Journal of Cellular & Molecular Anesthesia
Volume 11 · Issue 3 · e174420

OPEN PEER REVIEW

Association of Serum 25-Hydroxyvitamin D Levels with Diabetic Foot Ulcer: A Case-Control Study

Mehrdad Haghighi, Fatemeh Rahmani, Kourosh Shahkarami

SUBMITTED	REVISED	ACCEPTED	DOI
18 Aug 2026	23 Sep 2026	12 Oct 2026	10.5812/jcma-174420

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Elham Memary, Referee 2, Associate Editor, Editor-in-Chief 2

2 **Revision 1** Editor-in-Chief 10

Authors' reply to reviewers 11

Reviewer and editor comments 21

1 Original submission

5 comments · 6 Sep 2026 – 14 Sep 2026

Referee 1 Reviewer

REJECT 6 Sep 2026

Dear Authors,

We have completed the initial editorial assessment of your manuscript entitled “Association of Serum 25-Hydroxyvitamin D Levels with Diabetic Foot Ulcer: A Case-Control Study.”

The manuscript investigates serum vitamin D levels and associated clinical and laboratory characteristics in patients with type 2 diabetes, with and without diabetic foot ulcers. Although this is a clinically relevant subject, its primary focus falls within diabetes, endocrinology, nutrition, and wound care.

The Journal of Cellular & Molecular Anesthesia primarily publishes research concerning anesthesiology, perioperative medicine, anesthesia-related cellular and molecular mechanisms, and translational studies connecting laboratory findings with clinical anesthetic practice. The submitted study does not evaluate anesthetic agents, anesthesia techniques, perioperative interventions, surgical populations, or outcomes directly related to anesthesia and perioperative care. Therefore, the manuscript does not demonstrate sufficient alignment with the journal’s stated aims and scope.

For this reason, we are unable to proceed with peer review, and the manuscript is rejected on the basis of being outside the scope of the journal. This decision does not constitute an assessment of the scientific merit of the work. The manuscript may be more appropriately submitted to a journal specializing in diabetes, endocrinology, clinical nutrition, diabetic foot care, or wound management.

Thank you for considering the Journal of Cellular & Molecular Anesthesia for your work.

Kind regards,

Reviewer

Elham Memary Reviewer

MAJOR REVISION 10 Sep 2026

Dear Associated Editor ,
I have carefully reviewed the above-mentioned manuscript, a case-control study of 200 patients with type 2 diabetes mellitus (102 cases with diabetic foot ulcer [DFU] and 98 controls without DFU), investigating the association between serum 25-hydroxyvitamin D [25(OH)D] levels and DFU. The topic is clinically relevant and falls within the scope of the Journal’s interest in the cellular and molecular mechanisms underlying perioperative and wound-healing processes. Below is my section-by-section evaluation.

- Abstract:
• Structured abstract formatting (Background, Methods, Results, Conclusion) should conform to the Journal’s Instructions for Authors.

- Introduction:
• Several sentences are overly long and should be divided for readability.
• The hypothesis and primary objective should be stated more explicitly at the end of the Introduction.

- Materials and Methods:
1. Inclusion/Exclusion criteria: The authors must define:
o Diagnostic criteria for DFU (e.g., Wagner/Meggitt or University of Texas grade, and which grades were

included);
o Criteria for the control group (T2DM patients without DFU — how were they screened and confirmed?);
o Exclusion of conditions that independently alter 25(OH)D levels or wound healing (chronic kidney disease stage, parathyroid disorders, malabsorption, medications such as corticosteroids or anticonvulsants, pregnancy).
2. Sampling and matching: The authors state the groups were matched for age and sex, yet Table 1 shows significant between-group differences in BMI, systolic blood pressure, duration of diabetes, renal function, insulin use, and smoking.
3. The authors must clarify:
o Whether matching or frequency-matching was performed, and how controls were selected (medical records and hospital information system — with what safeguards against selection bias?);
o Exactly which covariates were entered into the multivariable model and whether BMI, diabetes duration, eGFR/creatinine, insulin use, and smoking were adjusted for. Without this, the reported association may be substantially confounded.
4. Vitamin D measurement: Specify the assay method.
5. Also define the vitamin D deficiency/insufficiency thresholds used (e.g., IOM vs. Endocrine Society cutoffs), since these differ and affect interpretation.
6. Data source and quality: Since data were collected retrospectively from medical records/HIS, describe missing-data handling and any quality-control measures.

