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Association of Various Anthropometric Indices with Sudomotor Dysfunction in Type 2 Diabetic Patients

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Abstract

Aim: To investigate the relationship between sudomotor dysfunction and various body composition analysis indices in type 2 diabetic patients. *Methods*: Between January 2016 and April 2021, 136 diabetic participants who had undergone body composition analysis (BCA) were recruited for this cross-sectional study. Sudomotor functions were assessed using SUDOSCAN, and participants were grouped into patients with normal (Group 1, n = 51), mildly reduced (Group 2, n = 46) and severely reduced (Group 3, n = 39) foot electrochemical skin conductance (FESC) levels. *Results*: The mean age was 60.4 ± 10.1 years, median diabetes duration was 12 (6 - 19) years, and 52.2% of participants were males. Among BCA parameters, the significant differences were found in total fat (TF) (p = 0.023), percentage of TF (%TF) (p = 0.025), percentage of android fat (%AF) (p = 0.048), fat mass (FM) in arms (p = 0.016), FM in legs (p = 0.002), appendicular fat mass (aFM) (p = 0.002), appendicular fat mass/body mass index (aFM/BMI) ratio (p = 0.009) between three groups. In Spearman correlation analysis, FESC was correlated with RBC, ESR and homocysteine (r = 0.171, r = −0.190, r = −0.192, p < 0.05), respectively. Multivariate linear regression analysis revealed that FM in arms, FM in legs, aFM and aFM/BMI ratio were independently associated with FESC even after adjustment for age, diabetes duration, WC, systolic BP, HbA1c, FPG, HOMA-IR, ESR, HDL-C, LDL-C, Total Cholesterol, ALT (β =

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0.161, 0.155, 0.165, 0.185, $p < 0.05$, respectively). *Conclusion*: The progressive decline of sudomotor function is positively associated with loss of subcutaneous fat in arms and legs, suggesting that subcutaneous fat of extremities may be necessary to prevent DPN progression in type 2 diabetic patients.

Keywords

Diabetic Neuropathy, SUDOSCAN, Subcutaneous Fat, Sudomotor Dysfunction, Anthropometric Parameters

1. Introduction

According to global estimation in 2019, diabetes had affected more than 463 million adults, mainly type 2 diabetics [1]. Diabetic peripheral neuropathy (DPN) is one of the leading diabetic complications in terms of prevalence [2] and diabetes-related medical costs [3], which has a negative impact on patients' quality of life [4]. Furthermore, future estimations related to diabetes are unfavourable, expecting that almost one-third of individuals living in 2050 will be affected by diabetes, and even worse, DPN will be present in nearly 50% of those patients [5].

On the other hand, sarcopenia-another global healthcare issue present in nearly 50 million people currently, is predicted to rise tenfold in 2050 [6]. Briefly, sarcopenia is a syndrome associated with a generalized and progressive decline of muscle mass and strength, resulting in reduced physical ability and life expectancy [7] [8]. Different tools have been implicated in muscle assessment in sarcopenia, including Computed tomography (CT), Magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA), etc. [9]. However, due to low cost and radiation risk, DXA is commonly applied in clinical practice for BCA [10]. Several studies [11] [12] have found that patients with type 2 diabetes mellitus (T2DM) have a higher risk for low appendicular muscle mass than non-diabetic individuals. Even more, a diabetes-sarcopenia association may be present in the very early stages of diabetes and may further progress due to diabetic complications, particularly nerve damage related to muscle atrophy [13] [14]. In addition to low muscle mass, diabetic neuropathy also contributes to the exacerbation of motor dysfunction in patients with sarcopenia [15]. Thus, early identification of both sarcopenia and diabetic neuropathy poses great importance.

Small fiber neuropathy (SFN) is considered an initial stage of DPN and is characterized by unmyelinated C fibers damage [16]. Although nerve conduction studies (NCS) and Michigan Neuropathy Screening Instrument (MNSI) questionnaires are mainly used in daily practice to diagnose DPN, and they are less effective and insensitive for SFN detection [17]. SUDOSCAN is a sensitive,

inexpensive diagnostic tool for SFN detection through sudomotor nerve function evaluation [18] [19].

Associations between different diabetic complications and low muscle mass have been previously investigated [20] [21] [22]. However, a possible relationship between sudomotor dysfunction, which indicates SFN, and low muscle mass in subjects with type 2 diabetes remains undiscovered.

