



RESPONSE TO COMMENT ON CREWS ET AL.

## Role and Determinants of Adherence to Off-loading in Diabetic Foot Ulcer Healing: A Prospective Investigation. *Diabetes Care* 2016;39:1371–1377

*Diabetes Care* 2016;39:e222–e223 | DOI: 10.2337/dci16-0032

Ryan T. Crews,<sup>1</sup> Biing-Jiun Shen,<sup>2</sup>  
 Laura Campbell,<sup>3</sup> Peter J. Lamont,<sup>4</sup>  
 Matthew Hardman,<sup>3</sup>  
 Andrew J.M. Boulton,<sup>4</sup> Mark Peyrot,<sup>5</sup>  
 Robert S. Kirsner,<sup>6</sup> and  
 Loretta Vileikyte<sup>4</sup>

We were pleased that van Netten et al. (1) appreciate the importance of our article (2) substantiating the relationship between adherence to off-loading modalities and healing of diabetic foot ulcers (DFUs). Their letter contained several comments regarding our article that we address here.

The first comment by van Netten et al. is regarding the rationale for using a surrogate clinical outcome (ulcer area reduction) rather than ulcer healing by a fixed time, preferably 12 weeks, which would allow for direct comparisons with other articles on off-loading. It is important to note, as was outlined in our article, that the study associated with our publication was not limited to examining off-loading adherence. The main focus of this multifaceted investigation (National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK071066) was to examine the hypothesized psychological stress-induced modulation of the molecular/cellular DFU profile in its relationship to healing. Well-documented difficulties associated with the acquisition of quality DFU specimens (3) influenced the duration and distribution of resources for this study. After evaluating available resources, the demands on participants, and the intent of the parent

study in which our adherence study was included, the investigation was designed with a 6-week monitoring period. In considering ulcer area reduction at 6 weeks of treatment as the outcome measure, a number of previous publications have demonstrated that the percentage of wound healing that occurs in as little as 1–4 weeks of monitoring is a significant predictor of whether a wound will have healed at a later date (4,5). Another reason for analyzing wound reduction rather than complete wound healing is because the latter measure discards information about the healing process (e.g., equating a wound that has worsened with one that has almost completely healed), which increases measurement error and reduces the statistical power of the analysis.

van Netten et al. also suggest we should have reported univariate and multivariate coefficients for all baseline variables from our study. However, bivariate associations are not informative when measures are confounded, as in this study, and the ratio of cases to variables is inadequate to estimate all multivariate parameters simultaneously.

The lack of plantar pressure measurements in our study also was noted as a

limitation. Having such data would certainly be of benefit in evaluating the outcomes associated with specific removable off-loading modalities. However, identifying responses to adherence levels of individual off-loading modalities was beyond the scope of this project. The intent of the analysis was to determine whether varying levels of adherence to off-loading impact the healing process. Future studies with funding available to ensure each participating center has the equipment and trained personnel to conduct pressure assessments would benefit from this additional assessment.

In conclusion, our study objectively demonstrated the positive association between adherence to off-loading modalities and DFU healing. With this in mind, investigators should consider incorporating adherence monitoring into future studies of any potential new therapies for DFUs.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

### References

1. van Netten JJ, Lazzarini PA, Bus SA. Comment on Crews et al. Role and determinants of adherence to off-loading in diabetic foot ulcer healing: a prospective investigation. *Diabetes Care*

<sup>1</sup>Center for Lower Extremity Ambulatory Research at the Dr. William M. Scholl College of Podiatric Medicine, Rosalind Franklin University, Chicago, IL

<sup>2</sup>Division of Psychology, Nanyang Technological University, Singapore

<sup>3</sup>The Healing Foundation Centre, Faculty of Life Sciences, University of Manchester, Manchester, U.K.

<sup>4</sup>Department of Medicine, University of Manchester, Manchester, U.K.

<sup>5</sup>Loyola University, Baltimore, MD

<sup>6</sup>Department of Dermatology and Cutaneous Surgery, University of Miami, Miami, FL

Corresponding author: Ryan T. Crews, ryan.crews@rosalindfranklin.edu.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

- 2016;39:1371–1377 (Letter). *Diabetes Care* 2016;39:e220–e221. DOI: 10.2337/dc16-1542
2. Crews RT, Shen B-J, Campbell L, et al. Role and determinants of adherence to off-loading in diabetic foot ulcer healing: a prospective investigation. *Diabetes Care* 2016;39:1371–1377
  3. Stojadinovic O, Landon JN, Gordon KA, et al. Quality assessment of tissue specimens for studies of diabetic foot ulcers. *Exp Dermatol* 2013;22:216–218
  4. Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. Surrogate end points for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care* 2003;26:1696–1700
  5. Lavery LA, Barnes SA, Keith MS, Seaman JW Jr, Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. *Diabetes Care* 2008;31:26–29