

Clinical Features and Comorbidities of Patients With Necrobiosis Lipoidica With or Without Diabetes

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 Supplemental content

IMPORTANCE Necrobiosis lipoidica (NL) is a rare granulomatous condition. Current knowledge of its key features is based on a limited number of studies and case reports, leading to wide variability in the characterization of its defining features, with limited comparison of patients with or without diabetes.

OBJECTIVE To evaluate the epidemiologic characteristics, clinical features, and disease associations of NL in patients with or without type 1 or 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective review included 236 patients aged 15 to 84 years who were evaluated and received a diagnosis of NL at the University of Pennsylvania Health System between January 1, 2008, and July 15, 2018; University of Iowa Hospitals and Clinics between January 1, 2000, and June 15, 2018; and Brigham and Women's Hospital and Massachusetts General Hospital between January 1, 2000, and February 15, 2018.

MAIN OUTCOMES AND MEASURES Patient demographics, clinical features, medical comorbidities, and biopsy status.

RESULTS Of the 236 patients with NL, 200 were women and 36 were men, and 182 were white, with a median age at presentation of 50.0 years (interquartile range, 33.0-59.0 years). The diagnosis was biopsy proven in 156 patients (66.1%). Of the 230 patients with location specified, 225 (97.8%) had NL on the lower legs. A total of 138 patients with NL (58.5%; 95% CI, 52.7%-65.3%) had diabetes. The median hemoglobin A_{1c} for patients with diabetes was 8.00% (interquartile range, 6.68%-9.50%) (to convert hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01). Patients with diabetes were significantly younger than patients without diabetes (median age, 45.0 vs 52.0 years; $P = .005$), and slightly less likely to be female (112 of 138 [81.2%] vs 87 of 96 [90.6%]; $P = .046$), but lesion characteristics were otherwise comparable. Other notable comorbidities included obesity in 95 of 184 patients (51.6%; 95% CI, 44.4%-58.9%), hypertension in 104 of 230 patients (45.2%), dyslipidemia in 98 of 225 patients (43.6%), and thyroid disease in 56 of 229 patients (24.5%).

CONCLUSIONS AND RELEVANCE This study of NL supports its associations with diabetes as well as obesity, hypertension, dyslipidemia, and thyroid disease. Younger age and female sex were observed more frequently in patients with diabetes. Otherwise, NL lesions in patients with or without diabetes shared many clinical features, suggesting that risk factors outside of elevated blood glucose may play an important role in the disease. Future studies should evaluate these associations with the goal of further elucidating NL's underlying pathophysiologic characteristics.

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Necrobiosis lipoidica (NL) is a rare granulomatous condition classically characterized by the development of well-circumscribed plaques affecting the anterior shins. Although NL has been reported in a wide range of presentations, its pathophysiologic characteristics are not fully understood. Hypothesized mechanisms include microangiopathy, immune-mediated reaction, and other combinations of inflammatory and structural abnormalities.¹ Given the range of characteristics, clinical features, and comorbidities that have been described in patients with NL, the objective of this retrospective cross-sectional study was to systematically evaluate these factors in a large sample of patients with NL with or without type 1 or 2 diabetes.

Methods

Study Design, Setting, and Participants

Patients were identified from electronic health records at the University of Pennsylvania Health System (UPHS), University of Iowa Hospitals and Clinics (UIHC), Brigham and Women's Hospital (BWH), and Massachusetts General Hospital (MGH) using *International Classification of Diseases, Ninth Revision* code 709.3 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code L92.1 and a free text search for "necrobiosis lipoidica." Patients were identified from January 1, 2008, to July 15, 2018, at UPHS; from January 1, 2000, to June 15, 2018, at UIHC; and from January 1, 2000, to February 15, 2018, at BWH and MGH. Cases were included if medical record review indicated the patient either had biopsy-proven NL or received a diagnosis of NL by the documenting board-certified dermatologist. The study was approved by the institutional review boards at the University of Pennsylvania, the University of Iowa, and Partners Healthcare. Patient consent was waived as the data were deidentified.

