Chronic venous ulceration in obese patients with diabetes mellitus. A therapeutic challenge.

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Abstract

Background: It is well known that chronic ulcers of the legs represent a formidable challenge in clinical practice and among them, Chronic Venous Ulcers are the most common. The expenses of the treatment, the impact on the quality of life and incapacities affect negatively the National Health Services worldwide. Little is known of the impact of the association of these ulcers with T2DM, obesity and life expectancy that is also in the rise globally.

The Aim of the Report: With the experience gained during several years treating Chronic Venous Ulcers, it was found that many patients present the complications described previously and the difficulty in treating these complications motivated the present report.

Material and Methods: Five highly complicated elderly patients with Chronic Venous Ulcers suffering from T2DM and obesity were selected and their summary of treatment and results constitute the present report. A new product used successfully in the treatment of this entity (PPZO) was used as a complementary part of the treatment.

Results: In 2 of the 5 patients an amputation was avoided, and complete healing was achieved in 3 instances though other complications required prolonged treatment.

Conclusion: Chronic Venous Ulcers the most common type of chronic leg ulcers, when complicated with advanced age, T2DM and Obesity represent a very difficult challenge in clinical practice and required multi-specialty assistance. The use of PPZO topically applied is very effective with additional advantages for its generalized use.

Keywords: Chronic venous ulcers (CVU), type 2 diabetes mellitus (T2DM), polymer polysaccharide with zinc oxide (PPZO).
Abbreviations: *Pebisut® Patents: USPTO, USA, #8,252,333. Canada #2,661,686. European Union #2,062,602. Mexico #280,754. External application in Mexico, #350080, USA #9,808,484, Canada #2,926,115; *Epifast: Human allografts of living keratinocytes cultivated and cryopreserved. CINVESTAV, Bioskinco Co, Mexico

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Introduction

Chronic Venous Ulcerations (CVU) are the most common type of Chronic Ulcers of the legs accounting for 70%-80% and are the cause of enormous expenses in the health systems, incapacities for many working patients and produces serious alterations in the quality of life of millions of patients worldwide [1-3]. Although external effective compression therapy is the mainstay of the treatment and improves venous ulcer healing, it does not solve the underlying causes and to this date the latest Consensus inform that there is no specific product/method of treatment that is really effective so the gold standard treatment in 2019 continues to be effective external venous compression and cleansing of the ulcers [3-6]. To complicate these issues, the continuous increase in Obesity and Diabetes worldwide, as well as the generalized increase in life expectancy, could very well increase the prevalence of this chronic type of troublesome ulcerations. In previous reports our group has published the experience of a new product, a Polymer Polysaccharide with Zinc Oxide (PPZO) in the treatment of refractory CVU [7-10] but during the selection of patients for inclusion in our protocols, it became noticeable that CVU may coexist with obesity and T2DM and that these patients represent a formidable clinical therapeutic challenge and the present report provides clinical examples of this complicated form of chronic leg ulcers.

Case Reports

Case 1

MRG, a 62 years old a widow, alcoholic, obese female was seen in April 2016 for a very large chronic painful ulcer of the right leg treated intermittently elsewhere for more than 6 years in different clinics with several products, ointments, and antibiotics with no improvement until a daughter insisted and that she should be seen in our clinic. She informed us that she suffered a fracture in "the right hip 6 years ago that healed with conservative treatment" but has produced a limping disability since then. In the right leg, there was a circumferential 35 cm × 12 cm irregular painful ulcer with greenish purulent secretions and cellulitis and edema surrounding it. No pulses were felt in

the leg nor ankle though they were present in the left leg where multiple dilated varicosities were seen (Figure 1).

