Bullosis Diabeticorum: Is There a Correlation Between Hyperglycemia and This Symptomatology?

Thomas C. Wilson, BHS; Robert J. Snyder, DPM, MSc; Charles C. Southerland, DPM

Abstract: Bullosis diabeticorum (bullous disease of diabetes or diabetic bullae) is a noninflammatory, blistering disease occurring spontaneously in diabetic patients. The bullae are usually located on acral skin surfaces, particularly the feet. While this disease is unique to patients with diabetes, it may mimic other blistering disorders. This article reviews a case of a 75-year-old Hispanic male with type II diabetes mellitus who suffered from chronic diabetic bullae during an 11-year span. Researchers recorded the patient’s blood glucose level on 50 occasions of bullae occurrence and 50 occasions when bullae were not present. It was discovered that the patient was more likely to experience bullae formation when his blood glucose level was elevated (t test analysis, $P < 0.007$). The etiology of bullosis diabeticorum may be multifactorial, but this study suggests poor regulation of blood glucose levels, particularly hyperglycemia, may have a significant impact on the manifestation of this dermopathy.

Case Study

A 75-year-old Hispanic male with chronic type II diabetes mellitus presented with a nonpainful intact bullous formation on the distal aspect of his left anterior leg with no history of trauma to the affected site. He was a long-time patient at the center since experiencing an injury at work that resulted in a transmetatarsal amputation on his left foot 15 years prior.

During this time, the patient had obtained treatment for several ulcerations on his feet and legs bilaterally, which were complicated by diabetes. These ulcerations were treated with multiple modalities over the years, including standard wound care, total contact casting, hyperbaric oxygen therapy, oral and topical antibiotics, bio-occlusive hydrocolloid dressings, whirlpool therapy, negative pressure wound therapy, and surgical intervention. On multiple occasions, he would also present with intact bullae on his feet and/or legs. He suffered from intermittent formation of diabetic bullae on 50 occasions during an 11-year span from March 2001 to October 2011. Treatment over time consisted of lancing intact bullae while keeping the roof intact; application of topical antibacterials, such as silver sulfadiazine or triple antibiotic ointment; and the application of dry, sterile dressings. These interventions would typically be effective in the short-term, but the patient was prone to
recurrence at the same anatomical location. Other times, he would suffer new bullae at different locations on the same lower extremity or the contralateral lower extremity. The patient always recorded his blood glucose level the morning of each office visit and would report these values during each visit. He also reported prior blood glucose levels, particularly during days of bullae formation, in order to provide a more accurate measure of his regulation since his last visit. He admitted to poor control of his glucose levels and believed the bullae formed at times when his glucose levels were elevated.

The patient's medical history consisted of hypertension, hyperlipidemia, morbid obesity, ischemic cardiomyopathy, congestive heart failure, pleural effusions, neuropathy, peripheral vascular disease, renal insufficiency, and positive HIV status. The patient's surgical history included incision and drainage of an abscess over a pedicle graft transfer extending from plantar ulceration to dorsal sinus tract, excision of plantar exostosis, skin grafts, transmetatarsal amputation of left foot, hydrocele surgery on right testicle, and cyst removal on the wrist. The patient did not have any family history of blistering or autoimmune diseases.

Physical Examination

Physical examination revealed a new bullous formation filled with serous fluid with an intact roof on the distal aspect of the left anterior leg. This bullous formation was similar in presentation to previous eruptions (Figure 1 and Figure 2). There was no pain on palpation and no clinical signs of infection. The patient was concomitantly being treated for ulcerations on the plantar and dorsal aspects of the left forefoot at the previous amputation site and at the distal anterior medial right leg. Nonulcerated skin was atrophic with hyperpigmentation noted at the anterior medial legs, and xerosis was observed on the distal lower extremity and foot bilaterally.

Vascular examination revealed non-palpable dorsalis pedis and posterior tibial pedal pulses bilaterally. Subpapillary venous plexus filling time was within the normal limits of ≤3 seconds to remaining digits. Nonpitting 1+ (minimal) edema was noted bilaterally. Hair growth was absent on remaining digits. Neurological exam revealed absent protective and vibratory sensation. Orthopedic examination revealed limited active and passive range of motion at the remaining major joints of the foot and leg. Muscle strength was also diminished to a +4/5 level for major pedal muscles.

Pathology

There are no specific tests for diagnosing bullous diabeticorum; it is diagnosed based upon clinical findings, including spontaneous bullous formation with no history.
of previous trauma that heals without scarring, and the absence of other possible diagnoses. In the present case, a biopsy was performed to exclude other etiologies, such as autoimmune/inflammatory, causing the bullae. The typical hematoxylin-eosin stained microscopic picture may include epidermal or subepidermal separation that will be negative for immunofluorescence.