Data Collection

The medical records of patients with NL were reviewed in detail, and clinical characteristics, comorbidities, and laboratory test values closest to the time of presentation were extracted using a standardized data collection instrument.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were summarized with medians and interquartile ranges. Categorical variables were reported as proportions and percentages. Patients were stratified by diabetes diagnosis, and comparisons were performed using a χ^2 test for categorical variables and *t* test for continuous variables. All *P* values were from 2-sided tests and considered statistically significant at *P* < .05, reduced by the Bonferroni method to *P* < .005 for comorbidities and *P* < .0125 for secondary changes. Statistical analyses were performed in Microsoft Excel for Mac, version 16.16.1 (Microsoft Corp).

Key Points

Question What patient characteristics, clinical features, and disease associations are seen in necrobiosis lipoidica in patients with or without diabetes?

Findings In this cross-sectional study, necrobiosis lipoidica was associated with diabetes as well as obesity, hypertension, hyperlipidemia, and thyroid disease. Younger age and female sex were observed more frequently in patients with diabetes; otherwise, necrobiosis lipoidica lesions in patients with or without diabetes shared many clinical features.

Meaning The findings of this study support an association between necrobiosis lipoidica and diabetes, but also highlight other potential contributing factors meriting further study.

Results

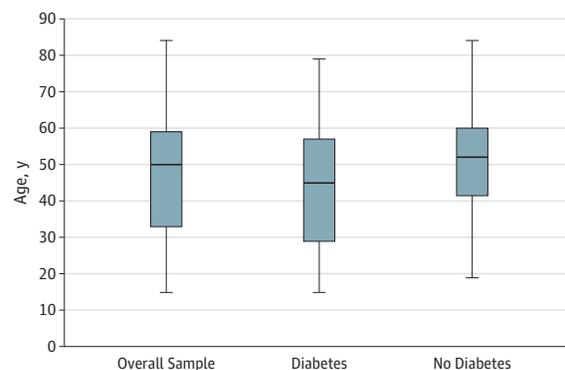
Patient and Lesion Characteristics

The initial search yielded 285 patients at UPHS, 146 patients at UIHC, and 487 patients at BWH and MGH. Ultimately, 99 patients at UPHS (34.7%), 55 patients at UIHC (37.7%), and 82 patients at BWH and MGH (16.8%) were included after medical record review. A total of 156 patients (66.1%) had at least 1 biopsy of suspected NL lesions, while 80 patients (33.9%) were diagnosed on a purely clinical basis (Table 1). Of the 230 patients with location specified, 225 (97.8%) had NL on the lower legs (Table 2). Ulceration was seen in 30 patients (12.7%; 95% CI, 8.5%-17.0%). A total of 48 of 188 patients (25.5%; 95% CI, 19.3%-31.8%) reported pain, while 49 of 183 patients (26.8%; 95% CI, 20.4%-33.2%) reported itch. Age at presentation ranged from 15 to 84 years (Figure), with a median of 50 years. Patient demographics and lesion characteristics are further outlined in Tables 1 and 2.

Associated Comorbidities

One hundred thirty-eight (58.5%; 95% CI, 52.7%-65.3%) patients with NL had diabetes (Table 1). Of the patients with

Figure. Age Distribution by Diabetes Status



The horizontal line within each box indicates the median, the bottom and top of each box indicates the 25th and 75th percentiles, respectively, and the vertical lines indicate the minimum and maximum range below and above the boxes, respectively.