Her BP was 148/90 mm Hg, weight 82 kg (BMI: 30 kg/m^2) and Laboratory results showed a Glucose of 186 mg%, a Hgb1A 9.2 g% with 12,000 WBC. She did not know that she had T2DM. She had a very large goiter that "had been present for more than 20 years". An extensive debridement was done in the Clinic under IM analgesia with Ibuprofen and topical lidocaine. After the debridement, PPZO was applied extensively and a diabetic 1200 Cal diet was prescribed and 12 U of NPH insulin QD were prescribed along with ferrous sulfate 200 mg tablets with Folic acid. Fortunately, she had a daughter who personally cared for her and did the daily local treatments with rapid improvement and fasting glucose of 120 mg% was observed at the 8th week of treatment. The ulcer was clean without cellulitis and the pain and insomnia had improved considerably (Figure 2).

Three months later she was started on Metformin 850 mg QD and the Insulin stopped, she was able to walk by herself and her weight was 73 kg with normal BP with the medication prescribed. She was seen monthly with continuous slow improvement and the Metformin was reduced to 500 mg Q/AM and the Hgb1A was reported as 6%. When the ulcer healed approximately 50% after 12 months of treatment, we lost her in the F/U until January 2018 when she was seen in the ER of a General Hospital for an "acute abdomen" and hospitalized several days for what finally was diagnosed as acute pyelonephritis treated with IV antibiotics but unfortunately the purulent secretions of the ulcer recurred and the previous treatment was restarted. In 2 different occasions and using local anesthesia 5-6 pinch grafts were taken from the left thigh and applied and the last visit on October 2018 showed a painless clean ulcer measuring 13 cm in the longest diameter (Figure 3), the patient now weighs 67 kg and she takes care of herself at her home and continue to improve.

Case 2

RHL, A retired 62 years white man, obese and known Diabetic for 8 years was seen at Hospital Juarez of Mexico City in February 2014, appeared depressed, did not leave his bedroom for the "stink produced by his large ulcer" in the left leg that had been treated during 8 months in different clinics and by different physicians and nurses elsewhere with different ointments, antibiotics, gels, etc. without any improvement (Figure 4).

Figure 1. *Large very painful irregular circumferential ulcer with purulent greenish secretions and cellulitis in neighboring tissues.*

Figure 2. *Two months later the ulcer is smaller, no secretions were present and the treatments at home and in the monthly visits produced much less pain.*

Figure 3. *After almost 2 years of treatment the ulcer is much smaller (82%), asymptomatic with general improvement of the patient´s health.*

He complained of pain in the ulcer, moderate at times, and insomnia. He was scheduled for a supracondylar amputation due to the fact that he did not respond to any treatment and the persistence of the chronic infectious process in the leg. He also had a small 5 × 4 cm ulcer in the medial aspect of the right leg. He was seen and treated for Reason of Compassion and he and his family were told of the type of treatment that would have to

be applied that had already been approved by the COFEPRIS (the Mexican FDA) recently. The patient was debrided under topical anesthesia and PPZO was applied extensively and after 3 minutes a Petrolated gauze covered the entire lesion. He cleansed and applied himself the PPZO daily and was seen weekly in the Clinic and by the 10th week the ulcer had decreased approximately 40% in size, without any secretions, he could sleep and he could walk aided with a cane and the smaller ulcer in the left leg was healed. The lesion healed completely in the 25th week, the patient had lost 20 kg, his glucose and Hgb1C were within normal limits and he was able to return to work (Figure 5).

Case 3

DFB, male, 73 years old a retired obese male known to have T2DM for "many years" was first seen in our office (October 10, 2014) because of swelling in both legs and a painful ulcer in the right leg, lateral aspect present for at least 2 weeks after he inadvertently hit a chair, complicated with malodorous secretions. He was controlled with a diabetic diet that he followed "most of the time". He lived by himself in an apartment on a 3rd floor with a cat and a dog that slept with him. He received Metformin 850mg and liraglutide 5 mgq AM. He was seen by an ophthalmologist for the progressive loss of vision and eyeglasses were prescribed. At PE, it was evident that both legs were swollen and no pulses were felt although a weak Doppler signal was present in the left leg in the posterior tibial trajectory. In the posterolateral aspect of the right lower extremity, there was an irregular circumferential ulcer 6 cm in length, with extensive cellulitis around it and with scanty purulent secretion. There were also 2 smaller posterior and superior ulcers 2-3 cm in the left leg anterior aspect (Figure 6).