Our present study aimed to investigate the relationship between sudomotor dysfunction and various body composition analysis indices in type 2 diabetic patients.

2. Method

2.1. Study Population

Overall, 136 diabetic patients visited Qilu Hospital of Shandong University in January 2016 and April 2021 with available BCA results were recruited for the current cross-sectional study. T2DM diagnosis was following World Health Organization (WHO) 1999 criteria [23]. All subjects were categorized into three groups according to previous studies [24]:

Group 1: Subjects with normal (>70 μS) foot electrochemical skin conductance (FESC) (n = 51)

Group 2: Subjects with mildly reduced (50 - 70 μS) FESC (n = 46)

Group 3: Subjects with severely reduced (<50 μS) FESC (n = 39)

Patients under 18 or over 80 years, those out of the 18 - 40 kg/m^2 body mass index (BMI) range, breastfeeding/pregnant, immobilized patients and patients with missing information in medical records were excluded. Moreover, patients using glucocorticoids, patients with arm/leg amputation, electrical implantable devices, those with type 1 diabetes or monogenic types of diabetes, cancer, history of seizures or epilepsy, severe vitamin B12 deficiency, Parkinson's disease, sciatic nerve lesion, hypothyroidism, advanced varices of lower extremities, end-stage renal disease (ESRD), severe hepatic disorders and those who abused alcohol (males with ≥140 g/week and females with ≥70 g/week alcohol consumption) [25] were also not enrolled in our study. Written informed consent has been provided by all participants before enrollment in the study. The Qilu hospital of Shandong University's ethical committee approved the study protocol.

2.2. Data Collection

Medical records were used to obtain data related to patient's demographics, medical history, lifestyle behaviours and current medication use, such as duration of diabetes, alcohol intake or smoking, present co-morbidities (hypertension, cardiovascular disease, dyslipidemia, osteoporosis) and complications (mainly, diabetic retinopathy). Anthropometric measurements including weight (kg), height (m), waist circumference (WC) (cm), along seated blood pressure (BP) levels were obtained under standardized protocols, and BMI was also cal-

culated before BCA measurement.

2.3. Biochemical Evaluation

The results of following biochemical parameters were collected: hemoglobin (Hb), red blood cells (RBC), erythrocyte sedimentation rate (ESR), fasting plasma glucose (FPG), HbA1c, eGFR (calculated using CKD-EPI 2009 formula), homocysteine, uric acid, total bilirubin, alanine aminotransferase (ALT) and standard lipid profile with triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C). In addition to these measurements, various indices including lipid accumulation product (LAP), visceral adiposity index (VAI), Chinese VAI, Triglyceride-glucose index (TyG) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were calculated using specific formulas. Particularly, following formula was used for TyG index calculation: ln[fasting triglycerides (mg/dl) × fasting plasma glucose (mg/dl)] [26]. VAI calculation was based on gender-specific equations described by Amato *et al.* [27]: men: [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL); women: [WC/36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL). LAP was calculated using the specific equation [28]: [WC (cm) − 65] × [TG (mmol/l)] for men; [WC (cm) − 58] × [TG (mmol/l)] for women. CVAI was calculated according to published formula [29]: Males: CVAI = −267.93 + 0.68 × age + 0.03 × BMI + 4.00 × WC + 22.00 × log10(TG) − 16.32 × HDL; Females: CVAI = −187.32 + 1.71 × age + 4.23 × BMI + 1.12 × WC + 39.76 × log10(TG) − 11.66 × HDL. Previously mentioned formula was used to calculate HOMA-IR [30]: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5.

2.4. Body Composition Evaluation

A qualified staff analysed the body composition analysis of all subjects using a HorizonTM DXA System (Hologic, Inc., Marlborough, MA, USA). Following body composition parameters were measured: percentage of android fat (%AF), total fat (TF), percentage of TF (%TF), total lean mass (TLM), fat (FM) and lean mass (LM) on both arms and legs. The sum of lean mass on arms and legs was defined as appendicular LM (aLM). aLM/BMI ratio and relative skeletal muscle index (RSMI) were also calculated using specific formulae [31] [32]. Additionally, we also proposed two novel body composition parameters: appendicular fat mass (aFM) = FM in arms + FM in legs; and aFM/BMI ratio.

