Response to Reviewer #1

1. Title can be "Understanding the multifaceted etiopathogenesis of diabetic foot complications in individuals with chronic diabetic complications"

We accepted the reviewer's suggestion and changed the title.

2. Abstract: "Due to neuropathy, diabetic foot infections most commonly occur in the form of ulcers". Not all ulcers are infected, hence this statement need to be revised.

We agree with this comment and would like to thank the reviewer for pointing this out. Therefore, this has been revised.
Due to neuropathy, diabetic foot infections might present in the form of ulcers.

3. Abstract can be more precise/rewritten to depict what is discussed in mini review. The flow of the abstract needs restructuring. Suddenly the abstracts switches to HBOT before discussing standard treatment modalities.

We wish to thank the reviewer for this valuable comment. We rewrote the abstract so that it follows the manuscript sections.

4. Please avoid the term "Diabetic patients" throughout the manuscript. People with diabetes or individuals with diabetes may be used.

We replaced the term' diabetic patients' with 'people with diabetes' or 'individuals with diabetes' throughout the manuscript.

5. The statements need to be revised "characterized by inadequate control of glucose blood levels". This does not define diabetes!

We rephrased the mentioned sentence into 'disease characterized by insufficient insulin production or insufficient insulin use'.

6. DFU also contribute to increased mortality which should be mentioned in introduction. There are excellent long term studies across the globe mentioning the same. (Diabet Med. 2016;33(11):1493–1498. doi: 10.1111/dme.13054 ; Diabetes Res Clin Pract. 2020 Apr;162:108113. doi: 10.1016/j.diabres.2020.108113; J Diabetes Res. 2016;2016:2879809. doi:10.1155/2016/2879809; PLoS One. 2017 Nov 27;12(11):e0188097. doi: 10.1371/journal.pone.0188097 etc)

We added information about the increased and high risk of mortality in people with diabetes and DFU.

People with diabetes and diabetic foot complications have a higher mortality rate than individuals with diabetes without foot complications[1,2]. People with diabetes

have a more increased risk of mortality after an incident DFU compared to people of the same age and duration of diabetes without a DFU[3]. The mortality rate increases in people with diabetes and associated amputations[2]. Ischemic heart disease is a significant cause of premature mortality in patients with DFU[4], and patients with neuropathic DFU have even more increased mortality[3,4].

7. Which guidelines authors are referring to that leave questions unanswered? IWGDF guidelines are quite comprehensive and may be mentioned.

The IWGDF guidelines are drawn on and cited throughout the manuscript. However, one manuscript can only cite up to three articles from the same journal due to journal restrictions. In addition, as most of the IWGDF guidelines are published in Diabetes/metabolism Research and Reviews, we could not cite absolutely all published guidelines. What is valid for all guidelines is also valid here, and the authors of the guidelines themselves explain in the methods section (Bus SA, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, van Netten JJ. Guidelines on preventing foot ulcers in persons with diabetes (IWGDF 2019 update) - when making recommendations, they used the GRADE system, which takes into account the LEVEL and QUALITY OF RESEARCH based on the recommendation was made. At the end of each recommendation (be it weak or strong), there is a classification of the same (here, specifically high, moderate, and low). Paying attention to it, you can see that most of the recommendations in the IWGDF guidelines (especially regarding the diagnosis and therapy of infections and PAD in the DFU) are marked LOW, which means that they are genuinely missing high-quality research that would support the same, primarily RCTs.

8. "there is only limited high-quality evidence for many critical questions" What are the unanswered questions need to discuss at least broad areas in introduction section.

The answer to this reviewer's point is the same as above.
The IWGDF guidelines are drawn on and cited throughout the manuscript. What is valid for all guidelines is also valid here, and the authors of the guidelines themselves explain in the methods section (Bus SA, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, van Netten JJ. Guidelines on preventing foot ulcers in persons with diabetes (IWGDF 2019 update) - when making recommendations, they used the GRADE system, which takes into account the LEVEL and QUALITY OF RESEARCH based on the recommendation was made. At the end of each recommendation (be it weak or strong), there is a classification of the same (here, specifically high, moderate, and low). Paying attention to it, you can see that most of the recommendations in the IWGDF guidelines (especially regarding the diagnosis and therapy of infections and PAD in the DFU) are marked LOW, which means that they are genuinely missing high-quality research that would support the same, primarily RCTs.

9. frank neuropathic ulcers are still more prevalent in low-income countries [16]. Reference 16 is related to Australian guidelines and do not mention about the cited statement. Please reconsider.

We added additional references to confirm our statement, as follows:
World Health Organization. Global Report on Diabetes. Geneva, Switzerland: 2016 [cited 2022 Nov 12].
Chuter V, Quigley F, Tosenovsky P, Ritter JC, Charles J, Cheney J, Fitridge R, Twigg S, Lazzarini P, Raspovic A, Prentice J, Commons R. Australian guideline on diagnosis and management of peripheral artery disease: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res*. 2022;**15**:51.
Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, Game F. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes Metab Res Rev*. 2020;**36**:e3273.
Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, Mills JL, Nikol S, Reekers J, Venermo M, Zierler RE, Schaper NC. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;**36**:e3276.

10. Authors can add section on poor immune response secondary to hyperglycemia as a contributing factor for DFI. (impaired cell mediated and humoral immunity).

We agree with this comment and would like to thank the reviewer for pointing this out. We added the section Immune response to hyperglycemia, which explains the dysfunctions of the immune system in diabetic foot infection and diabetic wound healing.

11. How does hyperglycemia impair wound healing in diabetes compared to controls? Is there any evidence that intensive glycemic control hastens wound healing? Please consider to include the discussion on these aspects as well.

