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The association between CONUT score, mRSS, and development of digital ulcers in SSc patients

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ABSTRACT

Objective: Digital ulcers (DUs) are a common manifestation of digital vascular damage in patients with Systemic Sclerosis (SSc), with more than half of SSc patients experiencing DUs at some point in their lives. Currently, there is a need for biomarkers related to inflammation or vascular damage that can predict the development of DUs.

Methods: In this cross-sectional study, we included 42 patients with diffuse (n=26) and limited cutaneous (n=16) SSc. All patients were followed for one year to monitor the occurrence of DUs. DUs occurred at least once in 20 patients, while 22 patients never developed DUs. Patient characteristics and baseline CONUT scores were compared between SSc patients with and without DUs. Data were analyzed using the SPSS 25.0 software (IBM SPSS Statistics 25, Armonk, NY: IBM Corp.). Continuous variables were presented as mean ± standard deviation, and the Independent samples t-test was used for parametric test assumptions, while the Mann-Whitney U test was used for non-parametric test assumptions to compare independent groups. The difference between categorical variables was analyzed using Chi-Square analysis. Statistical significance was set at $P<0.05$.

Results: The average age of the study group was 50.29 ± 13.9 years, and the disease duration was 9.31 ± 7.11 years. There were no significant differences in terms of age, disease duration, body mass index, serum levels of albumin and vitamin D, lipid panels, and inflammatory indexes (NLR, PLR) between SSc patients with and without digital ulcers ($p>0.05$ for all). The CONUT score was 0.86 ± 1.49 in patients without DUs and 1.2 ± 1.01 in patients with DUs (p: 0.092). The baseline modified Rodnan skin score (mRSS) was significantly higher in SSc patients with DUs.

Conclusion: The baseline CONUT score was not significantly different in SSc patients with and without DUs. However, a higher mRSS was positively correlated with an increased risk of developing DUs in SSc patients.

Keywords: CONUT score, systemic sclerosis, digital ulcers, nutrition, Raynaud phenomenon

INTRODUCTION

Digital ulcers (DUs) manifest digital vascular damage in Systemic Sclerosis (SSc) patients. More than half of the SSc patients have DUs in some part of their life (1). DUs are mainly related to hospitalizations, ischemic complications, ultimately, tissue loss (gangrene and amputation), and hand dysfunction when not treated appropriately. This condition reduces the quality of many patients' lives (2).

Raynaud phenomenon is often the earliest symptom in nearly all patients with SSc due to impaired digital perfusion in fingers and toes (3). The vascular system in these areas includes arteriovenous anastomoses that play a role in thermoregulation. Therefore, the Raynaud phenomenon primarily affects the arterial territories providing these specialized areas of skin (4). Although this knowledge diminishes the rationale behind our study hypothesis, the literature involves papers on impaired nutritional status in SSc patients (5). Severe protein and energy malnutrition is associated with a worse prognosis and increased death rate in SSc patients (6). In addition to protein and energy malnutrition, SSc patients have a deficiency of some elements and minerals in different studies with different effects. In a local single cohort study, iron and vitamin D deficiencies were the two most common ones (7). Low vitamin D levels were related to DU's increased development risk (8). In another study, folate deficiency was the most frequently seen, followed closely by selenium, prealbumin, and zinc. Several nutrient deficiencies were related to increased serum inflammatory markers (9).

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Recent trials defined the CONUT score to indicate the immune-nutritional situation. It is calculated using simple laboratory tests, including total lymphocyte count, serum albumin, and cholesterol levels. Its practicality, efficiency, and broad availability have provided widely accepted as a nutritional screening tool among variable cancer patients for short- or long-term prognosis. (10).

Its association with disease activities and patients' prognoses were evaluated in some rheumatic diseases. It was investigated in ANCA-associated vasculitis (11). The cut-off value for CONUT score above ≥3.5 (HR: 4.307) at diagnosis was accepted as a predictor of mortality in ANCA-associated vasculitis. Besides, the CONUT score was correlated with SLE disease activity in renal biopsy-proven lupus nephritis (LN) (12). A high CONUT score was also a predictor of severe infections in rheumatoid arthritis patients (13).