Table 1. Demographics and Comorbidities of Patients With Necrobiosis Lipoidica

Characteristic	Patients, No. (%) [95% CI]			P Value
	Overall (N = 236)	Diabetes (n = 138)	No Diabetes (n = 96)	
Age, median (IQR), y	50.0 (33.0-59.0)	45.0 (29.0-57.0)	52.0 (41.5-60.0)	.005
Sex				
Male	36 (15.3) [10.7 to 19.8]	26 (18.8) [12.3 to 25.4]	9 (9.4) [3.5 to 15.2]	.047
Female	200 (84.7) [80.2 to 89.3]	112 (81.2) [74.6 to 87.7]	87 (90.6) [84.8 to 96.5]	
Race/ethnicity				
American Indian or Alaskan Native	0	0	0	.22
Asian	4 (1.7) [0.0 to 3.3]	3 (2.2) [-0.3 to 4.6]	1 (1.0) [-1.0 to 3.1]	
Black or African American	15 (6.4) [3.2 to 9.5]	11 (8.0) [3.5 to 12.5]	4 (4.2) [0.2 to 8.2]	
Native Hawaiian or other Pacific Islander	0 (0) [0 to 0]	0 (0) [0 to 0]	0 (0) [0 to 0]	
White	182 (77.1) [71.8 to 82.5]	102 (73.9) [66.6 to 81.2]	78 (81.3) [73.4 to 89.1]	
Other race/ethnicity	4 (1.7) [0.0 to 3.3]	4 (2.9) [0.1 to 5.7]	0 (0) [0 to 0]	
Not specified	31 (13.1) [8.8 to 17.4]	18 (13.0) [7.4 to 18.7]	13 (13.5) [6.7 to 20.4]	
BMI, mean (95% CI) ^a	30.8 (25.6-37.8)	31.0 (26.0-38.7)	30.4 (25.2-36.1)	.18
Hemoglobin A _{1c} , mean (95% CI), %	6.90 (5.80-8.95)	8.00 (6.68-9.50)	5.60 (5.30-5.80)	<.001
Associated comorbidities, No./total No. (%)				
Obesity	95/184 (51.6) [44.4 to 58.9]	59/113 (52.2) [43.0 to 61.4]	36/71 (50.7) [39.1 to 62.3]	.37
Hypertension	104/230 (45.2) [38.8 to 51.6]	74/134 (55.2) [46.8 to 63.6]	30 (31.3) [22.0 to 40.5]	<.001
Dyslipidemia	98/225 (43.6) [37.1 to 50.0]	69/132 (52.3) [43.8 to 60.8]	29/93 (31.2) [21.8 to 40.6]	.002
Thyroid disease	56/229 (24.5) [18.9 to 30.0]	39/133 (29.3) [21.6 to 37.1]	17 (17.7) [10.1 to 25.4]	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

SI conversion factor: To convert hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01.

^a Calculated as weight in kilograms divided by height in meters squared.

Table 2. Clinical Features of Necrobiosis Lipoidica Lesions

Characteristic	Patients, No./Total No. (%) [95% CI]			P Value
	Overall (N = 236)	Diabetes (n = 138)	No Diabetes (n = 96)	
Location				
Lower legs only	208/230 (90.4) [86.6 to 94.2]	124/136 (91.2) [86.4 to 95.9]	82/92 (89.1) [82.8 to 95.5]	.57
Lower legs and additional location	17/230 (7.4) [4.0 to 10.8]	9/136 (6.6) [2.4 to 10.8]	8/92 (8.7) [2.9 to 14.5]	
Other location, sparing lower legs	5/230 (2.2) [0.3 to 4.1]	3/136 (2.2) [-0.3 to 4.7]	2/92 (2.2) [-0.8 to 5.2]	
No. of lesions				
Single	73/226 (32.3) [26.2 to 38.4]	42/134 (31.3) [23.5 to 39.2]	30/91 (33.0) [23.3 to 42.6]	.64
Multiple	153/226 (67.7) [61.6 to 73.8]	92/134 (68.7) [60.8 to 76.5]	61/91 (67.0) [57.4 to 76.7]	
Morphologic characteristics				
Patches	58/214 (27.1) [21.1 to 33.1]	27/123 (22.0) [14.6 to 29.3]	30/89 (33.7) [23.9 to 43.5]	.62
Plaques	158/214 (73.8) [67.9 to 79.7]	92/123 (74.8) [67.1 to 82.5]	65/89 (73.0) [63.8 to 82.3]	
Papules	14/214 (6.5) [3.2 to 9.9]	9/123 (7.3) [2.7 to 11.9]	5/89 (5.6) [0.8 to 10.4]	
Nodules	9/214 (4.2) [1.5 to 6.9]	5/123 (4.1) [0.6 to 7.6]	4/89 (4.5) [0.2 to 8.8]	
Other	7/214 (3.3) [0.9 to 5.7]	4/123 (3.3) [0.1 to 6.4]	3/89 (3.4) [-0.4 to 7.1]	
Secondary changes				
Telangiectasia	41/236 (17.4) [12.5 to 22.2]	24/138 (17.4) [11.1 to 23.7]	17/96 (17.7) [10.1 to 25.3]	.93
Atrophy	95/236 (40.3) [34.0 to 46.5]	53/138 (38.4) [30.3 to 46.5]	42/96 (43.8) [33.8 to 53.7]	.41
Ulceration	30/236 (12.7) [8.5 to 17.0]	23/138 (16.7) [10.4 to 22.9]	7/96 (7.3) [2.1 to 12.5]	.03
Other	21/236 (8.9) [5.3 to 12.5]	13/138 (9.4) [4.5 to 14.3]	7/96 (7.3) [2.1 to 12.5]	.55
Color				
Pink	53/207 (25.6) [19.7 to 31.5]	33/115 (28.7) [20.4 to 37.0]	19/91 (20.9) [12.5 to 29.2]	.75
Red	124/207 (59.9) [53.2 to 66.6]	65/115 (56.5) [47.5 to 65.6]	59/91 (64.8) [55.0 to 74.6]	
Violaceous	27/207 (13.0) [8.5 to 17.6]	14/115 (12.2) [6.2 to 18.2]	13/91 (14.3) [7.1 to 21.5]	
Yellow or orange	114/207 (55.1) [48.3 to 61.8]	63/115 (54.8) [45.7 to 63.9]	51/91 (56.0) [45.8 to 66.2]	
Brown	65/207 (31.4) [25.1 to 37.7]	38/115 (33.0) [24.4 to 41.6]	27/91 (29.7) [20.3 to 39.1]	
Symptoms				
Pain	48/188 (25.5) [19.3 to 31.8]	30/110 (27.3) [18.9 to 35.6]	18/77 (23.4) [13.9 to 32.8]	.55
Itch	49/183 (26.8) [20.4 to 33.2]	29/105 (27.6) [19.1 to 36.2]	19/77 (24.7) [15.0 to 34.3]	.65

