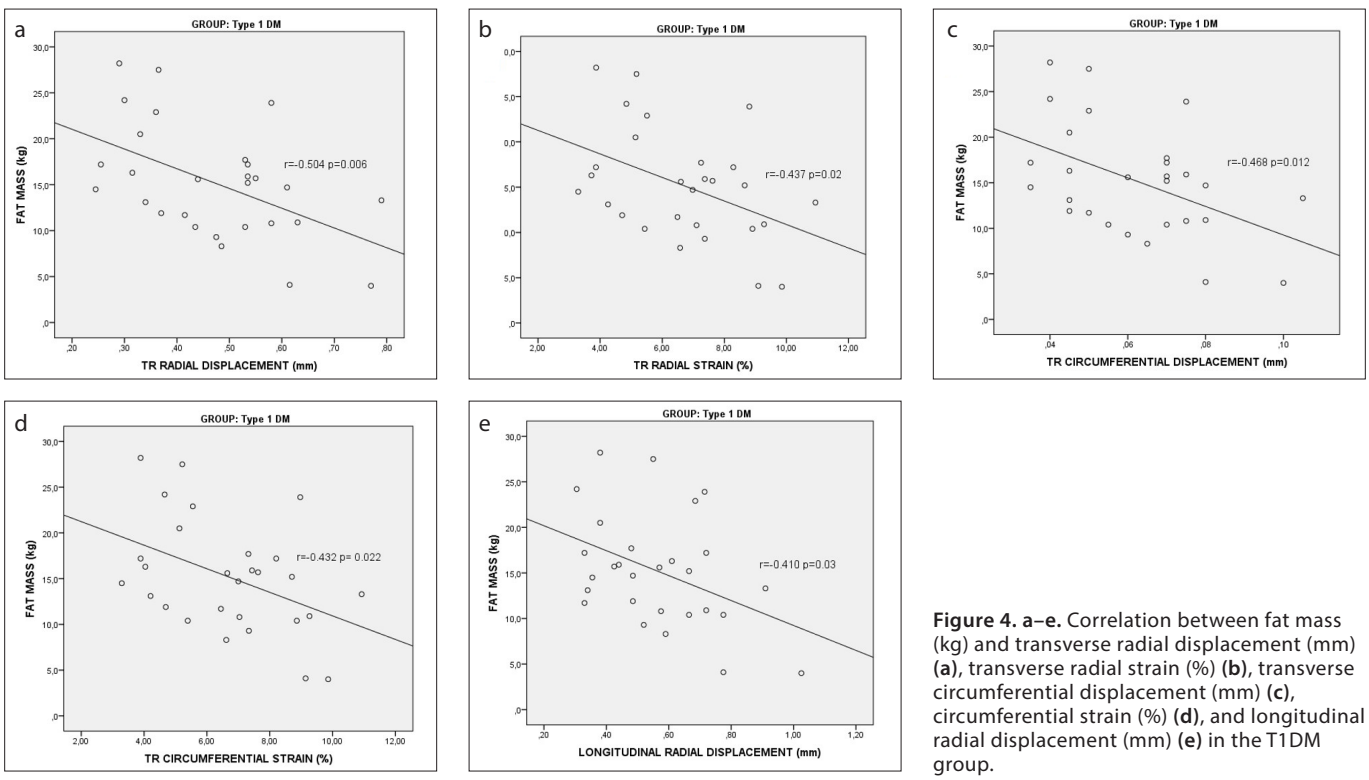

Figure 4. a–e. Correlation between fat mass (kg) and transverse radial displacement (mm) **(a)**, transverse radial strain (%) **(b)**, transverse circumferential displacement (mm) **(c)**, circumferential strain (%) **(d)**, and longitudinal radial displacement (mm) **(e)** in the T1DM group.

higher β-stiffness index values in the longitudinal plane compared with patients without nephropathy (p = 0.047). Patients with nephropathy had lower arterial compliance and distensibility values which were evaluated in the longitudinal plane compared with patients without nephropathy (p = 0.042, p = 0.026, respectively). In terms of the arterial stiffness indices and strain parameters, there were no differences between patients with retinopathy or neuropathy and patients without those conditions ($p > 0.05$) (Table 5).

In both groups, age was correlated with all arterial stiffness and strain parameters of the CCA in all planes ($p < 0.05$) (Table 6).