2.5. DPN Evaluation by SUDOSCAN

In order to assess sudomotor function, SUDOSCAN® device (Impeto Medical; Paris, France) was applied for electrochemical skin conductance (ESC) measurements from hands and the feet (both right and left sides). The procedure described in previous studies [33] was followed by trained staff, and results were obtained. The average of the right and left FESC and hand electrochemical skin conductance (HESC) values were used for statistical analysis, while feet asym-

metry (FASYM, %) and hands asymmetry (HASYM, %) values were not included.

2.6. Statistics

SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. For normally distributed and skewed quantitative variables, all data were presented as the mean ± SD or median (inter-quartile range). Shapiro-Wilk test was applied to analyze the normality of the distribution of continuous variables. Dichotomous variables were presented as percentages and were compared using the Chi-square test. Non-parametric variables were compared using the Kruskal-Wallis test, while the One Way ANOVA test was employed to compare normally distributed data between groups. The relationships between ESC in feet and other variables were analyzed using Spearman's correlation analysis. Different linear regression models (Model 1 is unadjusted; Model 2 is adjusted for age and diabetes duration; Model 3 is adjusted for age, diabetes duration, WC, systolic BP, HbA1c, FPG, HOMA-IR; and Model 4 is adjusted for age, diabetes duration, WC, systolic BP, HbA1c, FPG, HOMA-IR, ESR, HDL-C, LDL-C, TC, ALT were used to assess relationships between ESC in feet and various body composition parameters. P-value < 0.05 was considered statistically significant across all analyses.

3. Results

3.1. Demographic, Lifestyle and Clinical Parameters of the Three Groups

Among 136 T2DM subjects, 52.2% were males, 29.4% were current smokers, 25.7% were alcohol consumers, median diabetes duration was 12 (6 - 19) years, and mean age was 60.4 ± 10.1 years. For biochemical parameters, the average of HbA1c and TyG indices were 8.77% ± 1.85 and 4.85 ± 0.3, respectively. The median LAP was 45.4 (33.3 - 72.8), and the median VAI was 98.9 (67.3 - 164.4). Hypertension was the most prevalent among present co-morbidities accounting for 69.1%, while diabetic retinopathy was present in 52.9% of subjects. No significant differences were observed for compared parameters between groups, except for the presence of retinopathy ($p < 0.03$), BMI ($p < 0.012$), waist circumference ($p < 0.05$) and HESC ($p < 0.05$). The basic characteristics of subjects are illustrated in Table 1.

In terms of BCA parameters, the significant differences were found in TF ($p = 0.023$), %TF ($p = 0.025$), %AF ($p = 0.048$), FM in arms ($p = 0.016$), FM in legs ($p = 0.002$), aFM ($p = 0.002$), aFM/BMI ratio ($p = 0.009$) between three groups. The BCA parameters of patients are presented in Table 2.

3.2. Clinical Parameters Associated with FESC (Feet Electrochemical Skin Conductance)

According to Spearman correlation analysis, FESC was positively correlated with

Table 1. Baseline parameters of the study population.