Furuyama T et al. investigated factors that affect postprocedure ulcer healing in 89 patients with critical limb ischemia. The higher cut-off values (over >4) of the CONUT score were related to incomplete ulcer healing (14). Hence, we aimed to examine this index in SSc patients, the relationship between DUs, and inflammatory markers of patients.

MATERIAL and METHODs

Design of the study and selection of patients

The local Committee of Ethics approved the original cross-sectional designed study (protocol no: 41132 and (approval date: May 05, 2020) following the provisions of the Helsinki Statements. We included 42 patients with diffuse (n=26) and limited cutaneous (n=16) SSc in this study from May 2020 to May 2021. The magnitude of nutritional status was measured using the CONUT score.

Inclusion criteria: having a diagnosis with SSc following the 2013 ACR/EULAR classification criteria (15), patients age 18 years and above, and having regular follow-up (regularly defined as the presence of at least four clinical evaluations per year). All SSc patients were classified as diffuse or limited cutaneous forms of the disease following the criteria mentioned above set.

Exclusion criteria: having comorbidities related to vasculopathy such as diabetes mellitus with longer disease duration (above five years), peripheral arterial disease, patients with harmful habits such as smoking, or illicit drugs, small-medium vessel vasculitis, ongoing medications such as lipid-lowering drugs, and having baseline lymphopenia (lymphocyte<1000/mm3). Also, patients with severe malnutrition, body mass index (BMI) <16 kg/m2, and serum levels of albumin lower than 30 mg/dL, with an overt gastrointestinal system (GIS) involvement, with symptoms such as chronic diarrhea and involuntary weight loss of more than 10% were excluded from minimalizing the confounder effect of GIS involvement on the nutritional status.

Collection of the study data

Patient characteristics were obtained, including age, gender, job, disease duration, clinical presentations, ongoing treatment modalities, and disease complications. Disease duration was calculated as years after the diagnosis. Development of DUs was noted at each visit based on a comprehensive physical examination and the patient's past descriptions and photographs for thelast three months by the same rheumatology team. DUs were defined as an injury of epidermal integrity and the presence of visible underlying skin layers in the wound, accepted by ACR in 2016 (16). The presence of recurrent or new DUs (active or healed) based on the European Scleroderma Trials and Research group was positive (17). The severity of baseline skin hardness was noted using the modified Rodnan skin score (mRSS) (18). BMI was also accepted as an indicator of the nutritional status by calculated as the ratio of body mass (kg) and squared stature (m) (19).

Three parameters, including serum albumin, total cholesterol level, and peripheral blood lymphocyte count, were used for the CONUT score. Each variable was scored in 4 groups such as: albumin (≥3.5=0, 3.0-3.4=2, 2.5-2.9=4, <2.5=6), serum total cholesterol (≥180=0, 140-179=1, 100-139=2, <100=3), and total lymphocyte count (≥1600=0, 1200-1599=1, 800-1199=2, <800=3). The total CONUT score, the sum of the three variables, was accepted as in the follow-up: 0-1: normal, 2-4: mild, 5-8: moderate, and 9-12: severe (20).

Statistical analysis

The SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)) program analyzed data. The mean ± standard deviation defined continuous variables, whereas number and percent were used for categorical variables. Shapiro Wilk test was used for the determination of normal distribution. We used the Independent samples t-test for parametric test assumptions, whereas the Mann-Whitney U test for non-parametric test assumptions for independent group comparisons. Chi-Square analysis was used to analyze the difference between categorical variables. Logistic Regression Analysis was used to determine which variables affect digital ulcer development. P <0.05 was accepted as statistical significance.

RESULTs

Determinant characteristics of the whole study group

Twenty-six patients (n=26) had diffuse SSc, whereas sixteen (n=16) had limited cutaneous disease. Most patients were female in the whole group (38, 90.5%). In 20 patients, there was no comorbidity. Other concomitant diseases are shown in **Table 1**.