- Results:
1. Table 1 (p. 19) — critical error: In the "Duration of diabetes" column, the figures appear to be duplicated from the BMI column. This is a data-integrity issue and must be corrected and verified against the source data.
2. Table 1 formatting: Data should be consistently presented as mean ± SD or median (IQR) as appropriate to the distribution, with the statistical test used specified in the footnote (t-test vs. Mann–Whitney U; χ^2 vs. Fisher's exact test).
3. Consider a dose-response or subgroup analysis (e.g., DFU risk by vitamin D category: deficient/insufficient/sufficient), which would strengthen the biological interpretation.

- Discussion
• Patients with DFU are more likely to be hospitalized, less mobile, and less physically exposed to sunlight, which could lower their 25(OH)D independently of a causal effect.
• This should be discussed and explained further.

- Limitations
There is no dedicated "Limitations" section. The authors must add the limitations of their study.

- References
• Verify all citations for accuracy of author names, journal abbreviations, and page numbers per the Journal's Vancouver-style requirements.

Referee 2 Reviewer

MAJOR REVISION 14 Sep 2026

Please see the comments in the attached file.

Associate Editor

MAJOR REVISION 14 Sep 2026

Dear EIC
The manuscript has major issues that should be addressed. Please see the following:
Reviewer 1:
The manuscript addresses an important clinical issue regarding vitamin D deficiency and diabetic foot ulcers. However, the current study is primarily a clinical observational study with limited mechanistic relevance to the scope of the Journal of Cellular and Molecular Anesthesia. Major methodological issues exist, particularly regarding confounding factors, the absence of multivariate analysis, and insufficient characterization of diabetic foot ulcers. The conclusions regarding vitamin D supplementation are not supported by the case-control design.
Major revision is required before further consideration.
Introduction:
The Introduction provides extensive clinical background but lacks sufficient emphasis on the cellular and molecular mechanisms relevant to the journal's scope. The authors should substantially shorten the epidemiological and clinical descriptions of diabetes and DFU and strengthen the mechanistic rationale by discussing vitamin D/VDR signaling, inflammatory pathways, oxidative stress regulation, and tissue repair mechanisms.
The knowledge gap and rationale for the present case-control study should also be more clearly defined.
Several statements regarding vitamin D supplementation imply causality and should be revised considering the observational study design.
Methods section:
The study employs a case-control design to investigate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and diabetic foot ulcer (DFU) among patients with type 2 diabetes mellitus (T2DM). The research question is clinically relevant; however, several methodological issues require clarification and improvement before the validity and interpretation of the findings can be fully assessed.
Major Concerns
1. Study Population and Sampling Method
The authors state that participants were selected using:
"Convenience sampling without probability."
Although the case-control design is appropriate for exploring associations between vitamin D status and DFU, convenience sampling may introduce significant selection bias and limit the generalizability of the findings. Since all participants were recruited from hospitalized patients at a single center, the control group may not adequately represent the broader population of patients with T2DM without DFU.
The authors should clarify:
• How patients were identified and recruited.
• Whether all eligible patients during the study period were included.
• Whether cases and controls were derived from the same source population.
The Discussion section should also acknowledge the potential impact of convenience sampling as a limitation.
2. Definition and Characterization of Diabetic Foot Ulcer
• The definition of DFU is acceptable: "a full-thickness defect below the ankle in patients with diabetes." However, the clinical characterization of DFU is insufficient.
• The authors mention that infection severity was assessed according to IDSA/IWGDF criteria. Still, they do not report ulcer duration, ulcer size or depth, Wagner grade or University of Texas classification, presence of osteomyelitis, peripheral arterial disease status, or the severity distribution of DFU cases. DFU represents a heterogeneous clinical condition, and patients with superficial ulcers cannot be directly compared with those having severe infected ulcers. The authors should provide additional information regarding ulcer

severity and clinical characteristics.