Parameters	All (n = 136)	Group 1 (n = 51) FESC > 70 μS	Group 2 (n = 46) FESC 50 - 70 μS	Group 3 (n = 39) FESC < 50 μS	P-value
Age, (years)	60.4 ± 10.1	58.4 ± 11.8	61.4 ± 7.82	62.1 ± 9.68	0.168
Male, n %	52.2	43.1	54.3	61.5	0.209
DM duration, (years)	12.0 (6.0 - 19.0)	10 (2.0 - 17.0)	12.0 (7.0 - 17.5)	15.0 (7.0 - 20.0)	0.197
Smoker, n %	29.4	25.0	24.1	48.1	0.065
Drinker, n %	25.7	15.7	26.1	35.7	0.050
Hypertension, %	69.1	64.7	73.9	69.2	0.619
CVD, %	35.3	31.4	32.6	43.6	0.435
Osteoporosis, %	11.1	7.8	13.3	12.8	0.640
Dyslipidemia, %	66.9	66.7	67.4	66.7	0.996
Diabetic Retinopathy, %	52.9	41.2	52.2	69.2	***0.030***
OADD, %	57.4	60.8	60.9	48.7	0.435
OADD + Insulin, %	42.6	39.2	39.1	51.3	0.435
Antilipidemic, %	66.9	66.7	67.4	66.7	0.996
Antihypertensive,%	69.1	64.7	73.9	69.2	0.619
Aspirin, %	60.3	52.9	65.2	64.1	0.396
Beta-blockers, %	25.7	25.5	28.3	23.1	0.861
BMI (kg/m^2)	25.3 (23.2 - 27.8)	26.6 (24.2 - 29.6)	24.6 (22.7 - 27.2)	25.1 (22.6 - 27.9)	***0.012***
WC (cm)	95.0± 10.1	98.1 ± 9.30	92.7 ± 9.1	93.8 ± 11.2	***0.019***
Height (cm)	166.3 ± 7.38	165.5 ± 7.43	166.7 ± 6.82	166.8 ± 8.03	0.646
Systolic BP (mm Hg)	137.7 ± 18.7	137.6 ± 19.2	137.8 ± 20.0	137.6 ± 16.9	0.998
Diastolic BP (mm Hg)	79.2 ± 11.6	79.9 ± 13.3	78.6 ± 9.63	79.0 ± 11.5	0.864
HESC (μS)	64.0 (53.2 - 75.0)	74.0 (63.0 - 79.0)	63.0 (53.7 - 74.0)	49.0 (25.0 - 64.0)	***0.001***
TyG	4.85 ± 0.3	4.87 ±0.29	4.81 ± 0.32	4.85 ± 0.26	0.594
LAP	45.4 (33.3 - 72.8)	54.9 (37.7 - 86.4)	42.8 (27.5 - 72.5)	42.7 (25.0 - 67.9)	0.091
VAI	98.9 (67.3 - 164.4)	121.4 (69.0 - 170.9)	89.4 (66.5 - 150.9)	97.8 (65.1 - 138.9)	0.251
Chinese VAI	131.9 ± 37.9	139.9 ± 35.3	124.5 ± 33.1	130.5 ± 45.0	0.133
Hemoglobin (g/l)	137.3 ± 14.6	138.6 ± 13.4	136.1 ± 14.5	137.0 ± 16.3	0.695
Red Blood Cells (10^{12}/L)	4.56 (4.26 - 4.83)	4.65 (4.31 - 4.86)	4.56 (4.24 - 4.85)	4.43 (4.22 - 4.82)	0.233
ESR (mm/h)	18.0 (9.0 - 30.0)	15.0 (8.0 - 27.0)	20.0 (9.0 - 27.2)	19.0 (11.0 - 33.0)	0.314
FPG (mmol/l)	6.89 (5.73 - 8.61)	7.09 (5.92 - 8.62)	6.75 (5.28 - 7.99)	7.10 (5.91 - 9.60)	0.244
HbA1c (%)	8.77 ± 1.85	8.96 ± 1.90	8.36 ± 1.96	9.01 ± 1.60	0.175
HOMA-IR	3.89 (2.37 - 6.85)	4.09 (2.73 - 7.04)	3.24 (1.96 - 6.76)	3.60 (2.21 - 6.22)	0.498
eGFR (ml/min/1.73m^2)	97.2 (91.8 - 106.1)	98.5 (94.7 - 109.9)	96.2 (90.2 - 104.2)	97.2 (91.1 - 103.1)	0.193
HDL-C (mmol/l)	1.07 (0.92 - 1.33)	1.08 (0.94 - 1.32)	1.10 (0.94 - 1.35)	1.03 (0.89 - 1.37)	0.651
LDL-C (mmol/l)	2.74 ± 0.87	2.97 ± 0.90	2.63 ± 0.86	2.58 ± 0.81	0.065
Triglycerides (mmol/l)	1.38 (1.06 - 1.94)	1.44 (1.13 - 2.16)	1.26 (1.03 - 2.13)	1.01 (1.45 - 1.86)	0.754
TC (mmol/l)	4.50 ± 1.09	4.72 ± 1.10	4.46 ± 1.08	4.27 ± 1.07	0.144
Homocysteine (μmol/L)	11.5 (9.5 - 14.3)	10.5 (8.8 - 13.5)	12.2 (10.1 - 14.4)	11.6 (9.3 - 15.3)	0.051