Pulmonary arterial hypertension (PAH) was present in 4 patients (9.5%), whereas interstitial lung disease (ILD) was present in 26 patients (61.9%). Patients were on treatment with calcium channel blockers (CCBs), acetylsalicylic acid (ASA), phosphodiesterase 5 Inhibitors (PDE5i), and endothelin receptor antagonists (ETAs) due to the Raynaud phenomenon and/or PAH. All patients with ILD were on immunosuppressive treatments such as MMF or azathioprine. The average age was 50.29 ± 13.9 years, whereas disease duration was 9.31 ± 7.11 years among the whole study group. The mean BMI was 25.24 ± 4.06 kg/m2. All patients' features and baseline laboratory findings are summarized in **Table 1**.

Comparison of SSc patients with and without DUs.

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All patients were divided into two subgroups according to whether they developed DUs or not. DUs occurred in 20 patients at least once, whereas never in 22 patients in the follow-up. Both groups were similar in terms of age, disease duration, BMI, jobs, ILD, PAH, Scl-70 autoantibodies, concurrent comorbidities, and the use of variable drugs such as immunosuppressive agents (MMF or AZA), PDEIs and CCBs (**Table 2**). Serum levels of albumin and vitamin D, lipid panels, and inflammatory indexes (NLR, PLR) of SSc patients were similar with and without DUs (p>0.05 for all) (**Table 3**).

The CONUT score was close to being better in SSc patients without DUs. The CONUT score was 0.86 ± 1.49 in patients without DUs, whereas 1.2 ± 1.01 in patients with DUs (p=0.092). The baseline mRSS was higher in SSc patients with DUs with a statistical significance (Table 3). Logistic regression analysis revealed the only significant positive correlation between mRSS and the development of DUs in patients with SSc (OR:1.085, p:0.046, 95%CI (1.001-1.176)) (**Table 4**).

Table 1. Demographic features and laboratory values of the whole study group.

	mean ± S.D.	med (min - max)
Age (years)	50.29 ± 13.9	52.5 (27 - 78)
Disease duration (years)	9.31 ± 7.11	7 (1 - 28)
BMI (kg/m2)	25.24 ± 4.06	25.9 (17.1 – 37.9)
AST (IU)	18.71 ± 5.51	18 (10 - 30)
ALT (IU)	15.57 ± 7.08	15 (2 - 31)
Urea (mg/dL)	23.86 ± 6.93	23.5 (13 - 43)
Creatinin (mg/dL)	0.69 ± 0.15	0.7 (0.26 – 1.2)
Calcium (mg/dL)	9.39 ± 0.44	9.4 (8 – 10.4)
Albumin (g/dL)	43.83 ± 3.66	44.5 (33 - 50)
Vitamin D (ng/dL)	20.71 ± 17.65	15 (3.9 - 86)
CRP (mg/dL)	2.96 ± 3.99	1.5 (0.09 - 21)
ESR (mm/h)	19.64 ± 17.91	12.5 (2 - 87)
Total-cholesterol (mg/dL)	193.79 ± 39.22	197 (132 - 283)
LDL-cholesterol (mg/dL)	113.19 ± 30.88	113.5 (57 - 171)
Trygliceride (mg/dL)	151.31 ± 71.87	130.5 (50 - 329)
Hemoglobin (g/dL)	12.57 ± 1.82	12.5 (7.8 – 15.9)
Lymphocyte (k/IU)	1984.76 ± 731.56	2110 (500 - 3300)
NLR	3.02 ± 2.72	2.33 (1 – 16.6)
PLR	175.24 ± 93.28	152 (66 - 540)
CONUT score	1.02 ± 1.28	1 (0 - 6)
Digital ulcer (s) / year	2.35 ± 1.27	2 (1 - 5)
mRSS	15.1 ± 8.59	13.5 (3 - 35)

BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDL-cholesterol: low-density lipoprotein cholesterol, NLR: neutrophil/Lymphocyte ratio, PLR: platelet/Lymphocyte ratio, CONUT score: controlling nutritional status score, mRSS: modified Rodnan skin thickness score.