NL who had diabetes, most (78 of 138 [56.5%]) had a diagnosis of type 2 diabetes. At presentation, 34 of 115 patients with diabetes (29.6%) had documented diabetic neuropathy, 16 of 118 (13.6%) had diabetic retinopathy, and 9 of 110 (8.2%) had diabetic nephropathy. The median hemoglobin A_{1c} (HbA_{1c}) for patients with diabetes was 8.00% (interquartile range, 6.68%-9.50%) (to convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01) (Table 1). A total of 52 of 104 patients with diabetes (50.0%) had an HbA_{1c} indicating poorly-controlled disease (HbA_{1c} ≥8.00%). However, 96 patients in this study (40.7%; 95% CI, 34.7%-47.3%) did not have diabetes; these patients had a median HbA_{1c} of 5.60% (interquartile range, 5.30%-5.80%). Patients with diabetes were significantly younger than patients without diabetes (median age, 45.0 vs 52.0 years; *P* = .005) and were slightly less likely to be female (112 of 138 [81.2%] vs 87 of 96 [90.6%]; *P* = .046).

Other notable comorbidities included hypertension (104 of 230 [45.2%; 95% CI, 38.8%-51.6%]), dyslipidemia (98 of 225 [43.6%; 95% CI, 37.1%-50.0%]), and thyroid disease (56 of 229 [24.5%; 95% CI, 18.9%-30.0%]) (Table 1). Of the 184 patients with documented body mass index, 95 (51.6%; 95% CI, 44.4%-58.9%) patients were obese (body mass index, ≥30 [calculated as weight in kilograms divided by height in meters squared]), including 32 (17.4%; 95% CI, 11.9%-22.9%) who were morbidly obese (body mass index ≥40). Similar rates of obesity were observed between patients with or without diabetes (59 of 113 [52.2%; 95% CI, 43.0%-61.4%] vs 36 of 71 [50.7%; 95% CI, 39.1%-62.3%]), as were degrees of obesity. Atrophy was seen in 95 patients (40.3%) and telangiectasia was seen in 41 patients (17.4%).

Sensitivity Analyses

Patients who received a clinical diagnosis of NL without biopsy were more likely to have diabetes than patients with biopsy-proven NL (56 of 78 [71.8%] vs 82 of 156 [52.6%]; *P* = .005), more likely to be male (19 of 80 [23.8%] vs 17 of 156 [10.9%]; *P* = .009), and less likely to report pain (9 of 61 [14.8%] vs 39 of 127 [30.7%]; *P* = .02) (eTables 1 and 2 in the [Supplement](#)). Demographics, comorbidities, and clinical features were otherwise similar between patients with biopsy-proven NL and those with clinically diagnosed NL. Interinstitutional comparison demonstrated no significant differences in patient characteristics, but did show variability in biopsy rates and lesion characteristics (eTables 3 and 4 in the [Supplement](#)).

