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## Therapy with autologous adipose-derived regenerative cells for the care of chronic ulcer of lower limbs in patients with peripheral arterial disease.

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#### Abstract

**BACKGROUND:** An ulcer is a trophic lesion with loss of tissue that often has a multifactorial genesis. It typically diverges from the physiologic processes of regeneration because it rarely tends to heal spontaneously. In this study, we used purified adipose-derived stem and regenerative cells (ADRCs) extracted from autologous fat, for the care of chronic ulcers of the lower limbs of arteriopathic patients. The primary objective of this study was complete re-epithelization of chronic ulcers; the secondary objective was a decrease in diameter and depth.

**METHODS:** From January 2010 to January 2012, 20 patients with peripheral arterial disease, with an ankle-brachial index between 0.30-0.40, in the age range 60-70 y (14 men and six women), with chronic ulcers of the lower limb, were involved in the study. Only 10 arteriopathic patients (seven men and three women) with chronic ulcers of the lower limb were surgically treated. Using the Celution system, we isolated a solution of ADRCs in about 150 min. The isolated cells were injected through a 10-mL syringe into the edges of the ulcer, taking care to spread it in all directions. Using a small amount of Celution extract, we performed cell characterization by flow cytometry analysis and cell viability assay.

**RESULTS:** We monitored patients treated with ADRC or untreated at 4, 10, 20, 60, and 90 d. In all cases treated with ADRC, we found a reduction in both diameter and depth of the ulcer, which led to a decrease in pain associated with the ulcer process. In six of 10 cases there was complete healing of the ulcer. Characterization of the cells by FACS clearly showed that the ADRC cells contained adipose-derived stem cells. Viability assays demonstrated that partial or total closure of the ulcer was attributable exclusively to ADRC cells present in the Celution extract, and not to growth factors extracted during the process of purification of the Celution and injected together with the cells.

**CONCLUSIONS:** For the first time, the Celution method has been applied for the care of chronic ulcers in the lower extremity of patients with peripheral arterial disease. Our results demonstrate that the technique is feasible for autologous cell application and is not associated with adverse

events. Moreover, the transplantation of autologous stem cells extracted with Celution may represent a valuable method for the treatment of chronic ulcers in lower limbs of arteriopathic patients.

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**KEYWORDS:** Adipose stem cells; Arterial disease; Chronic ulcer

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In this article, Marino and coworkers investigated the effectiveness of autologous adipose tissue derived regenerative cells in the treatment of chronic lower extremity ulcers in patients with severe arterial obstruction. Adipose tissue, recently, has gained significant attention as a stem cell source and the contribution of adipose tissue derived stem cells (ADSC) to wound healing has been shown in several experimental studies ([Cherubino M, 2011](#)). However, the number of studies that use ADSC to accelerate wound healing in a clinical setting is low ([Cherubino M, 2011](#), [Uzun G, 2014](#)). The article by Marino et al., in this regard, is an important contribution to this field. We, therefore, read the article with great interest, yet would like to express some of our reservations.

First, the outcome of patients in the control group was not given in the article ([Marino G, 2013](#)). Marino et al. included twenty patients, whose ulcers have not healed despite several months of traditional and advanced wound care methods. Of the 20 patients, 10 have been treated surgically with ADSC and others have been used as 'controls'. In the Results, they also state that patients who were treated with ADSC and who did not were monitored at days 4, 10, 20, 60, and 90. At the end of the study, ulcers of the 6 (60%) patients in the treatment group completely healed, however, there is no mention about ulcer healing rate in the control group. If the authors have provided this information, the reader would be able to compare the outcomes

in the treatment and control groups and to reach a better conclusion on the effectiveness of ADSC.

Second, there is a discrepancy between the information provided in the text and in the tables. Identification of a factor that predicts those who would benefit from ADSC would be very useful. The authors propose baseline ankle brachial index (ABI) value as a predictor of treatment outcome. In the Results, it is stated that 'Patients who recovered completely had an ABI between 0.8-0.9, whereas others with a reduction in the diameter of the ulcer had an ABI between 0.5-0.6.' ([Marino G, 2013](#)). Baseline characteristics and ABI values of patients in the treatment and control groups were presented in Table 1 and Table 2, respectively ([Marino G, 2013](#)). It is seen on these tables that none of the patients had an ABI higher than 0.39. This issue needs clarification.

There is a need for more clinical studies that test ADSC as a potential treatment for non-healing lower extremity ulcers in patients with peripheral arterial disease. We applaud the efforts of Maroni et al., and acknowledge the importance of their study, however, we think that two points mentioned above need to be clarified.

Gunalp Uzun & Abdul Kerim Yapici

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