Continued

Uric Acid (μmol/L)	296.0 (247.0 - 352.0)	299.0 (246.0 - 337.0)	303.5 (250.2 - 367.5)	289.0 (246.0 - 338.0)	0.721
Total Bilirubin (μmol/L)	10.1 (7.02 - 14.7)	9.30 (7.10 - 13.50)	10.1 (6.45 - 15.3)	10.1 (7.40 - 14.9)	0.964
ALT (IU/L)	17.0 (12.0 - 23.0)	13.0 (17.0 - 30.0)	16.0 (12.0 - 23.0)	17.0 (11.0 - 22.0)	0.587

Abbreviations: FESC = Feet electrochemical skin conductance; DM = Diabetes mellitus; CVD = Cardiovascular disease; OADD = Oral antidiabetic drugs; BMI = Body mass index; WC = waist circumference; BP = blood pressure; HESC = Hand electrochemical skin conductance; TyG = Triglyceride-glucose index; LAP = Lipid accumulation product; VAI = Visceral adiposity index; ESR = Erythrocyte sedimentation rate; FPG = Fasting plasma glucose; HbA1c = Glycosylated hemoglobin; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; eGFR = estimated glomerular filtration rate; HDL-C = High-density-lipoprotein cholesterol; LDL-C = Low-density-lipoprotein cholesterol; TC = Total cholesterol; ALT = Alanine aminotransferase.

Table 2. Body composition analysis (BCA) parameters of participants.

BCA Parameters	All (n = 136)	Group 1 (n = 51) FESC > 70 μS	Group 2 (n = 46) FESC 50 - 70 μS	Group 3 (n = 39) FESC < 50 μS	P value
TF (kg)	22.4 (18.4 - 26.4)	23.0 (20.3 - 30.4)	21.3 (18.3 - 24.4)	22.9 (16.5 - 25.7)	***0.023***
%TF	32.3 ± 6.32	34.2 ± 6.79	31.2 ± 5.83	31.1 ± 5.77	***0.025***
%AF	36.3 ± 6.66	38.1 ± 6.62	35.4 ± 6.62	35.1 ± 6.40	***0.048***
TLM (kg)	46.2 (40.6 - 53.0)	47.7 (40.2 - 52.9)	44.4 (40.5 - 54.7)	47.2 (41.2 - 52.5)	0.958
LM in arms (kg)	4.72 (3.94 - 5.68)	4.72 (3.92 - 5.74)	4.76 (3.95 - 5.70)	4.67 (3.83 - 5.35)	0.872
LM in legs (kg)	13.5 (11.7 - 16.1)	13.8 (11.9 - 16.1)	13.3 (11.9 - 16.4)	13.5 (11.4 - 15.6)	0.797
FM in arms (kg)	2.80 (2.27 - 3.39)	2.97 (2.47 - 4.01)	2.74 (2.09 - 3.25)	2.51 (1.97 - 3.27)	***0.016***
FM in legs (kg)	5.65 (4.28 - 7.20)	6.40 (4.79 - 8.10)	5.48 (4.19 - 6.43)	4.94 (3.99 - 6.48)	***0.002***
aFM (kg)	8.5 (6.55 - 10.3)	9.08 (7.73 - 12.1)	8.22 (6.33 - 9.65)	7.46 (5.92 - 9.51)	***0.002***
aLM (kg)	18.1 (15.9 - 21.8)	18.3 (16.0 - 21.9)	17.8 (16.0 - 22.6)	18.4 (15.3 - 20.9)	0.820
aLM/BMI ratio	0.71 (0.62 - 0.85)	0.66 (0.60 - 0.81)	0.76 (0.67 - 0.86)	0.72 (0.62 - 0.86)	0.075
aFM/BMI ratio	0.33 (0.27 - 0.39)	0.37 (0.29 - 0.43)	0.33 (0.26 - 0.38)	0.30 (0.26 - 0.36)	***0.009***
RSMI (kg/m^2)	6.74 (6.03 - 7.54)	6.93 (6.16 - 7.64)	6.58 (6.05 - 7.58)	6.58 (5.96 - 7.23)	0.374

Abbreviations: FESC = Feet electrochemical skin conductance; TF = Total fat; AF = Android fat; TLM = Total lean mass; LM = lean mass; FM = fat mass; aFM = appendicular FM; aLM = appendicular lean mass; BMI = body mass index; RSMI = relative skeletal muscle index.

RBC ($r = 0.171$, $p = 0.047$) and HESC ($r = 0.569$, $p = 0.0001$), although negative correlations were also observed for ESR and homocysteine ($r = -0.190$, $r = -0.192$, $p < 0.05$), respectively. No significant correlations between FESC and other variables were observed (Table 3).