3. Incorrect Description of Eligibility Criteria

The manuscript states:

"Criteria for inclusion were an incomplete medical record, diabetes mellitus type I, NYHA classes III/IV of heart failure..."

This appears to be an error. The listed conditions represent exclusion criteria, not inclusion criteria. This section should be revised accordingly to avoid confusion.

4. Matching Procedure

The authors state:

"The two groups were matched as closely as possible for age and sex."

However, the matching methodology is unclear.

The authors should clarify:

- Whether individual matching was performed.
- The matching ratio between cases and controls.
- The criteria used for matching.

If formal matching was performed, the statistical analysis should account for this (e.g., conditional logistic regression). If age and sex were only statistically adjusted for, the term "matched" should be avoided.

5. Vitamin D Measurement Methodology

A major methodological concern is the lack of information regarding the measurement of serum 25(OH)D.

The manuscript should provide details regarding:

- The analytical method used (e.g., ELISA, chemiluminescent immunoassay, LC-MS/MS).
- The manufacturer and assay characteristics.
- Timing of blood sample collection.

Vitamin D levels are influenced by several factors, including:

- Seasonal variation
- Sun exposure
- Nutritional status
- Supplement use

Therefore, the methodology of vitamin D assessment should be clearly described.

6. Control of Potential Confounding Factors

Although the authors mention the use of multivariable logistic regression, the manuscript does not specify which variables were included in the model.

The association between vitamin D deficiency and DFU may be influenced by multiple confounders, including:

- Age
- Sex
- Body mass index (BMI)
- Duration of diabetes
- Glycemic control (HbA1c)
- Smoking status
- Hypertension
- Renal function
- Insulin therapy

The authors should report:

- Variables included in the regression model.
- Criteria for selecting covariates.

• Adjusted odds ratios (ORs) with 95% confidence intervals.

7. Absence of Glycemic Control Assessment

A major limitation is the lack of reporting of HbA1c levels. Glycemic control is one of the strongest determinants of diabetic foot complications and is also potentially associated with vitamin D status.

The authors should clarify whether HbA1c was measured and, if available, include it in the analysis. Failure to adjust for glycemic control may substantially affect the observed association between vitamin D levels and DFU.

8. Exclusion Criteria and Renal Function Findings

The authors excluded patients with:

"Severe renal and hepatic dysfunction."

However, the results indicate significantly higher creatinine and BUN levels among DFU patients.

The authors should clarify:

• How renal dysfunction was defined.

• Whether mild or moderate kidney impairment was allowed.

• Whether renal function was included as a covariate in regression analysis.

Because renal dysfunction can independently influence vitamin D metabolism, this issue requires careful consideration.

9. Statistical Analysis

The statistical methods are generally appropriate; however, several details require clarification.

The authors should specify:

Normality assessment:

Which statistical test was used to determine normality?

(e.g., Shapiro–Wilk test)

Multiple comparisons:

A large number of clinical and laboratory variables were compared. The authors should clarify whether any correction for multiple testing was applied.

Regression analysis:

The logistic regression model requires more detailed reporting, including:

• Dependent variable definition

• Independent variables included

• Model selection strategy

Minor Concerns

1. The study period is reported as 2024–2026. The authors should clarify whether data collection was completed before manuscript submission.