Figure 4. *Very large ulcer left leg with extensive cellulitis and abundant fetid greenish secretions throughout. He was scheduled for a A-K amputation for failure to improve with medical treatments and depression.*

He weighed 80 kg, (BMI: 28.2 kg/m^2). He had been seen by two vascular surgeons and prescribed several ointments and antibiotics for 4 weeks. An emergency glycemia was 206 mg% with a Hgb1A of 11.5%, a Hemoglobin of 11.2 g% and a wound culture was reported with Staphylococcus Intermedius sensitive to most antibiotics (double checked). His blood pressure was 164/90 mm Hg. He was prescribed Moxifloxacin 400 mg QD and instructed to follow the diet carefully and to elevate at night both legs and to use low-pressure antiulcer stockings, to use salt substitutes and to start Candesartan 16 mg with Hydrochlorothiazide 12,5 mgq AM and debridement was done and Pebisut® was applied daily followed by a petrolatum gauze. A vascular real-time ultrasound revealed calcified arteries in both legs and incompetence of the deep venous system and dilated perforator veins but no evidence of venous obstruction. The patient improved and 3 weeks later the edema decreased considerably and posterior tibial pulses were felt and the ulcer was almost healed as well as the other smaller ulcerations. The patient returned 9 weeks later after a holiday trip with his relatives with massive edema and a large ulcer with tissue necrosis in the right ankle posterior aspect that appeared "after he slept in a couch with no cushion for several days" (Figure 7).

This necrotic lesion progressed to complete exposure of the Achilles tendon (Figure 8) and an extensive debridement was done at the Emergency Room of the American British Hospital with local anesthesia and sedation. The lesion healed approximately an estimated 80% with the treatment prescribed initially and 2 months later an *Epifast 4 × 4 cm patch was applied with a satisfactory result (Figure 9). The patient returned 3 months later with another ulcer, smaller in the left medial aspect that grew *Pseudomonas aeruginosa* resistant to most antibiotics and after several debridements, he improved. A nephrology and ophthalmology consults were obtained for the Creatinine had risen to 3 mg%, and a Social Service consultation was obtained and his relatives accepted to care for him at home in a distant City and have informed us on two occasions of his unstable evolution given his age, severe alteration in the renal function and extremely poor vision.

Figure 5. *After 5 months of treatment with PPZO and external venous compression, the large ulcer decreased 90% in size and the patient was asymptomatic.*

Figure 6. *Edematous right leg with areas of ulcers and cellulitis.*

***Figure 7**. The Achilles tendon is exposed with areas of inflammation and cellulitis.*

***Figure 8**. Granulation tissue has replaced the necrotic area in the heel after daily treatments with PPZO and the application of an Epifast patch. The denuded area has been reduced with daily care with PPZO.*

Case 4

BPG, a 79 years old obese diabetic female sent to our office on December 07, 2014 for treatment of an ulcer in the right leg. The patient came in a wheelchair with relatives and said she had "a right hip fracture 5 years previously operated elsewhere" with a poor result and since that time she required total assistance at home. PE revealed an obese female weighing 93 kg (BMI: 30 kg/m^2), BP of 142/90 on Elapril twice daily. In the right leg, there was a large irregular ulcer with purulent secretions, very painful that also produced persistent insomnia that require analgesics and "sleep medications" for the last several years. The relatives informed us that she had been seen and treated in several clinics and by different physicians who prescribed different ointments and local and systemic antibiotics with poor results generally. Both ankles had discrete swelling and no pulses were felt in the right side and were normal in the left ankle. She had been prescribed several diabetic diets that she did not follow and was receiving Insulin regular and NPH irregularly. An emergency laboratory revealed a glycemia of 139 mg%, a Hg1A of 8.1% with normal electrolytes and creatinine. An initial debridement was done using ketorolac 30 mg IM and topical lidocaine. The treatment prescribed was a 1200 calorie diabetic diet with rigorous recommendations to the patient and relatives and initially she received 12 U of NPH Insulin, and Pebisut® was applied and the relatives were instructed during several visits how to clean the ulcer and apply the gel and as a secondary dressing a petrolated gauze and to use at all times an antiulcer stocking except at bedtime. She was seen again 7 days later complaining of less pain, a clean ulcer and a glycemia of 100 mg% and using less pain medication at bedtime. Two months after the treatment was started, the ulcer was clean and showed evidence of healing and 7 pinch grafts were taken from the left anterior thigh and applied in the ulcer. Three weeks later a 4 × 4 cm Epifast patch was applied in the ulcer with evidence of reduction of the ulcer (approximately 30% less in the major diameter) and absence of pain and complete control of insomnia following which the patient and relatives suggested another application of the Epifast and a similar patch was applied again in the ulcer 3 weeks later. On May 8, 2015, she looked and felt "much better", her weight now was 82 kg and the ulcer was clean and healing well with essentially no pain, secretions nor insomnia. The patient then did not return for treatment and the office unsuccessfully tried to contact her or the relatives (Figure 9).