3.3. Associations of BCA Parameters with FESC

FESC was positively correlated with both FM in arms ($r = 0.205$, $p < 0.017$), and FM in legs ($r = 0.225$, $p < 0.008$). Moreover, significant positive correlations were observed between FESC and newly proposed BCA indices, such as aFM and aFM/BMI ratio ($r = 0.006$, $r = 0.012$, $p < 0.05$), respectively. However, there were no significant correlations between FESC and muscle mass-related BCA parameters (TLM, aLM, aLM/BMI ratio, etc.) (Table 3).

Table 3. The results of Spearman correlation analysis between various parameters and FESC.

Variables	FESC	
	Correlation coefficient	P value
TF (kg)	0.144	0.094
%TF	0.167	0.051
%AF	0.123	0.155
TLM (kg)	0.004	0.968
LM in arms (kg)	0.031	0.724
LM in legs (kg)	0.037	0.668
FM in arms (kg)	0.205	***0.017***
FM in legs (kg)	0.225	***0.008***
aFM (kg)	0.234	***0.006***
aLM (kg)	0.036	0.675
aLM/BMI ratio	−0.101	0.244
aFM/BMI ratio	0.216	**0.012**
RSMI (kg/m^2)	0.098	0.258
BMI (kg/m^2)	0.167	0.053
WC (cm)	0.110	0.202
TyG	0.014	0.873
LAP	0.134	0.121
VAI	0.096	0.268
Chinese VAI	0.048	0.578
HESC (μS)	0.569	***0.0001***
Hemoglobin (g/l)	0.114	0.185
Red Blood Cells (10^{12}/L)	0.171	***0.047***
ESR (mm/h)	−0.190	***0.027***
FPG (mmol/l)	−0.030	0.729
HbA1c (%)	0.028	0.743
eGFR (ml/min)	0.141	0.102
HDL-C (mmol/l)	0.060	0.487
LDL-C (mmol/l)	0.128	0.138
Triglyceride (mmol/l)	0.030	0.728
TC (mmol/l)	0.148	0.085
Homocysteine (μmol/L)	−0.192	***0.025***
Total Bilirubin (μmol/L)	0.029	0.734
ALT (IU/L)	0.047	0.586

Abbreviations: FESC = Feet electrochemical skin conductance; TF = Total fat; AF = Android fat; TLM = Total lean mass; LM = lean mass; FM = fat mass; aFM = appendicular FM; aLM = appendicular lean mass; BMI = body mass index; RSMI = relative skeletal muscle index; BMI = Body mass index; WC = waist circumference; TyG = Triglyceride-glucose index; LAP = Lipid accumulation product; VAI = Visceral adiposity index; DM = Diabetes mellitus; HESC = Hand electrochemical skin conductance; ESR = Erythrocyte sedimentation rate; FPG = Fasting plasma glucose;HbA1c = Glycosylated hemoglobin; eGFR = estimated glomerular filtration rate; HDL-C = High-density-lipoprotein cholesterol; LDL-C = Low-density-lipoprotein cholesterol; TC = Total cholesterol; ALT = Alanine aminotransferase.

To further assess their independent associations with FESC, those BCA parameters significantly correlated with FESC in Spearman correlation were analyzed in multivariate linear regression. In Model 2 (adjusted for age and diabetes duration) and Model 3 (further adjusted for WC, systolic BP, HbA1c, FPG, HOMA-IR), FM in arms, FM in legs, aFM and aFM/BMI ratio were independently associated with FESC (β = 0.201, 0.190, 0.204, 0.205, $p < 0.05$, respectively). Moreover, even after further adjustments for ESR, HDL-C, LDL-C, Total Cholesterol, ALT, the same BCA parameters remained independently associated with FESC (Table 4). None of the other well-known indices (TyG, LAP, VAI and Chinese VAI) was significantly associated with FESC (data are not illustrated).

4. Discussion

The fat distribution has a significant influence on DPN development and progression. As the primary source of anti-inflammatory adipokines such as leptin and adiponectin, subcutaneous fat deposition is accompanied by a better lipid profile and improved glucose control [34]. Especially gluteofemoral subcutaneous

Table 4. Association of FESC with BCA parameters by univariate and multivariate linear regression analysis.

