Background: In 1929, Oppehein first described necrobiosis lipoidica diabeticorum and called it dermatitis atrophicans lipoidica diabetica, but it was later renamed necrobiosis lipoidica diabeticorum (NLD) by Urbach in 1932. In 1935, Goldsmith reported the first case in a nondiabetic patient. Other cases of NLD in nondiabetic patients were described by Meischer and Leder in 1948. Rollins and Winkelmann in 1960 also described this condition in nondiabetic patients, and a renaming of this disorder was suggested to exclude diabetes from the title. Today, the term necrobiosis lipoidica (NL) is used to encompass all patients with the same clinical lesions regardless of whether or not diabetes is present.

Pathophysiology: NL is a disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition. The exact cause of NL is unknown, but the leading theory of NL has focused on diabetic microangiopathy. Other theories suggest trauma or inflammatory or metabolic changes. Still other theories suggest that an antibody-mediated vasculitis may cause the changes seen in NL.

Frequency:
In the US: NL has been described in about 0.3% of diabetic patients. In one study, NL was shown to precede the onset of diabetes mellitus in 15% of patients. In addition, 60% of patients had the diagnosis of diabetes mellitus prior to the onset of NL, while 25% of patients had lesions that appeared with the onset of diabetes mellitus. The presence or progression of NL does not correlate with how well the diabetes is controlled.

Mortality/Morbidity: Treatment for NL is not very satisfactory. The disease is typically chronic with variable progression and scarring. Squamous cell cancers have been reported in older lesions of NL related to previous trauma and ulceration.

Race: NL has been reported to occur in all races with no predilection.

Sex: NL is 3 times more common in women than in men.

Age: The average age of onset is 30 years, but it can occur at any age. The age of onset ranges from infancy to the eighth decade. NL tends to develop at an earlier age in patients with diabetes.

History:
Patients usually present with asymptomatic shiny patches that slowly enlarge over months to years. The patches are initially red-brown and progress to yellow, depressed atrophic plaques. Ulcerations can occur typically after trauma and occasionally with associated pain.

The patient’s main complaint is the unsightly cosmetic appearance of the lesions.

The clinical appearance of NL is distinctive, yet there are many atypical presentations and early forms can be hard to recognize.

Superficial annular lesions can resemble granuloma annulare.

Yellow annular lesions of NL with a fatty infiltration can resemble xanthomas.

Necrobiotic xanthogranuloma (NXG) is a rare disease that can mimic NL clinically and histologically. NXG has been associated with paraproteinemia and some hematologic malignancies, which is not the case with NL.

Sarcoidosis of the skin can appear like NL both clinically and histologically.

Rheumatoid nodules also have a histologic appearance similar to NL but clinically appear like subcutaneous nodules rather than atrophic plaques.

Ulcerated necrobiotic lesions also have been described in patients with rheumatoid arthritis.

Physical:
Skin lesions of classic NL begin as 1- to 3-mm well-circumscribed papules or nodules that expand with an active border to become waxy, atrophic, round plaques centrally. Initially, these plaques are red-brown in color but progressively become more yellow and atrophic in appearance.

Most cases of NL occur on the pretibial area but cases have been reported on the face, scalp, trunk, and upper extremities where the diagnosis is more likely to be missed.

Multiple telangiectatic vessels can be seen on the surface of the thinning epidermis.

Ulceration at the site of trauma and subsequent infection are occasional complications of NL.
The Koebner phenomenon has been well established in patients with NL, especially in patients with vasculitis at the site of trauma. Miller reported a case of a woman with known type 1 diabetes mellitus who developed biopsy-proven NL in a cholecystectomy scar and also on her abdomen at insulin injection sites. In most patients, the lesions of NL are typically multiple and bilateral. The lesions may become painless because of cutaneous nerve damage in 75% of the cases, or they can be extremely painful in 25% of the cases.

Causes: NL remains a disease of questionable etiology despite extensive studies. The pathogenesis has not been demonstrated to be linked to genetic factors. Because of the strong relationship between diabetes and NLD, many studies have focused on diabetic microangiopathy as the leading etiologic theory. Diabetic alterations of the kidney and eye vasculature are similar to the vascular changes seen in NL. A deposition of glycoprotein in blood vessel walls may be the cause of diabetic microangiopathy. A similar glycoprotein deposition is seen in NL.

Another theory is based on the deposition of immunoglobulins, the third component of complement and fibrinogen in the blood vessel walls of patients with NL. Some believe an antibody-mediated vasculitis may initiate the blood vessel changes and subsequent necrobiosis in NL. An additional etiologic theory focuses on the abnormal collagen in NL. It is well established that abnormal and defective collagen fibrils have been responsible for diabetic end-organ damage and accelerated aging. Lysyl oxidase levels have been found in some diabetic persons to be elevated and are responsible for increased collagen cross-linking. Increased collagen cross-linking could explain basement membrane thickening in NL.

Other theories link trauma and inflammatory and metabolic changes as a possible etiology. It also has been found that there may be impaired neutrophil migration leading to an increased number of macrophages possibly explaining the granuloma formation in NL.

