Electric impedance and the healing of diabetic foot ulcers

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Abstract: Diabetic foot (DF) is a complication of people suffering from diabetes mellitus (DM) with an overall prevalence estimated as 6.3%. Healing of diabetic ulcers takes several weeks, and follow up is needed both to assess the improvement of the wound and to detect possible complications. Ulcer diameter, pH and temperature have been used for such purpose and some authors have also proposed the use of Electric Bioimpedance (EBI). The results presented in this paper are taken from a small pilot study carried out to evaluate the healing effect of high quality, unrefined, whole cane sugar (“panela”) in people with unilateral diabetic foot ulcers in one of the legs. 6 volunteers (3 male and 3 female, aged between 51 and 85 mean age 71) were treated either with Triticum vulgare or with “panela” and EBI measurements (resistance or \( R \), reactance or \( X_c \), and phase angle or \( \theta \) at 50 kHz) on both legs were taken during a follow up period of 5 weeks. Although the healing process ran well with no complications, EBI parameters did not rise during the treatment, as expected. Differences between the ulcerated and the not-ulcerated legs seem to be present (higher values for \( R \) in the affected side and lower for \( X_c \) and \( \theta \)), but it does not seem to be a trend of the former towards the values of the latter. EBI values of the sample with DM are much lower than those of a sample of the 8 healthy volunteers measured for this study.

1. Introduction
In the Medical Subject Headings (MeSH), the thesaurus of PubMed, diabetic foot (DF) is defined as: “Common foot problems in persons with DIABETES MELLITUS, caused by any combination of factors such as DIABETIC NEUROPATHIES; PERIPHERAL VASCULAR DISEASES; and INFECTION. With the loss of sensation and poor circulation, injuries and infections often lead to severe foot ulceration, GANGRENE and AMPUTATION.” (see: https://www.ncbi.nlm.nih.gov/mesh/?term=diabetic+foot). This type of ulcer is also known as diabetic foot ulcer (DFU) and, until very recently, but probably no longer, this condition had been considered as “…the Cinderella of diabetic complications…” [1], with little research done in the topic, in part due to its conceptualization as gangrene [2]. Its study is considered as a relatively new discipline [2], in part due to the fact that, in the era of insulin and penicillin, DFU has replaced diabetic coma as the major cause of mortality among people with diabetes [2].

Global epidemiology of DF has been analysed by [3] in a recent systematic review and meta-analysis, showing that its overall prevalence can be estimated at 6.3%, with a 95% confidence interval...
(CI) between 5.4 and 7.3%. Regrettably, according to [3], no English language articles are available with data that allow an estimation of DFU prevalence in South America. Nevertheless, the World Health Organization (WHO, [4]) estimates an age adjusted prevalence of diabetes mellitus for 2014 as 8.9% for men and 9.6 for women, above the average for the Americas as a whole (8.6% and 8.4%, respectively). Some estimates [1,5] suggest an average annual cost for the treatment of a non-complicated DFU in Europe as 10,000 Euros (€) and 17,000 € for an infected diabetic ulcer with concurrent peripheral arterial disease, while, in the USA, the cost for a below-knee amputation after severe infection and non-response to treatment was around $190,000 in 2012. It is estimated that about 25% of diabetic patients present at least one episode of DFU during their lifetime, with about 60% infected at presentation for treatment and approximately 5% of all patients with DFU requiring major amputation in a follow-up period of 12 months [1].

Basic steps in the management of DFUs are: initial patient and ulcer evaluation, election of a treatment, debridement, initial covering of the ulcer/s with a dressing, periodical change of dressing (at 1-3 day intervals [6]) with eventual initiation of a different treatment if the DFU is not healing after 4 weeks [7], and follow up of between 2 weeks to 3 months [5]. Measures of some wound parameters or biomarkers during the healing process are considered relevant regarding treatment plans and outcomes, healing ability and cost containments, therefore having medical, legal and financial implications [8]. These same authors analyse three of the most commonly used measures for this purpose: pH, temperature and exudate composition (the latter in terms of metalloproteinase-9 or MMP-9, matrix metalloproteinase-2 or MMP-2, tissue inhibitor of metalloproteinase or TIMP, neutrophil elastase or NE and albumin). Of these, pH seems to be very promising, especially due to its low cost and ease of use. Research suggests that a decrease in wound pH from alkalinity towards a more neutral pH is associated with reduction in wound size, absence of wound infection and improvement in wound bed tissue [8]. Moisture in the wound is also a variable considered by some authors, as it seems that there is an optimum range favourable for the healing of DFUs [6]. Another issue that has drawn the attention of some authors is the need for a technique that can be readily performed by the patient or a family member in order to facilitate a more active role in wound management, without the need of a professional clinician’s intervention and without the removal of wound dressings, as this can disturb the wound healing process and increase the risk of contamination [9].