2. The manuscript should clarify whether laboratory measurements were performed at admission or during hospitalization.

3. The timing between DFU diagnosis and vitamin D measurement should be reported.

4. Medication history, particularly insulin therapy and vitamin D supplementation, should be clearly described.

Results section:

The Results section provides useful descriptive comparisons between patients with and without DFU; however, the interpretation of the association between vitamin D levels and DFU is limited by insufficient adjustment for important clinical confounders. The groups differ significantly in BMI, renal function, smoking status, and treatment regimen, all of which may influence vitamin D status and DFU risk. A detailed multivariable analysis including diabetes duration, HbA1c, renal function, smoking, and metabolic parameters is essential. Furthermore, DFU severity characteristics and diabetes-related complications should be reported to better understand the clinical relevance of the findings.

• Avoid repeating information already provided in Table 1. The text should summarize the most important findings rather than reproduce all values.
• The phrase "The mean age was 63.6 ± 3.5 years (range 56–70)" is unnecessary if Table 1 already provides this information.
• The terms "case group" and "control group" should be used consistently throughout the manuscript.
• The authors should report the number of missing values, if any.
• The manuscript states: BUN levels were significantly elevated in the case group compared to the control group: 23.81 mg/dL [range: 20–28] vs. 18.12 [range: 15–201]. The control group range appears to contain a typographical error: 15–201. This should be corrected.
• The authors stated: "no statistically significant difference was found in the distribution of comorbidities." However, the text describes differences in hypertension, ischemic heart disease, and chronic kidney disease.
The authors should provide:
o exact numbers
o percentages
o p-values
and avoid descriptive statements that are not supported by statistical testing.
Discussion section:
The Discussion provides a plausible biological rationale linking vitamin D status with diabetic foot ulcer; however, it requires substantial condensation and refinement. The authors should avoid causal interpretations given the observational design and should emphasize that the findings demonstrate association rather than proof of therapeutic benefit. The molecular discussion is relevant to the journal's scope but should be more focused on VDR signaling, inflammatory pathways, oxidative stress, immune modulation, and tissue repair mechanisms. The Conclusion should be tempered, and a clear limitations section should be added before clinical recommendations are made.
The Discussion provides a comprehensive interpretation of the association between vitamin D status and diabetic foot ulcer (DFU). However, it is too repetitive, overly lengthy, and occasionally overstates causal relationships beyond what can be supported by the case-control design. The discussion should be more concise and should better distinguish between association and causality.
The Discussion should be shortened by combining repetitive paragraphs and focusing on:
• Main findings,
• Comparison with previous studies,
• Possible mechanisms,
• Clinical implications and limitations.

Causal interpretation should be avoided. The authors should use more cautious language, such as:
• "was associated with"
• "may be involved in"
• "could represent a marker of disease severity"
rather than implying a causal effect.

The molecular mechanisms should be better integrated but not overstated.
The lower vitamin D levels observed in DFU patients may reflect:
• reduced mobility and sunlight exposure,
• poorer nutritional status,
• longer diabetes duration,
• renal dysfunction,
• systemic inflammation.

The Discussion should acknowledge that vitamin D deficiency may be a consequence or marker of advanced disease, rather than an independent cause.

Because vitamin D metabolism is strongly affected by kidney function, the higher creatinine and BUN levels in the DFU group are important. The authors should discuss whether reduced vitamin D levels may partly reflect renal impairment rather than DFU itself.

REVIEWER 2
Dear Associate Editor,
I have carefully reviewed the above-mentioned manuscript, a case-control study of 200 patients with type 2 diabetes mellitus (102 cases with diabetic foot ulcer [DFU] and 98 controls without DFU), investigating the association between serum 25-hydroxyvitamin D [25(OH)D] levels and DFU. The topic is clinically relevant and falls within the Journal's scope of cellular and molecular mechanisms underlying perioperative and wound-healing processes. Below is my section-by-section evaluation.

- Abstract:
• Structured abstract formatting (Background, Methods, Results, Conclusion) should conform to the Journal's Instructions for Authors.

- Introduction:
•Several sentences are overly long and should be divided for readability.
•The hypothesis and primary objective should be stated more explicitly at the end of the Introduction.