Table 2: Characteristics of SSc patients with and without digital ulcers (Dus).

	Without DUs (n=22) (Mean ± S.D)	With DUs (n=20) (Mean ± S.D)	p value
Age (years)	50.68 ± 12.3	49.85 ± 15.79	0.849 (t=0.191)
Disease duration (years)	8.77 ± 7.24	9.9 ± 7.1	0.449 (z=-0.758)
BMI (kg/m2)	26.21 ± 3.8	24.17 ± 4.17	0.137 (z=-1.487)
Female gender (n, %)	19, %86.3	19, %95	0.608
Job (housewife, n, %)	19, %86.3	19, %95	0.442
Presence of co-morbidities (n, %)	11, %50	11, %50	1
Anti-SCL70 positivity (n, %)	9, %40.9	12, %60	0.217
PAH (-), (n, %)	19, %86.3	19, %95	0.608
ILD (+), (n, %)	12, %54.5	14, %70	0.303
CCBs (+), (n, %)	12, %54.5	15, %75	0.167
PDEi (+), (n, %)	2, %9	1, %5	1
Use of immunosuppressive agents (MMF or AZA), (n, %)	12, %54.5	14, %70	0.124

SSc: systemic sclerosis, BMI: body mass index, F: female, Scl-70: anti-topoisomerase I antibody, PAH: pulmonary arterial hypertension, ILD: interstitial lung disease, CCBs: calcium channel blockers, PDE5i: phosphodiesterase 5 Inhibitors, MMF: mycophenolate mofetil, AZA: azathioprine.

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Table 3. Comparison of laboratory parameters, CONUT score, and mRSS in SSc patients with and without digital ulcers (DUs).

	DUs (absent, n=22)		DUs (present, n=20)		
	Mean ± S.D.	Med (min - max)	Mean ± S.D.	Med (min - max)	P value
Albumin (mg/dL)	44.42 ± 3.79	45 (33 - 50)	43.19 ± 3.49	43 (36 - 49)	0.279 (t=1.097)
Vitamin D (ng/dL)	19.32 ± 10.29	16.1 (3.9 - 43)	22.23 ± 23.47	12 (4.4 - 86)	0.302 (z=-1.033)
Total-cholesterol (mg/dL)	203 ± 38.29	203 (141 - 283)	183.65 ± 38.64	182 (132 - 248)	0.111 (t=1.629)
LDL-cholesterol (mg/dL)	120.95 ± 30.06	117 (72 - 171)	104.65 ± 30.19	105 (57 - 159)	0.087 (t=1.752)
Trygliceride (mg/dL)	158.09 ± 81.78	129 (53 - 329)	143.85 ± 60.36	141.5 (50 - 288)	0.782 (z=-0.277)
NLR	3.24 ± 3.49	2.21 (1 - 16.6)	2.78 ± 1.54	2.46 (1.13 - 7)	0.554 (z=-0.592)
PLR	176.73 ± 116.76	146 (66 - 540)	173.6 ± 60.85	156.5 (81 - 315)	0.378 (z=-0.882)
CONUT score	0.86 ± 1.49	0 (0 - 6)	1.2 ± 1.01	1 (0 - 3)	0.092* (z=-1.687)
mRSS	12.5 ± 8.2	10.5 (3 - 35)	17.95 ± 8.29	18 (4 - 31)	0.037** (z=-2.081)

DUs: digital ulcers, BMI: body mass index, LDL-cholesterol: low-density lipoprotein cholesterol, NLR: neutrophil/Lymphocyte ratio, PLR: platelet/Lymphocyte ratio, CONUT score: controlling nutritional status score, mRSS: modified Rodnan skin thickness score.

Table 4. Logistic regression analysis of variables on the development of digital ulcers.