All these considerations have led some authors to propose the use of Electric Bioimpedance (EBI) as a possible technique to overcome at least some of the above-mentioned difficulties and give information about some variables associated with wound healing such as extracellular fluid volume, fibrin clot formation, epithelialisation, cell mass, epidermal proliferation and granulation [10]. There are two different approaches for this purpose: a) an array of multiple electrodes in a planar configuration that make contact with the wound, as in [9], b) a tetrapolar arrangement placed on the sides of the wound as in [11 and 12]. The authors of [13] did not study DFU, but, instead, they evaluated the foot skin of diabetic patient using EBI in a bipolar arrangement. We used neither of these and, instead, we measured the leg impedance in both legs, with the idea of not only follow up to the affected side but also to compare these readings with those of the contralateral leg. The information available so far suggests that the values of three of the parameters most commonly considered when EBI is used (resistance or $R$, capacitive reactance or $X_c$ and phase angle or $\theta$) show a positive slope with the improvement of the healing process [9-12].

The present study was carried out as a small pilot study of a project aimed at validating the use of a product obtained from sugar cane (Saccharum officinarum) for the healing of diabetic foot ulcers. The product used in this study (unrefined, whole cane sugar obtained from the sugar cane juice and known as “panela” in Colombia) is a very popular food in sugar cane producing countries, Colombia among them. Some authors have proposed the use of other products rich in saccharides (such as sugar and honey) for the treatment of different types of wounds [14-16] and, in Colombia, it has a popular veterinary use in the treatment of wounds.
2. Methods
Initially, in order to see if the contralateral leg can be used as a permanent control to measurements taken on an affected leg, EBI readings were taken on both legs of a small sample of 8 healthy volunteers (4 male and 4 female, mean age 29.5 and an age range of 22-47). The assumption here is that, considering overall body symmetry, there should not be significant differences between both sides. EBI measurements were carried out with a Bio-Impedance Spectrum Analyzer System 4000B (XITRON Technologies, San Diego, USA). According to the nomenclature proposed by [17] electrodes were placed as follows (figure 1): the two current electrodes at points L99 (left foot) and R99 (right foot), and the four voltage electrodes at R09 (right knee) and R11 (right ankle) for the right leg, and L09 (left knee) and L11 (left ankle) for the left leg. Electrocardiogram electrodes were attached at each point and, for the readings, only the voltage lead initially used at the right knee was displaced to the left knee. Data at 50 kHz were used as this is the frequency reported by [11]. Figure 1 illustrates the experimental set up used for the EBI measurements. The t-test for paired data was used to determine if the two sets of data (left limb versus right limb) can be considered as equal (coming from the same population data), with a significance level $< 0.05$.

Figure 1. Experimental setup. On the left, the equipment used in the study and, on the right, placement of the electrodes. In this case, the resistance of the left lower limb in a patient with DFU is being taken.

The small sample of volunteers for the pilot study on the treatment of ulcers ($n=6$, 3 males, 3 females, mean age 71 years old with an age range between 51-85 years old) was recruited among people attending a private wound clinic located in the city of Pereira, Risaralda in Colombia owned by one of the authors (SMT). The study was approved by the Ethics Committee of the University of Caldas in Manizales, Caldas, in Colombia, where two of the authors (RARG and SMT) study and the main author (CAGC) is a full time professor. After reading the information sheet of the study, all participants signed a consent form. Three of the participants were treated with high quality “panela” provided by BEKDAU (Supía, Colombia, a government funded research and innovation centre on “panela”) and packed by the pharmaceutical company COSVAL SAS (Santa Rosa de Cabal, Risaralda, Colombia, South America) and the other three were treated with aqueous extract of Triticum vulgare (Fitoestimulina from Euroetika, France). The only inclusion criteria were to have a unilateral diabetic foot ulcer in one of the legs and agree to participate in the study. The recruitment
was carried out sequentially and the first patients were randomly allocated to one of the two treatments (by tossing a coin) until both of the two groups had 3 patients.

