Diabetic Foot Ulcers: A Neglected Complication of Lipodystrophy

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Onur Saydam,[1] Basak Ozgen Saydam,[2] Cem Suleyman Adiyaman,[2] Melda Sonmez Ince,[3] Mehmet Ali Eren,[4] Fatma Ela Keskin,[5] Habib Bilen,[6] Murat Dagdeviren,[7] Seher Kaya,[8] Gulcin Akinci,[9,10] Ali Balci,[11] Canan Altay,[11] Firat Bayraktar,[2] Elif Arioglu Oral,[12] and Baris Akinci[2,12]

Lipodystrophy is a group of rare disorders characterized by generalized or partial loss of adipose tissue. Diabetes secondary to lipodystrophy is hardly responsive to standard treatment modalities and may lead to microvascular and macrovascular complications (1). Diabetic foot ulcers (DFUs) are a chronic complication of diabetes and a leading cause of lower-limb loss due to amputations. DFUs are an important cause of diabetes-related mortality (2).

In this observational retrospective cohort study, we report on 18 DFU episodes that developed in metreleptin-naive patients with lipodystrophy. These DFU episodes were compared with a series of DFUs ($n = 399$) that occurred in a well-established cohort of patients with type 2 diabetes ($n = 290$). The study was approved by the Dokuz Eylul University ethical review board.

Among 206 patients with lipodystrophy registered in our national cohort, DFUs were observed in 9 of 90 subjects with diabetes (10%). Four of these patients (44.4%) had multiple DFU episodes. Six patients had generalized lipodystrophy: five congenital generalized lipodystrophy (CGL) type 1 caused by *AGPAT2* p.R68X (c.202C>T), p.E229X (c.685G>T), p.K216X (c.646A>T), and p.D180PfsX5 (c.538_539delGA) variants, and one CGL type 2 caused by *BSCL2* p.Q94X (c.280C>T) variant. Three patients had partial lipodystrophy: one familial partial lipodystrophy (FPLD) type 1, one FPLD type 2 caused by *LMNA* p.R482W (c.144C>T) variant, and one acquired partial lipodystrophy. The median age at first DFU episode was 32 years, ranging from 24 to 66 years (one male and eight females). Median leptin level was 0.79 ng/mL (range <0.10–12.57 ng/mL). Median HbA_{1c} at DFU admission was 9.3% (79 mmol/mmol), ranging from 6.6% (49 mmol/mmol) to 13.3% (122 mmol/mmol). All patients were on insulin. Neuropathy was involved in all episodes, though several patients also had peripheral arterial disease.

Table 1 summarizes wound characteristics and ulcer outcomes in patients with lipodystrophy. Ulcer size and localizations were similar to those in subjects with type 2 diabetes, but patients with lipodystrophy were significantly younger when they presented with a DFU episode (median age 31 years [interquartile range 26–35] vs. 63 [55–70]; $P < 0.001$). Osteomyelitis was more frequently detected (12 episodes [67%] vs. 158 [40%]; $P = 0.027$). The risk of amputation was higher in patients with lipodystrophy than in their matched counterparts with type 2 diabetes (odds ratio 3.53 [95% CI 1.09–11.46], $P = 0.036$; data controlled for age, sex, and smoking history). One of the patients with CGL died during short-term follow-up due to sepsis caused by a disseminated foot infection.

Here, for the first time, we report on DFUs in a population with lipodystrophy. Our observations reveal that DFUs tend

[1]*Division of Cardiovascular Surgery, Izmir University of Health Sciences Tepecik Training and Research Hospital, Izmir, Turkey*
[2]*Division of Endocrinology and Metabolism, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey*
[3]*Department of Internal Medicine, William Beaumont Royal Oak Hospital, Royal Oak, MI*
[4]*Division of Endocrinology and Metabolism, Faculty of Medicine, Harran University, Sanliurfa, Turkey*
[5]*Division of Endocrinology and Metabolism, Faculty of Medicine, Demiroglu Bilim University, Istanbul, Turkey*
[6]*Division of Endocrinology and Metabolism, Ataturk University Training and Research Hospital, Erzurum, Turkey*
[7]*Division of Endocrinology and Metabolism, Kecioren Training and Research Hospital, Ankara, Turkey*
[8]*Department of Internal Medicine, Gulhane Training and Research Hospital, Ankara, Turkey*
[9]*Division of Pediatric Neurology, Behcet Uz Children's Hospital, Izmir, Turkey*
[10]*Department of Neurology, University of Michigan, Ann Arbor, MI*
[11]*Department of Radiology, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey*
[12]*Brehm Center for Diabetes Research and Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI*

Corresponding author: Baris Akinci, barisakincimd@gmail.com

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F.B., E.A.O., and B.A. share senior authorship.