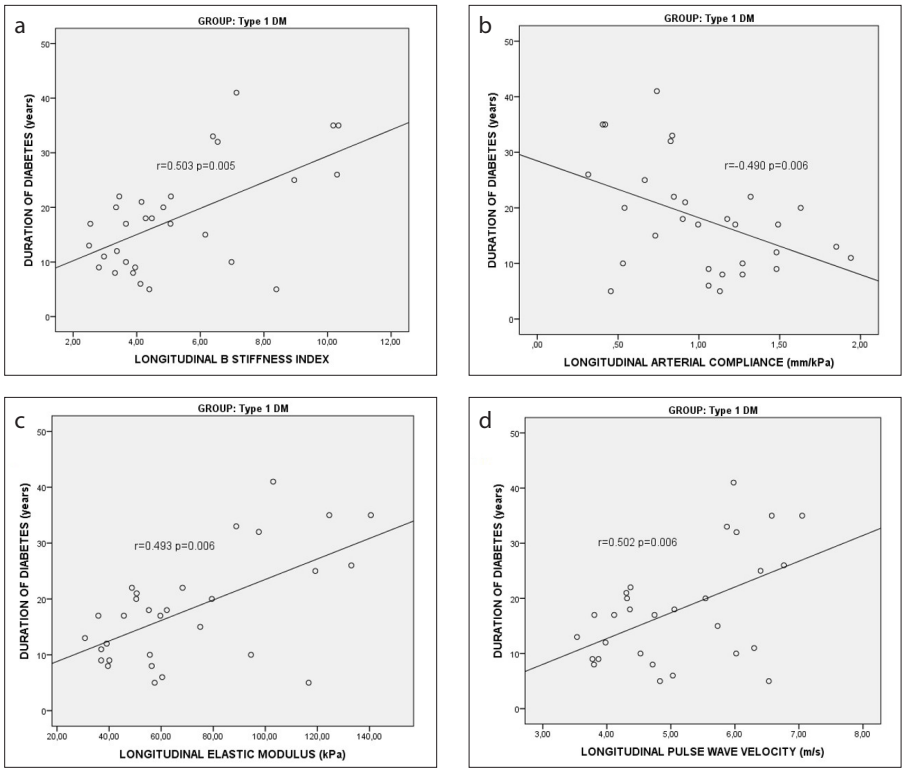

Figure 5. a–d. Correlation between duration of diabetes (years) and longitudinal β-stiffness index **(a)**, longitudinal arterial compliance (mm/kPa) **(b)**, longitudinal elastic modulus (kPa) **(c)**, and longitudinal pulse wave velocity (m/s) **(d)** in the T1DM group.

In the diabetic group, abdominal fat ratio, whole-body fat ratio, and fat mass were negatively correlated with radial displacement in the longitudinal plane (r= -0.416 p = 0.028, r= -0.434 p = 0.014, r= -0.410 p = 0.030, respectively), as well as with radial strain (r= -0.437 p = 0.020, r= -0.470 p = 0.012, r= -0.437 p = 0.020, respectively), circumferential displacement (r= -0.554 p = 0.002, r= -0.540 p = 0.003, r= -0.468 p = 0.012, respectively) and circumferential strain (r= -0.442 p = 0.019, r= -0.466 p = 0.013, r= -0.432 p = 0.022, respectively) in the transverse plane (Figs. 2–4).

In the diabetic group, the duration of diabetes was correlated with β-stiffness index (r= 0.503 p = 0.005), arterial distensibility (r= -0.490 p = 0.006), arterial compliance (r= -0.447 p = 0.013), elastic modulus (r= 0.493 p = 0.006) and PWV (r= 0.502 p = 0.006) in the longitudinal plane. Also, the duration of diabetes was correlated with β-stiffness index (r= 0.390 p = 0.033), arterial compliance (r= -0.384 p = 0.036), elastic modulus (r= 0.387 p = 0.034) and PWV (r= 0.426 p = 0.019) in the transverse plane (Fig. 5).