**Keypoints**
- Bullosis diabeticorum is diagnosed based upon clinical findings, including spontaneous bullous formation with no history of previous trauma that heals without scarring, and the absence of other possible diagnoses.
- In the present case, a biopsy was performed to exclude other etiologies causing the bullae.

**Diagnosis**

The patient was diagnosed with bullosis diabeticorum.

**Discussion**

Bullosis diabeticorum (bullous disease of diabetes or diabetic bullae) is a noninflammatory, blistering disease occurring spontaneously in patients with diabetes. The bullae are usually located on acral skin surfaces, particularly the dorsal aspect of the toes and the plantar aspect of the feet. A spontaneous bullous disease of diabetes was first described in 1930 by Kramer, followed in 1950 by Cope, and again in 1963 by Röccia and Pereyra. It was finally named bullosis diabeticorum in 1967 by Cantwell and Martz. Dermatological problems are quite common in this disease, affecting 30% - 70% of all individuals with diabetes. Cutaneous manifestations include bacterial and fungal infections, diabetic dermopathy, nail pathology, and, less commonly, bullosis diabeticorum, necrobiotic lipoidica diabeticorum (NLD), and granuloma annulare. Some cutaneous manifestations may precede the diagnosis of diabetes mellitus, including NLD and bullosis diabeticorum. Most of the diabetic bullae literature consists of case studies or short case series, and the condition has long been thought to be a fairly rare manifestation of diabetes. However, Lipsky et al believe this malady is not uncommon. Larsen et al reported a yearly incidence of 0.16%. This represents the most comprehensive study to date, consisting of 25 patients with 35 outbreaks, and 93 bullae in a population of 5000 patients with diabetes over a 3-year period. Additional research by El Fekih et al revealed a yearly incidence of 0.5%.

While this disease is unique to patients with diabetes, the differential diagnosis of blistering disorders may include bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa simplex, epidermolysis bullosa acquisita, drug-induced bullae, dermatitis herpetiformis, porphyria cutanea tarda, and pseudoporphyria. Although autoimmune bullous dermatoses such as bullous pemphigoid, pemphigus vulgaris, and dermatitis herpetiformis have a low incidence, their morbidity can be significant. If an inflammatory and immune-mediated process is suspected, a biopsy should be obtained. The presence of autoantibodies in skin or mucous membranes, as detected by direct immunofluorescence microscopy of a perilesional biopsy, is the gold standard in diagnosing autoimmune bullous diseases. While direct immunofluorescence is used to detect tissue-bound autoantibodies in perilesional skin, indirect immunofluorescence is used to detect circulating autoantibodies. However, there is no immunological component in bullosis diabeticorum. Since there is an increased risk for infection and morbidity in the diabetic lower extremity, particularly when comorbidities exist, skin biopsies should only be performed in recurrent cases to exclude other possible etiologies.

Bullosis diabeticorum has a higher incidence in men and is typically seen in patients with long-standing diabetes mellitus. Varying sizes of diabetic bullae have been reported in the literature, ranging from 0.5 cm - 10cm; recurrence is common. Inconsistent descriptions of skin separation within the bullae are described in the literature; intraepidermal or subepidermal separation may be present.

The exact mechanism of pathophysiology in bullosis diabeticorum has yet to be established. Several authors have studied the role of skin perfusion and dermatological conditions associated with diabetes mellitus. There have been several studies concerning skin perfusion and

**Keypoints**
- Larsen et al of bullosis diabeticorum] 0.16%. This represents the most comprehensive study to date, consisting of 25 patients with 35 outbreaks, and 93 bullae in a population of 5000 patients with diabetes over a 3-year period. Additional research by El Fekih et al revealed a yearly incidence of 0.5%.
- Bullosis diabeticorum has a higher incidence in men and is typically seen in patients with long-standing diabetes mellitus.
- The exact mechanism of pathophysiology in bullosis diabeticorum has yet to be established.
diabetic dermopathy. A prospective study by Brugler et al.\(^2\) consisting of 25 patients with type 1 diabetes and diabetic dermopathy; 58 patients with type 1 diabetes without diabetic dermopathy; and 67 nondiabetic control subjects, reported a markedly higher blood flow at the dermopathy sites as compared to contiguous uninvolved skin sites. Wigington et al.\(^\text{7}\) studied 61 diabetic patients and 41 nondiabetic control subjects, and reached similar conclusions. Additionally, the prospective research conducted by Ngo et al.\(^\text{28}\) suggested NLD was actually not a manifestation of microvascular ischemic disease of the skin. However, no such research has confirmed or denied a causative role of microvascular disease in the manifestation of bullosis diabeticorum. Many authors believe microangiopathy may play a role in the etiology of bullosis diabeticorum.\(^\text{29-32}\) In a case report and literature review, Basarab et al.\(^\text{31}\) postulated a combination of increased venous pressure and microangiopathy as inciting factors for bullosis diabeticorum. Microangiopathy in diabetes may be caused by excess sorbitol formation, increased glycation end products, oxidative damage, and protein kinase C overactivity.\(^\text{21}\) Other possible etiologies include neuropathy,\(^\text{4,16,22,29}\) nephropathy,\(^\text{8,33}\) and calcium and magnesium imbalances secondary to nephropathy leading to weakened skin structure.\(^\text{8}\) Whether these possible etiologies are causative for bullosis diabeticorum still remains undetermined.