Discussion

This study presents data on 236 patients with NL and represents the largest comprehensive retrospective review of NL in the literature to our knowledge, both supporting associations described in the past and highlighting additional associations. Necrobiosis lipoidica occurred at a female to male ratio of approximately 5:1, even higher than the approximate 3:1 ratio reported in previous studies.²⁻⁴ It involved the lower legs in nearly all (97.8%) cases, consistent with a 1966 study of 171 patients with NL reporting leg involvement in all but 2 patients.² These data reinforce the importance of maintain-

ing a high index of suspicion for alternate diagnoses in patients presenting with NL-like lesions not involving the legs. Ulceration was seen in 12.7% of patients, within but at the lower end of the 7% to 35% ulceration rate ranges reported in previous studies.²⁻⁶ Although NL is classically described as asymptomatic,^{7,8} our findings suggest nearly half of patients report pain (25.5%), itch (26.8%), or both (6.8%).

Our finding of diabetes in 58.5% of patients with NL falls within, but toward the upper end of, the wide reported range of 11% to 65%.^{2,3,9,10} Of the patients with NL who have diabetes, most (56.5%) had a diagnosis of type 2 diabetes. This finding may represent a higher proportion than previously reported, with a 2016 German study reporting a higher proportion of patients with type 1 diabetes (59.9% of patients with NL and diabetes).⁵ This finding may partially reflect the higher prevalence of impaired glucose tolerance in North America vs Europe (54% vs 36%),¹¹ but highlights the importance of considering NL in patients with any type of diabetes.

Half the patients with diabetes in this study had an HbA_{1c} indicating poorly-controlled disease (HbA_{1c} ≥8.00%). However, 40.7% patients in this study did not have diabetes; these patients had a median HbA_{1c} of 5.60% (interquartile range, 5.30%-5.80%), possibly suggesting that factors other than elevated blood glucose may play an important role in the pathogenesis of NL. Although NL is classically thought to present with yellow-orange, atrophic, or telangiectatic plaques, our findings demonstrate a range of potential clinical appearances. This variation in appearance may be consistent with presentations at different stages of the disease course, as NL is traditionally believed to begin as papules and nodules that slowly coalesce into plaques and become more yellow-orange to brown with time.

Atrophy and telangiectasia were the most commonly observed secondary changes, but were described in only 40.3% and 17.4% of cases, respectively. Thyroid disease was seen in 24.5% of patients, compared with previously reported rates of 13% to 15%.^{3,4} In prior literature, the association between NL and thyroid disorders appears to extend beyond the association of diabetes with thyroid disease, with a 2017 study finding higher rates of thyroid antibodies in patients with type 1 diabetes with NL than those without (24.8% vs 17.5%; *P* = .004).¹² Our study also demonstrated a higher percentage of patients with hypertension (45.2%) and dyslipidemia (43.6%) compared with prior reports of 9.2% of patients with hypertension and 2.3% with dyslipidemia.⁵ The correlation of obesity with NL, seen at similar rates between patients with diabetes and without diabetes (52.2% vs 50.7%), supports a possible role for metabolic factors outside of blood glucose in the pathophysiologic characteristics of this disease. These findings are colinear and not independent risk factors.

Some studies have suggested an association between NL and microvascular complications of diabetes.¹³ In our study, 29.6% of patients had documented diabetic neuropathy, within the range of estimates of neuropathy incidence in the general population of patients with diabetes, which has been reported between 8% and 50%.¹⁴⁻¹⁶ Estimates of diabetic nephropathy and retinopathy vary widely and are strongly associated with duration and control of diabetes,¹⁷ but the 8.2% of patients with diabetes with nephropathy and the 13.6% of

patients with retinopathy in our study are generally lower than those reported in the literature. Given that many of the patients in our study had primary care physicians or endocrinologists outside the hospital systems where they were seen for NL, it is possible that the low levels of reported microvascular complications simply represents a lack of available detailed documentation regarding the patients' diabetes.