3. Results
Figure 2 shows $R$, $X_c$ and $\theta$ for the eight healthy patients recruited for the first stage of the study, with $p$-values for the comparison between both sides.

In this article, the authors were not interested in comparing the two different treatments offered to the 6 patients, but rather in the behaviour of three EBI parameters ($R$, $X_c$ and $\theta$) during the five week long study. However, it is worth mentioning that all ulcers evolved well in the 6 subjects, with two of them being completely closed at week 5 (one per treatment). Figure 3 shows, for the whole sample,
the mean ± standard deviation (SD) lines and a trend line (as obtained with Excel from Microsoft®) for: a) area (cm²), b) pH and c) temperature (°C) of the wounds during the 5 weeks of treatment.

**Figure 3.** Values (mean ± SD line) are shown for week 0 (before treatment began) to week 5 of the follow up, for: a) area, b) pH of the exudate, and c) temperature of the wounds.
In relation to the parameters $R$, $X_c$ and $\theta$, figure 4 shows their respective means from week 0 to week 5 on both legs, as well as the trend line for each of the measurement sets. At this stage of the research, the authors are only interested in the trends, but also for clarity, the SD lines have been omitted.

Finally, although both sets of data (those taken from diabetic volunteers and those taken from healthy subjects) may not be comparable (especially due to differences in age, small sample size and lack of more strict inclusion and exclusion criteria for the selection of participants), the values for the healthy people seem to be much higher than those from the patients with DFU.

**Figure 4.** Means of and trend lines for $R$, $X_c$ and $\theta$ in both legs of the six patients treated.
Figure 5. EBI data of all participants in the study (healthy and those with DFU) plotted in the complex plane, showing the separation between those from healthy people from those with DM and DFU. Data from patients with DFU is the average of all measurements taken during the study.

4. Analyses
As trends, smaller areas of the wounds, lower pH and lower temperature (figure 1) seem to be indicators of wound healing from week 1 to week 5 of the follow up. EBI values were expected to increase with time, accordingly, as suggested by [11], but this was not the case (figure 4). Variations in the parameter values obtained from the non ulcerated leg were expected to show few longitudinal variations, but this was not the case either. Data obtained from the healthy volunteers indicate few differences between both legs, especially for $R$ and $X_c$, as $\theta$ shows some variations among them (figure 2). Although both sets of data (diabetic and healthy subjects) may not be comparable (especially due to differences in age, small size of the sample and lack of more strict inclusion and exclusion criteria for its selection), it is clear that healthy participants seem to show much higher impedance values than diabetic subjects (figure 5).

5. Conclusions
As mentioned in the introduction, this small trial was conducted as a pilot study in order to improve the study design of a larger one looking at the healing effect of unrefined whole cane sugar extracted from sugar cane ($Saccharum officinarum$). This is a product which is especially consumed in sugar cane producing tropical and subtropical regions of the world, such as most of Latin America (in Colombia it is known as “panela”). Although the main outcome was the healing process, the authors also wanted to explore the feasibility of electrical impedance as a tool to follow up wound healing. This could help to monitor this process with people at home as well as bedridden patients who are at risk of developing pressure ulcers.

Our approach was different to those more commonly used in studies looking at the use of EBIS to monitor wound healing in that ours did not make measurements directly on the wound or place the electrodes near to the wound, but rather measured the whole segment (the leg) allowing the use of devices aimed at measuring total and segmental body impedance. Although electric impedance readings on the patients did not give the expected trends, the authors still think they could be useful and will include them in the larger study that is about to begin, which will have an adequate sample size and a longer follow up period. In this larger study, a frequency range for the impedance measurements will be used in order to calculate the Cole parameters and include them in the analysis, instead of merely raw data. Another aspect that may be worth exploring, is the follow up on patients with high risk of developing DFU, as a decrease both in $R$ as in $\theta$ could highlight an increase in risk.
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