Discussion

In the present study, the STCS method was effectively applied in both the control group and the diabetic patients. T1DM and control groups were compared in terms of carotid artery wall elasticity characteristics by evaluating strain and stiffness parameters and no statistically significant difference was found in arterial stiffness and strain parameters measured in transverse and longitudinal planes. However, higher CIMT values were found in the diabetic group than in the control group. In both groups, age was positively correlated with the arterial stiffness indices but negatively correlated with the CCA strain parameters. In the T1DM group, duration of diabetes was positively correlated with β-stiffness index, elastic modulus and PWV, but negatively correlated with the arterial distensibility. When T1DM patients with and without diabetic nephropathy were compared, those with diabetic nephropathy had higher transverse and longitudinal elastic modulus and PWV, as well as longitudinal β-stiffness index, but lower longitudinal arterial compliance and distensibility. In terms of CIMT, there was no difference between patients with and without nephropathy. When diabetic patients with non-HDL cholesterol >130 mg/dL and ≤130 mg/dL were compared, patients with high non-HDL cholesterol had higher β-stiffness and elastic modulus values which were evaluated in the longitudinal plane. In terms of CIMT, there was no difference between patients with higher versus normal non-HDL cholesterol levels.

Arterial stiffness has been defined as an early marker of atherosclerosis in T1DM patients (3, 33). Many studies have shown that subclinical signs of arterial wall stiffening due to increased cardiovascular risk can be detected by speckle tracking techniques (15, 17–22). Arterial analysis software using ultrasound-based speckle tracking method evaluates arterial wall stiffness by providing measurement of regional mechanical properties of the arterial wall by ultrasound. To the best of our knowledge, no prior study has evaluated the effectiveness of the STCS method for detecting early atherosclerotic signs in adult T1DM patients. Several studies have revealed that the strain values obtained using the STCS method can be used to effectively evaluate alterations in the elasticity of the carotid artery due to aging or cardiovascular risk factors (17, 32, 36). In a study evaluating arterial stiffness using speckle tracking method in 50 children with T1DM, it was found that stiffness parameters (strain, strain rate) derived from STCS imaging were lower in diabetic children than in controls (11). In a study including 26 elderly diabetic patients (Type 1 and 2) and 26 healthy young volunteers, the mean amplitude value for diameter change and the longitudinal displacement of arterial wall were lower in diabetes patients than in healthy young volunteers (37). Kim et al. (27) previously found that carotid artery elasticity, as measured with a STCS technique, significantly increased after short-term high-dose statin treatment, but they found no change in CIMT or maximum plaque thickness as a result of this treatment. This suggests that STCS imaging-based measurements allow for an early assessment of statins' potential effects on vascular function. Furthermore, Seals et al. (38) reported that regular exercise can attenuate age-related increase in arterial stiffness, and Pugh et al. (13) found that in comparison to conventional arterial stiffness measures, STCS is superior to demonstrate cardiorespiratory fitness related alterations on arterial stiffness in young individuals. Taken together, these findings suggest that STCS imaging has the potential to be a valuable tool in the determination of arterial stiffness and may aid in prevention of cardiovascular events.

Applanation tonometry is the gold standard technique used to evaluate arterial wall stiffness. However, this technique is time consuming, requires dedicated equipment and is not widely used in clinical routine (11, 12). Studies have shown that speckle tracking method can be an alternative to applanation tonometry in the evaluation of arterial wall stiffness (15–17). In a study evaluating arterial stiffness using applanation tonometry and speckle tracking method in 50 children with T1DM, stiffness parameters derived from tonometry and sonography were significantly correlated with each other (11). Unlike applanation tonometry, measuring local stiffness with speckle tracking method in CCA provides additional information about arterial wall compliance and local changes in the heterogeneous movement pattern, and in this way it assures to be a superior index of whole artery wall stress (13, 17). Publications which reported that 2D strain imaging is more sensitive than conventional stiffness parameters, such as PWV, elastic modulus, β-stiffness index, in detecting age-related changes in CCA elastic properties also support this (17).

In this study, we compared individuals with and without T1DM in terms of carotid artery wall elasticity characteristics by evaluating strain and stiffness parameters using the STCS method and no significant difference was found in arterial stiffness and strain parameters in both transverse and longitudinal planes between the diabetic and control groups. Our study population consisted of 30 T1DM patients without known cardiovascular disease and 30 non-diabetic sex, age, and BMI matched controls without any known disease. There were no individuals over 52 years of age in the study. There was no significant difference in the prevalence of hypertension, smoking status, BMI, which could influence the arterial stiffness and strain parameters, between diabetic and control groups. However, in control individuals who were accepted as healthy at the beginning of the study, fat mass values, which were found to have a negative correlation with strain parameters, were higher than in the diabetic patients. Moreover, HDL values were lower in the control group. These unexpected findings of the control group may have contributed to the inability to clearly demontrate the effect of T1DM on arterial stiffness.