Limitations

The findings of this study must be interpreted in the context of its design. The UPHS, UIHC, BWH, and MGH are tertiary centers, which may affect the generalizability of results. Although a standardized data collection tool was used to minimize variability, because the data were collected from physician notes, there may be inconsistent reporting. Features of patients' NL were documented as described at the time of initial presenta-

tion to these tertiary centers, and hence may have differed compared with their initial presentation to their primary care physician, endocrinologist, or previous dermatologist.

Conclusions

This study demonstrated that more than half of patients with NL had diabetes, and rates of comorbid obesity, hypertension, dyslipidemia, and thyroid disorder were higher than previously reported. Patients with or without diabetes shared many comorbidities and clinical features, suggesting that risk factors outside of elevated blood glucose levels may play an important role in NL. Future studies should evaluate these associations with the goal of further elucidating the underlying pathophysiologic characteristics of NL.

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REFERENCES

- Sibbald C, Reid S, Alavi A. Necrobiosis lipoidica. *Dermatol Clin*. 2015;33(3):343-360. doi:10.1016/j.det.2015.03.003
- Muller SA, Winkelmann RK. Necrobiosis lipoidica diabetorum: a clinical and pathological investigation of 171 cases. *Arch Dermatol*. 1966;93(3):272-281. doi:10.1001/archderm.1966.01600210008002
- Erfurt-Berge C, Dissemond J, Schwede K, et al. Updated results of 100 patients on clinical features and therapeutic options in necrobiosis lipoidica in a retrospective multicentre study. *Eur J Dermatol*. 2015;25(6):595-601.
- Erfurt-Berge C, Seitz AT, Rehse C, Wollina U, Schwede K, Renner R. Update on clinical and laboratory features in necrobiosis lipoidica: a retrospective multicentre study of 52 patients. *Eur J Dermatol*. 2012;22(6):770-775.
- Jockenhöfer F, Kröger K, Klode J, Renner R, Erfurt-Berge C, Dissemond J. Cofactors and comorbidities of necrobiosis lipoidica: analysis of the German DRG data from 2012. *J Dtsch Dermatol Ges*. 2016;14(3):277-284. doi:10.1111/ddg.12749
- Hu SW, Bevona C, Winterfield L, Qureshi AA, Li VW. Treatment of refractory ulcerative necrobiosis lipoidica diabetorum with infliximab: report of a case. *Arch Dermatol*. 2009;145(4):437-439. doi:10.1001/archdermatol.2009.6
- Reid SD, Ladizinski B, Lee K, Baibergenova A, Alavi A. Update on necrobiosis lipoidica: a review of etiology, diagnosis, and treatment options. *J Am Acad Dermatol*. 2013;69(5):783-791. doi:10.1016/j.jaad.2013.05.034
- Lowitt MH, Dover JS. Necrobiosis lipoidica. *J Am Acad Dermatol*. 1991;25(5, pt 1):735-748. doi:10.1016/S0190-9622(08)80961-9
- Muller SA, Winkelmann RK. Necrobiosis lipoidica diabetorum histopathologic study of 98 cases. *Arch Dermatol*. 1966;94(1):1-10. doi:10.1001/archderm.1966.01600250007001
- O'Toole EA, Kennedy U, Nolan JJ, Young MM, Rogers S, Barnes L. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. *Br J Dermatol*. 1999;140(2):283-286. doi:10.1046/j.1365-2133.1999.02663.x
- International Diabetes Foundation. IDF diabetes atlas, 8th edition 2017. <http://www.diabetesatlas.org/>. Accessed August 12, 2018.
- Hammer E, Lilienthal E, Hofer SE, Schulz S, Bollow E, Holl RW; DPV Initiative and the German BMBF Competence Network for Diabetes Mellitus. Risk factors for necrobiosis lipoidica in type 1 diabetes mellitus. *Diabet Med*. 2017;34(1):86-92. doi:10.1111/dme.13138
- Boulton AJ, Cutfield RG, Abouganem D, et al. Necrobiosis lipoidica diabetorum: a clinicopathologic study. *J Am Acad Dermatol*. 1988;18(3):530-537. doi:10.1016/S0190-9622(88)70076-6
- Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333(2):89-94. doi:10.1056/NEJM199507133330203
- Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29(7):1518-1522. doi:10.2337/dc05-2228
- Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 [in French]. *Diabete Metab*. 1977;3(2):97-107.
- Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes*. 1990;39(9):1116-1124. doi:10.2337/diab.39.9.1116