	O.R.	95% C.I for O.R. (lower-upper)		P value
Age	0.996	0.953	1.041	0.845
Disease duration	1.023	0.938	1.116	0.605
BMI	0.871	0.734	1.033	0.112
Albumin	0.907	0.761	1.081	0.277
Vitamin D	1.01	0.975	1.046	0.593
CONUT score	1.242	0.752	2.053	0.397
mRSS	**1.085**	**1.001**	**1.176**	**0.046***

BMI: body mass index, CONUT score: controlling nutritional status score, mRSS: modified Rodnan skin thickness score.

DISCUSSION

Today, unmet needs related to predictors of vascular complications are present in SSc patients. In a recent study, potential 19 biomarkers were investigated as predictors of DUs. After adjusting variables, any of these inflammatory or angiogenic markers were involved in developing DUs (21). Despite there being underlying different pathogenetic mechanisms in pressure ulcers, Lizaka S et al. showed nutritional status and dietary high protein intakes of patients affect the granulation tissue of pressure ulcers (22). However, Bergersen TK et al. supported the dysfunction of arteriovenous anastomoses in SSc-related DUs' pathogenetic mechanism beyond the nutritional status and microvascular system (23). This paper is the first study that evaluated the CONUT score in SSc patients. Although there was no statistical significance, the baseline CONUT score was close to being better among the patients who did not develop digital ulcers in the following year. We included diffuse and limited cutaneous SSc patients on regular follow-ups in our health center to obtain accurate results. Meaningful statistical significance could be reached with multicentre large study populations.

Today, it is well-known that DUs are more commonly seen in patients with severe skin and lung involvement. In recent investigations, recurrent DUs were associated with higher mRSS, longer disease duration, presence of ILD, and Scl-70 antibodies (24). In our study, these parameters, including disease duration, presence of ILD, and Scl-70 antibodies, were similar between groups with or without DUs. In addition, a wide range of treatments are available to prevent and heal DUs, including CCBs, prostacyclin analogs, and ETAs (25). The use of variable agents, including ETAs, CCBs, PDE5i, and immunosuppressive drugs, was similar between the two groups.

All patients who developed a DU in the follow-up were treated with short-time iloprost infusions. This condition may affect the subsequent development of new DUs. Despite all these confounding factors, such as more intensive treatment, patients with higher baseline mRSS developed more DUs in the follow-up, supporting the recent medical literature.

Park EK et al. revealed a potential adverse effect of insulin resistance on micro-vasculopathy of DUs. The homeostatic model assessment of insulin resistance was positively correlated with the presence of DUs in SSc patients (26). The reduced fat-free mass index has also been reported as a risk factor for developing new DUs and other vascular complications in SSc patients (27). BMIs were similar between SSc patients with and without DUs in our study. Although we included mild diabetes mellitus and stage1 chronic kidney disease with relatively short disease duration (<five years) without any possible microvascular complications, their confounding effects can not be completely ruled out.

There are a few limitations of our study. Firstly, the patient group's small size due to the disease's rarity requires further support with more extensive multicenter studies. Ongoing treatment modalities could also affect the future DUs in SSc patients with higher mRSS. Absolute GIS involvement that may confound the results related to the nutritional status was not verified by endoscopic methods. Also, the vast majority of patients were on treatment with proton pump inhibitors due to having symptoms of gastroesophageal reflux disease. This treatment may be related to decreased absorption of magnesium. Levels of magnesium, selenium, and zinc that may affect ulcer healing have not been analyzed. Further studies may be increased by adding age- and BMI- matched healthy control groups. Despite all the limitations, we believe the results show relatively new data in this area.

CONCLUSION

The baseline CONUT score was similar in SSc patients with and without DUs. The higher mRSS was positively correlated with increased development risk of DUs in SSc patients. CONUT score should be evaluated in randomized controlled studies with large, more homogeneous study populations.

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Author Contributions: FU, VÇ: Study design, collecting data, **FU:** Manuscript preparation, Literature search and revisions

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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