Variables	MODEL 1			MODEL 2			MODEL 3			MODEL 4		
	β	t	P value	β	t	P value	β	t	P value	β	t	P value
TF (kg)	0.225	2.667	***0.009***	0.13	1.499	0.136	0.081	1.219	0.225	0.099	1.446	0.151
%TF	0.132	1.536	0.127	0.172	2.05	***0.042***	0.153	1.894	0.061	0.141	1.782	0.077
%AF	0.124	1.445	0.151	0.142	1.66	0.099	0.112	1.430	0.155	0.091	1.102	0.273
TLM (kg)	0.162	1.897	0.06	−0.05	−0.604	0.547	−0.093	−1.29	0.196	−0.071	−1.034	0.303
LM in arms (kg)	0.178	2.091	***0.038***	0.006	0.069	0.945	−0.031	−0.403	0.688	−0.002	−0.031	0.975
LM in legs (kg)	0.016	0.191	0.849	−0.035	−0.418	0.676	−0.074	−0.960	0.339	−0.044	−0.572	0.569
FMin arms (kg)	0.204	2.412	***0.017***	0.201	2.346	***0.020***	0.161	2.162	***0.032***	0.167	2.287	***0.024***
FM in legs (kg)	0.198	2.337	***0.021***	0.19	2.227	***0.028***	0.155	1.990	***0.049***	0.182	2.346	***0.021***
aFM (kg)	0.210	2.489	***0.014***	0.204	2.392	***0.018***	0.165	2.188	***0.030***	0.240	2.979	***0.013***
aLM (kg)	0.03	0.343	0.732	−0.024	−0.296	0.767	−0.064	−0.839	0.403	−0.033	−0.451	0.653
aLM/BMI ratio	−0.082	−0.956	0.341	−0.116	−1.36	0.176	−0.121	−1.42	0.158	−0.103	−1.253	0.212
aFM/BMI ratio	0.189	2.223	***0.028***	0.205	2.430	***0.016***	0.185	2.214	***0.029***	0.214	2.642	***0.022***
RSMI (kg/m^2)	0.088	1.028	0.306	0.032	0.386	0.702	−0009	−0116	0.908	0.027	0.361	0.719

Model 1, Unadjusted; Model 2, adjusted for Age and DM duration; Model 3, adjusted for Age, DM duration, WC, systolic BP, HbA1c, FPG, HOMA-IR; Model 4, adjusted for Age, DM duration, WC, systolic BP, HbA1c, FPG, HOMA-IR, ESR, HDL-C, LDL-C, TC, ALT; Abbreviations: TF = Total fat; AF = Android fat; TLM = Total lean mass; LM = lean mass; FM = fat mass; aFM = appendicular FM; aLM = appendicular lean mass; BMI = body mass index; RSMI = relative skeletal muscle index; DM = diabetes mellitus; WC = waist circumference; BP = blood pressure; HbA1c = Glycosylated hemoglobin; FPG = Fasting plasma glucose; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; ESR = Erythrocyte sedimentation rate; HDL-C = High-density-lipoprotein cholesterol; LDL-C = Low-density-lipoprotein cholesterol; TC = Total cholesterol; ALT = Alanine aminotransferase.

fat indirectly decreases lipotoxicity and prevents excess ectopic fat accumulation, particularly in intermuscular compartments [35] [36]. Such protective properties of subcutaneous fat can be explained by its preferential intake of excess free fatty acid (FFA) levels that prevent muscle tissue from ectopic fat accumulation [35] [37].

