Response to Reviewer 1 Comments

Dear Reviewer,
Thank you for your questions and suggestions. We are grateful for the in-depth analysis of our manuscript. Please, find enclosed our responses and corrections and improvements implemented to the manuscript following your requests.

Point 1: In the first place, the manuscript is written in a confusing language and without a scientific order. In general terms, the authors must completely rewrite the manuscript.

Response 1: The manuscript has been revised and improved according to your suggestions. The conclusion section has been added to the text.

Point 2: The summary of the manuscript must be rewritten, in its current state it seems like a popular article and not a scientific manuscript.

Response 2: Thank you very much for this suggestion. The conclusion section has been added and every effort has been made to ensure that the current summary has a more scientific tone.

Point 3: The authors should improve the introduction to the state of the art, focusing on the mechanisms of the disease itself and justifying the need for the study.

Response 3: The introduction section has been extended and improved – important information including the mechanisms of diabetic foot syndrome development has been added to the manuscript.

Point 4: Authors should review and update references.

Response 4: References have been reviewed and some new literature references have been added to the text.

Point 5: The methodology section should be explained better.

Response 5: The methodology section has been revised and extended. We have added some important information about inclusion and exclusion criteria, and hemodynamic parameters measurements of lower limb arteries.

Point 6: The authors must justify the sample size statistically.

Response 6: We want to apologize for this oversight on our part. We assume a moderate (r=0.2 to r=0.4) association between circulating angiogenesis regulating factors and clinical characteristics. Given a significance level of 0.05 and power set at 0.80, the required sample size for a one-sided hypothesis is at least 37 patients.

This fragment has been added to the methodology.

Point 7: Authors must calculate the statistical potential of the sample size.

Response 7: See the comment above.

Point 8: Authors must adequately specify the inclusion criteria. The authors should improve the characterization of the patients in Table 1.

Response 8: The description of inclusion criteria in methodology section has been improved according to your suggestions. The characterization of the patients has been presented in Table A1, which has also been revised.

Point 9: In global terms, the authors should better describe the results in all points.

Response 9: Thank you for this suggestion – the results section was incomplete. We have improved the results by adding more information in each subsection and by adding a comparison of angiogenic factors and clinical characteristics according to patients' age.

Point 10: The authors should improve the quality of the figures and unify the format.

Response 10: The quality of the figures has been improved and format has been unified according to your suggestions.

Point 11: Authors must show data as interquartile range.

Response 11: The median (IQR) is provided as an additional characteristic in the Table 1 and Table 2.

Point 12: Authors should divide the four figures into more and should be more self-explanatory.

Response 12: Figures 1-4 were divided into more (Figures 1-8) and every abbreviation in all tables and figures was explained.

Point 13: Authors must include a control.

Response 13: Thank you for bringing attention to this important issue. In our study, we did not include a healthy control group as our objective was to assess angiogenic biomarkers in relation to the severity of DFS in the context of trophic changes. Therefore, it is difficult to compare the results to a healthy control group (without diabetes or with diabetes without trophic changes). Elevated levels of circulating FGF-2 among patients with diabetes and DFUs compared to those without DM and DFUs have already been demonstrated in studies (19,20) - and the aim of the study was not to re-analyze these relationships. Moreover, there are reference values available for the assessment of most angiogenic factors used in our analysis.
This is a pilot study - based on the obtained and presented results, we have planned a new project that includes a larger group with a one-year follow-up and a control group of diabetic patients without DFUs to verify the predictive value of FGF-2.

Point 14: Aging must be a key point. Authors must stratify patients based on this very important criterion.

Response 14: Thank you very much for suggesting these additional analyses. We have added these calculations to our results and divided patients into 2 groups (<= 68 years vs >68 years old). You can see the results in Table B1.

Point 15: The authors should improve the discussion with more clinical aspects in order to justify the translation of the study.

Response 15: The discussion section has been revised and improved – clinical aspects like future trends for research in this area have been added to the conclusions.

Point 16: Authors should improve the use of English grammar with professionals.

Response 16: English grammar in our manuscript has been improved with professionals according to your suggestions.

Point 17: Authors must include a graphic summary.

Response 17: Thank you very much for this comment. We have added a diagram illustrating the suggesting double pathway of FGF-2 action on impaired wound healing in the course of diabetic foot syndrome. You can find it in Figure 9.