CIMT is an important marker of atherosclerosis and an independent predictor of cardiovascular events. Studies have shown that CIMT is increased in patients with T1DM (39). In this study, in accordance with the literature, we found that CIMT was higher in the T1DM group than in the control group, and CIMT was correlated with age (2, 40, 41).

Studies have shown that advanced age can change the elastic composition of the arterial wall matrix (increase in collagen-elastin ratio due to age-related degeneration of elastin fibers and compensatory increases in collagen), which causes the stiffening of the large central arteries (4, 13). In our study, age was positively correlated with the arterial stiffness indices but negatively correlated with the CCA strain parameters in both groups. These results are concordant with previous studies which also demonstrated that CCA strain measurements, elastic modulus, and β-stiffness index correlate significantly with increasing age, which is a well-defined risk factor in atherosclerosis (17–19, 42–44).

In the diabetic group, statistically significant differences were found between arterial stiffness parameters between groups with and without high non-HDL cholesterol. However, there was no statistically significant difference between the groups in terms of CIMT. This finding suggested that in T1DM patients with dyslipidemia, functional changes may exist, even in the absence of morphological changes, and the STCS technique may provide for the early assessment of atherosclerosis in patients with T1DM, especially in those with dyslipidemia.

Mortality risk due to cardiovascular disease increases remarkably after the development of nephropathy (10). In addition, mortality rates increase in T1DM patients with prominent kidney disease (2, 45). Thus, we evaluated our T1DM patients for the presence of nephropathy. Patients with diabetic nephropathy had higher values in transverse and longitudinal elastic modulus and PWV, as well as for longitudinal β-stiffness index, but lower values for longitudinal arterial compliance and distensibility, than patients without nephropathy. Whereas, in terms of CIMT there were no statistically significant differences between patients with or without diabetic nephropathy. Our findings suggest that, in T1DM patients with diabetic nephropathy, functional changes may exist, even in the absence of morphological changes.

Non-HDL cholesterol level has been identified as a significant predictor of persistent dyslipidemia and atherosclerosis for diabetic patients (46). In our study, when diabetic patients were divided into subgroups according to the presence of dyslipidemia, no difference was found between the two groups in terms of CIMT, while arterial stiffness parameters were found to be higher in the group with high non-HDL cholesterol. This finding suggests that, in T1DM patients with dyslipidemia, functional changes may exist, even in the absence of morphological changes.

Weight problems and visceral body-fat deposition play leading roles in the development of metabolic syndrome in the overall population (47–49). Generally, patients with T1DM have normal weight, but researchers have associated central fat accumulation with insulin resistance and metabolic syndrome in T1DM patients (50–53). In this study's T1DM group, abdominal fat ratio, whole-body fat ratio, and fat mass all were negatively correlated with the radial and circumferential displacement and strain parameters in transverse plane, as well as with radial displacement in the longitudinal plane.

Several researchers have proven a relationship between atherosclerosis and duration of diabetes (45, 53). In our study, in the diabetic patient group; as the duration of diabetes increased, parameters indicating vascular stiffness such as β-stiffness index, elastic modulus and PWV values increased, whereas parameters indicating strain ability values such as distensibility decreased. These results strongly support the deterioration of vascular function as duration of diabetes increases.

The main limitation of this study is that the control group did not consist of normal healthy patients. The unsuitability of the control group to act as a true control masked the true CCA stiffness profile of the T1DM patients. In addition, the small number of patients in the diabetic subgroups, varied disease duration, and the heterogeneous disease severity associated with nephropathy, neuropathy, and retinopathy are other limitations of the study. A large group of diabetic patients with prespecified disease duration and homogeneous disease severity and a control group with healthy individuals may be more valuable for demonstrating whether there are significant differences between these groups.

In conclusion, functional changes may exist in T1DM patients with diabetic ne-

phropathy and dyslipidemia, even in the absence of morphological changes, and the STCS technique may provide for the early assessment of atherosclerosis in patients with T1DM, particularly those with nephropathy and dyslipidemia. Also, functional changes in the carotid artery may be demonstrated with the STCS technique in T1DM patients with high abdominal fat ratio, whole-body fat ratio, and fat mass. Thus, together with CIMT measurement, STCS analyses may be used to detect subclinical damage and stratify atherosclerosis in patients with T1DM. However, before implementing this technology in routine clinical applications, further studies are necessary to validate its utility.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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