To our knowledge, it is a pioneering study conducted to evaluate the association between sudomotor dysfunction and various anthropometric measurements, especially newly proposed parameters including aFM, aFM/BMI ratio. The current study revealed an association between DPN, assessed by sudomotor function, and leg subcutaneous fat. Similarly, such a relationship was highlighted previously [38] [39]. Zhen *et al.* (2018) suggested that the rise of leg subcutaneous fat for 1 kg results in a 30% reduction of DPN likelihood. In addition to this, Bittel *et al.* (2015) has found that diabetic patients without DPN have more subcutaneous and less intermuscular deposition of fat than counterparts with DPN. He also proposed that the transition from T2DM to T2DM with DPN may be accompanied by a progressive shift of subcutaneous fat deposition towards intermuscular compartments. Such a gradual rise in fat deposition in the intermuscular region may lead to excess cytokines secretion [40], resulting in further degenerative changes of nerve fibers [41]. It is well studied that β-oxidation of excessive FFA by the nerve structures during hyperlipidemic state leads to Schwann cells damage via increased reactive oxygen substrates (ROS) generation [42]. Additionally, local rise of cholesterol concentration occurring in ectopic fat accumulation state results in increased oxysterols levels that contributes to neuronal damage [43]. Moreover, intermuscular fat volume was negatively correlated with both muscle strength and performance [39]. However, in the studies mentioned above [38] [39], DPN diagnosis was confirmed through nerve conduction studies or MNSI questionnaires. Our results suggest that such fat redistribution may be present even in the early stages of DPN characterized by sudomotor dysfunction. According to some authors [44], the shift in fat deposition from the subcutaneous region towards intermuscular is age-related. Nonetheless, even after adjustment for age, a decline in FESC was still correlated with subcutaneous fat loss in our research. The present study's findings may further confirm the protective role of subcutaneous fat in the progression of DPN. In addition to this, we also found similar associations between FESC and fat in arms, aFM, aFM/BMI ratio. However, ongoing studies are required to further investigate the predictive value of these novel indices in both healthy and diabetic individuals.

Our study also revealed that the progression of DPN has been associated with a decrease in neither aLM nor aLM/BMI ratio. Interestingly, the mean aLM results of patients with severely reduced FESC were higher than those of those with mildly reduced FESC. Possibly, aLM increased due to excess fat accumulation, not because of muscle hypertrophy in the current study. It was also confirmed in The Health ABC study that appendicular muscle mass does not accurately reflect the muscle strength in elderly diabetic patients [8]. Moreover, di-

abetic patients had more appendicular muscle mass than non-diabetic participants in the same study.

We found that sudomotor dysfunction was significantly associated with the presence of retinopathy. Similarly, previous studies have explored this relationship, where sudomotor dysfunction was assessed using different techniques [45] [46]. It can be explained by the fact that sudomotor dysfunction is associated with microvascular complications [47]. The inverse association between sudomotor dysfunction and total bilirubin levels in type 2 diabetic patients has been found previously [48], although no relationship has been revealed in the current study.

We finally investigated the relationship between sudomotor dysfunction and various anthropo-metabolic indices. Noticeably, no associations were identified between sudomotor dysfunction and commonly used anthropo-metabolic indices, such as TyG index, VAI, LAP and Chinese VAI. Although these indices have already been considered useful predictors of different metabolic alterations [47] [48], their importance in early DPN evaluation seems limited. Since several studies have revealed conflicting results regarding the relationship between lipid profile parameters and DPN [49] [50], our findings supporting no association between those factors should be carefully interpreted.

The current study has some limitations. Firstly, this investigation was monocentric. We also consider the relatively small number of participants as another limitation, although each investigated group had a similar number of subjects. Besides this, we proposed that excess intermuscular fat deposition increased appendicular muscle mass, although we did not clarify it by using MRI because of its high cost. Since we aimed to investigate the early stage of DPN and, even more, nerve conduction studies were not available for a significant number of patients, we used only SUDOSCAN results for DPN assessment. Nonetheless, SUDOSCAN has already been considered an effective DPN detection tool with high sensitivity and specificity [18].

5. Conclusion

In conclusion, the present pioneering study revealed that progressive decline of sudomotor function is positively associated with loss of subcutaneous fat in the extremities. Therefore, it is reasonable to suggest that a decrease of subcutaneous fat in extremities may even be present in the early stages of DPN in type 2 diabetic patients. Since aFM and aFM/BMI ratios were used for the first time in the current study, future studies should investigate their importance. Further studies are needed for a comprehensive understanding of this relationship and exploration of the importance of subcutaneous fat as a protective factor against DPN progression.

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CRediT Authorship Contribution Statement

Bekzod Odilov: Conceptualization, Methodology, Writing-original draft, Investigation, Validation. **Danfeng Yu:** Resources, Data Curation. **Amir Musa Mohamud:** Software, Formal analysis, Validation. **Ruxing Zhao:** Resources. **Ying Zou:** Writing—Review & editing, Visualization. **Xinguo Hou:** Conceptualization, Methodology, Validation, Resources, Writing—Review & editing, Supervision, Project administration.

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Conflicts of Interest

The authors reported no conflict of interest.

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