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Table 1—Wound characteristics and ulcer outcomes in patients with lipodystrophy who develop DFUs

Patient/ episode	Age at presentation (years)	Wound localization	Type of ulcer	Outcome	Hospital stay
P1/E1	66	Dorsum, R	Mixed (ischemia dominant)	Healed	None
P2/E1	27	Middle toe, R	Neuropathic	Toe amputation	42 days
P2/E2	28	Big toe, anterior tibia, R	Neuropathic	Cellulitis healed, discharged with wound care	11 days
P2/E3	29	Big and little toes, R	Mixed (neuropathy dominant)	Healed after debridement	35 days
P2/E4	30	Metatarsal head, R	Mixed (neuropathy dominant)	Curettage of first metatarsal bone, healed	22 days
P2/E5	31	Big toe, L	Mixed (neuropathy dominant)	Healed	None
P2/E6	33	Medial plantar aspect, R	Mixed (neuropathy dominant)	Below-the-knee amputation	50 days
P3/E1	24	Big toe and 1st metatarsus, L	Mixed (neuropathy dominant)	Above-the-knee amputation	5 days
P3/E2	26	Lateral malleolus, R	Neuropathic	Healed	7 days
P3/E3	26	Big toe, R	Neuropathic	Healed	None
P4/E1	50	Metatarsal head, R	Mixed (neuropathy dominant)	Healed after debridement	14 days
P5/E1	25	Big toe, R	Neuropathic	Toe amputation	N/A
P6/E1	24	Big and 4th toes, L	Mixed (neuropathy dominant)	Autoamputation of the left big and 4th toes, ulcer not healed, later died because of sepsis	10 days
P7/E1	65	Forefoot, R	Mixed (ischemia dominant)	Transmetatarsal amputation	N/A
P7/E2	65	Stump extending the suture line, R	Mixed (ischemia dominant)	Below-the-knee amputation	15 days
P8/E1	32	Plantar surfaces of toes, L	Neuropathic	Healed	None
P9/E1	35	Forefoot/midfoot, L	Neuropathic	Healed	21 days
P9/E2	34	Big toe, forefoot/midfoot, R	Neuropathic	Toe amputation, not healed yet	16 days

E, episode; L, left; N/A, not available; P, patient; R, right.

to develop at younger ages in patients with lipodystrophy and are associated with serious outcomes. Neuropathy, one of the most important predictors of DFUs, was involved in all cases (2). The loss of subcutaneous fat pads in pressure areas would be an additional potential mechanism contributing to the increased risk of ulceration, although it is known that adipose tissue can be partially preserved in the soles of patients with several subtypes of lipodystrophy (1).

Infections related to DFUs seem to progress rapidly in patients with lipodystrophy, as evidenced by the fact that osteomyelitis was more commonly detected at presentation. It is unclear whether this observation can be explained by an immune system dysfunction secondary to leptin deficiency. Leptin stimulates the immune response by activating antigen-presenting cells, enhancing T helper 1 cell action, and modulating cytokine secretion by immune system cells. The defective immune system is a well-documented characteristic of leptin-deficient *ob/ob* mice (3). Immune defects have been reported in humans with congenital leptin deficiency (4). Also, circulating low levels of leptin have been associated with defective immune responses and bacterial infections in malnutrition (3). On the other hand, the association between low leptin levels and infections is not clear in humans with lipodystrophy, although T-cell abnormalities were previously reported (5) and sepsis seems to be a major cause of mortality in CGL (1).

The limitations of our study include the sample size, multicenter data collection, and its retrospective design. The sample size and multicenter design of the study reflect the rarity of these syndromes. Data on DFUs in lipodystrophy were collected from five different tertiary centers in Turkey; however, the type 2 diabetes cohort is from Dokuz Eylul University. Differences in clinical care are likely; however, all Turkish centers follow a similar algorithm.

In conclusion, patients with lipodystrophy represent a high-risk group for DFU, which can develop in relatively younger patients and lead to severe clinical outcomes. Our observations highlight the importance of developing preventive strategies against DFUs in this rare patient population.

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