Case 5

GM, a 48 years old obese diabetic hypertensive female treated in different hospitals for Rheumatoid Arthritis was seen with a large irregular painful ulcer in the lateral aspect of the right leg with an obvious loss of substance and a pronounced concavity deformation with mild cellulitis and greenish secretions. The ulcer had been present "for many years" and she brought recent Laboratory cultures positive for *Pseudomonas aeruginosa* Multi-resistant. She had been treated elsewhere with oral Prednisone 30 mgqd during several months and "different antibiotics and

***Figure 9.** After weeks of daily treatments and an Epifast 4 × 4 cm patch applied, the ulcer looks clean, and the pain and insomnia had disappeared.*

Figure 10. *Ulcer completely healed after 9 weeks of treatment. The deformity seen initially persists.*

ointments" by different physicians but since there was no response she decided to be seen in our clinic. The treatment prescribed after the initial debridement done under sedation and topical anesthesia was daily lavage and PPZO applications with a petrolatum gauze to be applied afterward and continuous use of an antiulcer compressive type of elastic stockings. Candesartan was prescribed 16 mgqd, and Paracetamol 500 mg several times daily for pain. Oral Prednisone was tapered down progressively. The response to treatment was very impressive and the pain, secretions, and insomnia disappeared after 8 days and complete healing was observed after 2 months and a few days of such treatment. In spite of this improvement she has not returned for follow up visit and the Clinic has been unable to contact her or her relatives (Figure 10).