Lab Studies: Laboratory findings are not helpful in the diagnosis of NL. Some advocate checking for glucose intolerance to evaluate for the presence or absence of diabetes mellitus. NL has been the first sign of diabetes in some patients and a clue to possible diabetic potential in others. Histologic Findings: Histopathologically, NL presents with interstitial and palisaded granulomas that involve the subcutaneous tissue and dermis. At low magnification, lesions of NL have a very characteristic appearance. The granulomas are arranged in a tierlike (layered) fashion and are admixed with areas of collagen degeneration. The granulomas are composed of histiocytes, some of them multinucleated lymphocytes, occasional plasma cells, and eosinophils. Reduction in the number of intradermal nerves is an additional feature of NL. The main findings on histopathology are thickening of the blood vessel walls and endothelial cell swelling found in the middle to deep dermis, characteristics shared with diabetic microangiopathy.

Direct immunofluorescence microscopy of NL has demonstrated immunoglobulin M, immunoglobulin A, C3, and fibrinogen in the blood vessels, which cause the vascular thickening. In nondiabetic patients with NL, the vascular changes are not as prominent.
prevents T-cell activation. Cyclosporine at doses of 2.5 mg/kg/d has also been used with success in treating ulcerated NL.

Antiplatelet aggregation therapy with aspirin and dipyridamole has been tried because it was believed that NL was caused by platelet-mediated vascular occlusion or immune mechanisms that altered platelet survival. These drugs are believed to prolong platelet survival time and, hence, prevent further worsening of NL. The results of double-blind studies with aspirin and dipyridamole have varied but overall have shown some beneficial effects. Littler et al reported a case of NL that was treated successfully with pentoxifylline, a drug used in the treatment of intermittent claudication. Pentoxifylline is believed to decrease blood viscosity by increasing fibrinolysis and red blood cell deformity. It also inhibits platelet aggregation.

In several case reports, infliximab has been shown to improve chronic granulomatous skin disorders. Infliximab is a chimeric monoclonal antibody and acts to inhibit tumor necrosis factor-alpha. Tumor necrosis factor-alpha has a potentially critical role in conditions such as disseminated granuloma annulare and NL. It is found in high concentrations in the sera and skin in patients with these conditions. Kolde et al reported infliximab as a successful treatment option for ulcerated NL. Spence et al recently described a case of ulcerated NL that was treated successfully with topically applied bovine collagen. Collagen is believed to improve granulation tissue by supporting fibroblast activity and promoting wound debridement by increasing the number of macrophages and neutrophils at the wound site.

De Rie et al reported successful treatment with topical psoralen plus UV-A light therapy. Thirty patients were treated with twice weekly courses of topical psoralen plus UV-A light therapy. Five patients had complete clearing of their ulceration and erythema, and 11 patients showed significant improvement in their disease. Ticlopidine, nicotinamide, clofazimine, and perilesional heparin injections have been used in uncontrolled studies and appeared to benefit some patients with NL.

According to W.R. Heymann, tretinoin has been used to diminish the atrophy associated with NL (personal communication).

Surgical Care:
Excision and grafting have been successful, but recurrence may occur secondary to the underlying vascular damage. Poor healing of the graft site is not uncommon.
Laser care is also described. Moreno-Arias and Camps-Fresneda treated NL with a pulse dye laser (Candela SPTL; Irvine, Mass). They reported overall cosmetic improvement after 3 treatment sessions with respect to erythema and telangiectasis. Stabilization of the lesions was also achieved with the laser treatments.

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The goals of pharmacotherapy are to reduce morbidity and to prevent complications.

Drug Category: Hemorheologic agents -- Reduce complications resulting from increased blood viscosity.

Drug Name
Pentoxifylline (Trental) -- May alter rheology of red blood cells, which, in turn, reduces blood viscosity. Increases fibrinolysis and red blood cell deformity. Also inhibits platelet aggregation.

Adult Dose 400 mg PO tid with meals; may reduce frequency to bid if GI or CNS adverse effects occur
Pediatric Dose Not established

Contraindications Documented hypersensitivity; cerebral and/or retinal hemorrhage
Interactions Coadministration with cimetidine or theophylline increases effects/toxic potential; increases effect of antihypertensives

Pregnancy C - Safety for use during pregnancy has not been established.

Precautions Caution in renal impairment

Drug Category: Antiplatelet agents -- Inhibit platelet aggregation.

Drug Name
Ticlopidine (Ticlid) -- Second-line antiplatelet therapy for patients who fail aspirin therapy.

Adult Dose 250 mg PO bid
Pediatric Dose Not established
Contraindications Documented hypersensitivity; neutropenia or thrombocytopenia; liver damage; active bleeding disorders

Interactions Effects may decrease with coadministration of corticosteroids and antacids; toxicity increases when taken concurrently with theophylline, cimetidine, aspirin, and NSAIDs

Pregnancy B - Usually safe but benefits must outweigh the risks.