In the section Immune response to hyperglycemia, we referred to the difficulty of wound healing in hyperglycemic states. We wrote about how controlling hyperglycemia in glycemia can accelerate diabetic wound healing.

12. They can also discuss the stages of wound healing and how diabetes affects different phases of wound healing. This shall provide deep insights into the pathophysiology of foot complications as the title suggests.

Also, as mentioned above, in the section Immune response to hyperglycemia, we referred to stages of wound healing and diabetes' impact on different phases.

13. Charcot Neuroarthropathy of foot is also a foot complications which is entirely missed by the authors with passing remark as "special entity called Charcot's

foot". CN is also associated with significant morbidity (amputation) and even increased mortality which needs to be mentioned in manuscript.

Thank you for this important observation. We expanded the part of the manuscript related to Charcot neuroarthropathy of the foot and highlighted the association of CN with increased morbidity and mortality, especially in people with DFU.

Charcot neuroarthropathy (CN) is a severe diabetic foot complication that significantly increases morbidity and mortality, primarily in patients with concomitant DFU. Such patients have reduced life expectancy by 14 years. CN is characterized by bone and joint destruction and can be asymptomatic or mimic other more common conditions such as cellulitis, osteomyelitis, deep vein thrombosis, inflammatory arthritis, or ankle sprain, which is why it remains a poorly recognized complication. In the acute phase, it presents as a warm, swollen red joint which is often not painful. In the early stages of CN, there are no clinical signs of bone fractures, but radiological examination usually shows microfractures. 58% of patients with CN present with DFU. CN can lead to mid-foot collapse, rocker-bottom foot (collapse and inversion of the plantar arch), acute fractures, and dislocation if not treated.

14. Section on microbiology can be truncated to discuss polymicrobial infections, Types of organisms observed in meta analysis, Varied bacteriological profile that depends on foot care facility/ geography, Biofilms and then fungal infections. (doi: 10.1016/j.jdiacomp.2016.11.001)

In the section Microbiological profile of diabetic foot infections, we discussed polymicrobial infections, biofilms, and fungal infections. Also, we mentioned the suggested article that indicates the antimicrobial resistance of pathogens isolated from DFU samples.

15. Presentation of diabetic foot with deformities like pas planus, mid foot collapse, rocker bottom, fractures etc is not mentioned (mainly seen in people with CN)

We wish to thank this reviewer for this valuable comment. In the part of the manuscript related to Charcot neuroarthropathy of the foot, we mentioned different deformities.

16. Diagnostic evaluation: Can be presented better by providing table and flow charts.

We wish to thank this reviewer for this valuable comment. Diagnostic evaluation is presented as a flow diagram that displays screening for foot complications in persons with diabetes.

17. However, I think that the manuscript is intended to provide review of the "multifaceted nature of foot complications" that means etiopathogenesis. Hence, diagnostic and treatment considerations should not be included as these aspects

need further detailed review. The present review misses/ could not concise many aspects for diagnosis and therapy.

Thank you for this important observation. However, another reviewer asked that traditional approaches to the diabetic foot, such as surgery and vascular radiology, be mentioned. Therefore, we are not able to exclude the diagnostic assessment. Also, we were asked to refer to the interventional approach of Cangiano, and for this reason, we cannot exclude the part about the treatment of the diabetic foot.

18. English language in whole manuscript needs reconsideration and formatting.

The English language was reviewed throughout the manuscript and reformatted.

Response to Reviewer #2

We would like to thank this reviewer for a positive outlook on our manuscript and for valuable comments to improve its merit.

On some aspects, the authors should address:

1. I believe that at least a mention about "traditional" approaches to the diabetic foot, for example surgery or vascular radiology. For example, I suggest you read this commentary about the interventional radiology in the treatment of diabetic foot: -Reekers JA. The Role of Interventional Radiology in the Treatment of Arterial Diabetic Foot Disease. Cardiovasc Intervent Radiol. 2016;39(10):1369-1371. doi:10.1007/s00270-016-1337-y

We wish to thank this reviewer for this valuable comment. We have read the proposed paper and added a section on new endovascular techniques in the treatment of diabetic foot and cited the mentioned paper.

Today significant progress is occurring in endovascular medicine, and there are emerging endovascular techniques, such as drug-eluting technologies. Nevertheless, high-quality randomized studies to evaluate their efficiency in this specific group of patients are still lacking.

2. Additionally, I suggest you refer to innovative interventional approach such as Cangiano one, who have treated chronic critical limb ischemia (cCLI) patients with no surgical options approach by the creation of an AVF with a IVUS-guided percutaneous deep vein arterialization (pDVA). I would like you briefly discuss about it, citing the following article: -Cangiano G, Corvino F, Giurazza F, et al. Percutaneous Deep Foot Vein Arterialization IVUS-Guided in No-Option Critical Limb Ischemia Diabetic Patients. Vascular and Endovascular Surgery. 2021;55(1):58-63. doi:10.1177/1538574420965743

We have added a section where we discuss the treatment of patients without endovascular and surgical techniques and briefly describe the IVUS method of Cangiano et al.

Furthermore, recent reports suggest an innovative treatment alternative for patients with no-endovascular or surgical options. Intravascular ultrasound (IVUS) - guided percutaneous deep vein arterialization with the creation of an arteriovenous fistula between the posterior tibial artery and its satellite deep vein showed promising results in such no-option patients with critical limb ischemia.

3. The iconography is poor. It would be necessary to insert clinical images, instrumental images and their comments (for example, Doppler ultrasound, angio-CT, angio-MRI images).

As this is a review manuscript, we did not enjoy inserting clinical pictures of the diabetic foot because everyone knows how it looks. However, presentations of different radiological techniques in a patient with a diabetic foot are not available to us because they are not routinely performed, and due to the current burden on the healthcare system, we cannot obtain them.