Discussion

It is generally accepted that CVU constitutes 70% of chronic leg ulcerations and that approximately 1% of the population will suffer from CVU at some point in their lives [1-3]. It is also known that these ulcers affect in a very negative way their quality of life (QoL) therefore producing incapacities and an enormous cost to the Health systems as well as to the patients and their families everywhere [4,5]. To complicate matters for the clinicians that care for these patients, it is well accepted that the "gold standard" of treatment in 2017 still remains effective external venous compression and cleansing of the ulcers in spite of the fact that there are a large number of new methods and products that to this date have not proven to be superior to that treatment that was popularized in the late 1950s [6]. In fact, after reviewing over 20 years of publications and 10,000 papers, the Agency for Healthcare Research Quality concluded that "Most of the studies of advanced wound dressings that regulate moisture, facilitate debridement, include antimicrobial activity, or incorporate putative wound healing accelerants did not demonstrate a statistically higher percentage of wounds healed compared with adequate compression with simple dressings" [6] Recently the use of a new product with favorable initial results in the treatment of these patients has been reported with potent anti-inflammatory and enhancing healing properties, a Polymer Polysaccharide with Zinc Oxide, PPZO* with rapid improvement in the QoL and without any adverse reactions [7-10]. Reviewing the literature very little has been published dealing with the problem of T2DM complicating these CVU. In a recent report Zakharova, describe the results of treating 52 elderly patients with Sulodexide during 50 days and concluded that this treatment achieved significant healing of CVU complicated with T2DM [11]. On the other hand, Wu et al, in a recent Cochrane Systemic Review on the results of Sulodexide in the treatment of CVU, concluded that this glycosaminoglycan with antithrombotic and profibrinolytic properties may have some positive effects on healing, but that the evidence at this time is of low quality and its use may have adverse effects. The authors suggested that well-designed RCTs could clarify the effects on healing, recurrence QoL and costs [12]. Dumville et al. report on the usefulness of topical antimicrobial agents in infected leg ulcers in diabetic patients-nor necessarily CVU, and found no conclusive proof of their effectiveness and that given the high and increasing frequency of infected ulcers in diabetic patients, properly designed randomized trials should be done to determine their ultimate effects in these chronic lesions [13]. Another fact to be considered in this group of patients with both CVU and T2DM is the fact that in every case we have documented clinically and by Ultrasound the presence not only of decrease arterial perfusion but additionally findings of pathological venous insufficiency present in these patients [1] that produces troublesome extensive edema that further jeopardizes the circulation of the affected limb. In the clinical experience of our group with refractory CVU, we found that careful debridement is a must when the patient is seen initially and subsequent cleansing as needed is likewise useful and the same method was applied in this group of patients with CVU and T2DM as mentioned by Gethin [2]. In this regard, the help provided by family members at home resulted in a much better clinical result and vice-versa when this help was not available the opposite results have been seen. In fact Joaquim et al in a recent review [14] arrived at a well-known and accepted conclusion that it is crucial for CVU patients to receive comprehensive and professional care throughout the healing process, including strict home care and this of course is impacted by the fact that limitations at home such as the impossibility for mobilization of the patient (2 patients herein reported had suffered from hip fractures), severe and/or continuous pain, the presence and staining of malodorous secretions, insomnia, etc. and other related issues affect negatively the treatment and the emotional status of the patient that produces depression present in 30%-50% of these patients [15] unless they have dedicated family relatives and\or attached friends to support them as we observed particularly in case 1. The well-known economic limitations in many countries are likewise worth mentioning too. It is well known that National Health systems, as well as private Institutions, invest huge amounts of money to treat CVU, but in addition, the patients and relatives themselves spend a lot of resources on medications and missed working hours, due to the ulcer complications. Patients living alone, isolated with no economic support is forced to leave the treatment and consequently lose all the progress achieved [1-3,14]. The finding of Staphylococcus Intermedius twice in the cultures in the patient (Case 3), is probably related to the close contact with a cat and a dog at home, since this is a Gram-positive member of the bacterial genus Staphylococcus consisting of clustered cocci

that were originally isolated from the anterior nares of pigeons, dogs, cats, mink, and horses. As to the use of grafting these ulcers, we frequently use pinch grafts with local anesthesia after cleansing the wound and found the procedure most useful and well tolerated by the patients. Additionally and as suggested by Santema [16] and his group, we have used liberally other newer products such as Epifast and the advantages were obvious in the progress of patients of Case 3 and 4 described above. The use of the Polymer Polysaccharide with Zinc Oxide has been used in refractory complicated CVU and reported with satisfactory results without any neither adverse nor undesirable effects [7-10]. Recently, a very complicated septic diabetic patient requiring an amputation has been treated with PPZO and surgical debridements and healed completely even in the presence of abundant remodeling substances injected subcutaneously 20 years previously in both legs [17]. Additionally, it is important that these patients have to be treated for metabolic syndrome complications by their responsible physicians [18]. Finally, recent reports of venous excisional or thermal ablation surgery performed during the treatment of CVU have shown promising results and considering the paucity of favorable results it should probably be kept in mind [19,20].

Conclusion

Among chronic ulcers of the lower limbs the most commonly found are CVU that to date do not have a really effective product and/or therapeutic method, and among these patients, the presence of T2DM certainly complicates the treatment as discussed in this report. The addition of locally applied PPZO daily and complementary grafting has shown promising results that need to be confirmed in a larger clinical trial.

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