Precautions Discontinue if absolute neutrophil count decreases to <1200/mm3 or if platelet count falls to <80,000/mm3

Drug Category: Antihyperlipidemic agents -- Can reduce blood lipids.

Drug Name
Niacin (Nicotinamide, Nicobid, Nicolar) -- Source of niacin used in tissue respiration, lipid metabolism, and glycogenolysis.

Adult Dose 1.5-6 g/d divided tid

Pediatric Dose Not established

Contraindications Documented hypersensitivity; active liver disease or unexplained, significant increases in AST and ALT; large doses of niacin, especially when administered in SR form (associated with severe hepatotoxicity); definite and recent history of peptic ulcer disease (can reactivate ulcers)

Interactions Cutaneous vasodilation may be a problem if high-dose used with peripheral dilators such as nitroglycerine; taking aspirin 30-60 min before first dose of day may help alleviate prostaglandin-mediated adverse effects (eg, flushing, itching); clonidine may inhibit niacin-induced flushing

Pregnancy A - Safe in pregnancy

Precautions Pregnancy category C when used at doses greater than RDA; caution in gallbladder disease or diabetes and those predisposed to gout; monitor blood glucose; may elevate uric acid levels

Drug Category: Leprostatic agents -- May have immunomodulatory effects.

Drug Name
Clofazimine (Lamprene) -- Inhibits mycobacterial growth, binds preferentially to mycobacterial DNA. Has antimicrobial properties, but mechanism of action is unknown.

Adult Dose 100 mg/d PO qd

Pediatric Dose 1 mg/kg/d PO qd

Contraindications Documented hypersensitivity

Interactions Dapsone may inhibit anti-inflammatory activity of clofazimine

Pregnancy C - Safety for use during pregnancy has not been established.

Precautions Severe abdominal symptoms may require exploratory laparotomies; caution in patients with GI problems (eg, abdominal pain, diarrhea); skin discoloration due to drug may result in depression or suicide; apply oil to skin for dryness and ichthyosis

Drug Category: Anticoagulants -- Inhibit formation of blood clots resulting from blood disorders.

Drug Name
Heparin -- Augments activity of antithrombin III and prevents conversion of fibrinogen to fibrin. Does not actively lyse but can inhibit further thrombogenesis. Prevents reaccumulation of clot after spontaneous fibrinolysis.

Adult Dose Initial dose: 40-170 U/kg IV

Maintenance infusion: 18 U/kg/h IV; alternatively, 50 U/kg/h IV initially, followed by continuous infusion of 15-25 U/kg/h; increase dose by 5 U/kg/h q4h prn using PTT results

Pediatric Dose Initial dose: 50 U/kg IV

Maintenance infusion: 15-25 U/kg/h IV; increase dose by 2-4 U/kg/h q6-8h prn using PTT results

Contraindications Documented hypersensitivity; subacute bacterial endocarditis; active bleeding; history of heparin-induced thrombocytopenia

Interactions Digoxin, nicotine, tetracycline, and antihistamines may decrease effects; NSAIDs, aspirin, dextran, dipyriramole, and hydroxychloroquine may increase heparin toxicity

Pregnancy C - Safety for use during pregnancy has not been established.

Precautions In neonates, preservative-free heparin is recommended to avoid possible toxicity (gasping syndrome) by benzyl alcohol, which is used as preservative; caution in severe hypotension and shock; monitor for bleeding in peptic ulcer disease, menstruation, increased capillary permeability, and when giving IM injections

Drug Category: Retinoids -- Regulate cell growth and differentiation.

Drug Name
Tretinoin (Avita, Retin-A) -- Inhibits microcomedo formation and eliminates lesions present. Makes keratinocytes in sebaceous follicles less adherent and easier to remove. Available as 0.025%, 0.05%, and 0.1% creams. Available also as 0.01% and 0.025% gels.

Adult Dose Begin with lowest tretinoin formulation and increase as tolerated; apply hs or qod; lower frequency of application if irritation develops

Pediatric Dose <12 years: Not established
>12 years: Administer as in adults

Contraindications
Documented hypersensitivity

Interactions
Toxicity increases with coadministration of benzoyl peroxide, salicylic acid, and resorcinol; avoid topical sulfur, resorcinol, salicylic acid, other keratolytics, abrasives, astringents, spices, and lime

Pregnancy
C - Safety for use during pregnancy has not been established.

Precautions
Photosensitivity may occur with excessive sunlight exposure; caution in eczema; do not apply to mucous membranes, mouth, and angles of nose

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Complications:
The main complication of NL is ulceration, usually occurring after trauma. Infections can occur but are uncommon. There have been rare reported cases of squamous cell carcinomas developing in chronic lesions of NL.

Prognosis:
From a cosmetic standpoint, the prognosis of NL is poor. Treatment is helpful in halting the expansion of individual lesions, which tend to run a chronic course. Lesional ulcerations can cause significant morbidity requiring prolonged wound care. These ulcerations can be painful, become infected, and heal with scarring.