While many complications of diabetes occur due to poor blood glucose regulation, little has been written in the literature about the correlation between the patient’s blood glucose level and the onset of bullae formation. Larsen et al.\(^\text{1}\) suggests poor regulation of blood glucose may play an important role in diabetic bullae formation, with instances of hypoglycemia, in particular, as an inciting factor. In their study of 25 patients with 35 total outbreaks (1 patient had 5 outbreaks; 1 patient had 4 outbreaks; 3 patients had 2 outbreaks; and 20 patients had 1 outbreak) resulting in 93 bullae, patients reported hypoglycemic episodes near the time of bullae formation in 20 out of 35 outbreaks. Five outbreaks occurred in patients with severe longstanding hyperglycemia, and 9 outbreaks occurred in patients with highly varied glycemic control. HbA1c levels were also recorded 3 months before, as well as at the time of the outbreak, but no significant change was observed.\(^\text{1}\)

In this case study, the patient presented with a new bullous formation on 50 separate occasions during an 11-year span. Researchers recorded blood glucose levels on 50 occasions of bullae occurrence and 50 occasions when bullae were not present (Figure 3 and Figure 4).
The study revealed the patient was more likely to experience bullae formation when his blood glucose level was elevated (t test analysis, $P < 0.007$). Poor blood glucose control was evident as the patient’s levels varied from 79 mg/dl - 340 mg/dl at the time of new bullous formations with a mean of 172 mg/dl. No hypoglycemic episodes occurred during new bullae formation. The patient’s bullae formation may have been multifactorial due to the chronicity of his diabetes, with highly variable and typically elevated blood glucose levels, and his concomitant neuropathy, angiopathy, and nephropathy.

Although most diabetic bullae heal within 2 weeks - 6 weeks of palliative treatment, and usually do not exhibit scarring, $^{12,15,21,25,26,34,35}$ cases have been reported in which severe chronic ulceration, skin necrosis, infections, scarring, and amputations have occurred. $^{1,15,32,36}$ Due to the possibility of these severe complications, an emphasis should be placed on the need for foot and ankle specialists to accurately diagnose and treat diabetic bullae in a timely manner as to prevent further sequelae. There also must be continual emphasis on proper blood glucose level regulation and patient education regarding morbidity associated with poor regulation.

**Limitations of the Study**

This was a retrospective case study analysis; although 50 occasions with bullae and 50 occasions without bullae were recorded, the sample was only from 1 patient; the findings, therefore, are not strictly generalizable. Prospective studies with a larger sample size should be conducted to support adequate evidence regarding the possible contribution of hyperglycemia in increased incidence of bullosis diabeticorum. Additionally, blood glucose levels were recorded during the mornings of the office visits on days when no bullae had erupted and recorded in a relatively short time period following the onset of bullae. This could have added a degree of variability when analyzing the data. Lastly, another variable in this case was the patient’s positive HIV status. However, no associations between HIV status and the incidence of bullosis diabeticorum have been reported.

**Conclusion**

Although bullosis diabeticorum may be multifactorial in nature, blood glucose level regulation plays a central role in all of the proposed etiologies. This case emphasizes the importance of adequate glucose control and how the lack of adequate control, particularly hyperglycemia, may lead to increased dermatological morbidity. To the authors' knowledge, this is one of only 2 published studies where the correlation between blood glucose levels and the onset of diabetic bullae has been reviewed, and it is the first study to discover a statistically significant correlation between elevated blood glucose levels and the onset of diabetic bullae. However, adequate evidence for this association cannot be established from a single case report, so additional research is required to further elucidate this relationship.

**Key Points**

- In a case report and literature review, Basarab et al.$^{31}$ postulated a combination of increased venous pressure and microangiopathy as inciting factors for bullosis diabeticorum.
- Other possible etiologies include neuropathy,$^{4,16,22,29}$ nephropathy,$^{8,33}$ and calcium and magnesium imbalances secondary to nephropathy leading to weakened skin structure.$^{3}$
- Larsen et al.$^{1}$ suggests poor regulation of blood glucose may play an important role in diabetic bullae formation, with instances of hypoglycemia, in particular, as an inciting factor.

**References**