-Materials and Methods:
1. Inclusion/Exclusion criteria: The authors must define:
o Diagnostic criteria for DFU (e.g., Wagner/Meggitt or University of Texas grade, and which grades were included);
o Criteria for the control group (T2DM patients without DFU — how were they screened and confirmed?);
o Exclusion of conditions that independently alter 25(OH)D levels or wound healing (chronic kidney disease stage, parathyroid disorders, malabsorption, medications such as corticosteroids or anticonvulsants, pregnancy).
2. Sampling and matching: The authors state the groups were matched for age and sex, yet Table 1 shows significant between-group differences in BMI, systolic blood pressure, duration of diabetes, renal function, insulin use, and smoking.
3. The authors must clarify:
o Whether matching or frequency-matching was performed, and how controls were selected (medical records and hospital information system — with what safeguards against selection bias?);
o Exactly which covariates were entered into the multivariable model and whether BMI, diabetes duration, eGFR/creatinine, insulin use, and smoking were adjusted for. Without this, the reported association may be substantially confounded.
4. Vitamin D measurement: Specify the assay method.
5. Also define the vitamin D deficiency/insufficiency thresholds used (e.g., IOM vs. Endocrine Society cutoffs), since these differ and affect interpretation.
6. Data source and quality: Since data were collected retrospectively from medical records/HIS, describe missing-data handling and any quality-control measures.

-Results:
1. Table 1 (p. 19) — critical error: In the "Duration of diabetes" column, the figures appear to be duplicated from the BMI column. This is a data-integrity issue; please correct it and verify against the source data.
2. Table 1 formatting: Data should be consistently presented as mean ± SD or median (IQR) as appropriate to the distribution, with the statistical test used specified in the footnote (t-test vs. Mann–Whitney U; χ^2 vs.

Fisher's exact test).
3. Consider a dose-response or subgroup analysis (e.g., DFU risk by vitamin D category: deficient/insufficient/sufficient), which would strengthen the biological interpretation.

-Discussion
• Patients with DFU are more likely to be hospitalized, less mobile, and less physically exposed to sunlight, which could lower their 25(OH)D independently of a causal effect.
• This should be discussed and explained in more detail.

-Limitations
There is no dedicated "Limitations" section. The authors must add the study's limitations.

-References
• Verify all citations for accuracy of author names, journal abbreviations, and page numbers per the Journal's Vancouver-style requirements.

Editor-in-Chief MAJOR REVISION 14 Sep 2026

Dear authors
The manuscript has major items that should be addressed. Please revise and resubmit in a point-by-point manner.
We appreciate your contribution.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Review

#Reviewer 1:

Major Concerns

1. Study Population and Sampling Method
The authors state that participants were selected using:
"Convenience sampling without probability."
Although the case-control design is appropriate for exploring associations between vitamin D status and DFU, convenience sampling may introduce significant selection bias and limit the generalizability of the findings.
Since all participants were recruited from hospitalized patients at a single center, the control group may not adequately represent the broader population of patients with T2DM without DFU.
The authors should clarify:
• How patients were identified and recruited.
• Whether all eligible patients during the study period were included.
• Whether cases and controls were derived from the same source population.
The Discussion section should also acknowledge the potential impact of convenience sampling as a limitation.

Response: We sincerely thank the reviewer for this insightful methodological comment. We fully agree that control selection and sampling methodology are critical to the validity and generalizability of hospital-based case-control studies. In response, we have revised both the Materials and Methods and Discussion sections to clarify. (study population and limitation part). Moreover, we acknowledge the potential impact of convenience sampling as a limitation.

2. Definition and Characterization of Diabetic Foot Ulcer
• The definition of DFU is acceptable: "a full-thickness defect below the ankle in patients with diabetes." However, the clinical characterization of DFU is insufficient.
• The authors mention that infection severity was assessed according to IDSA/IWGDF criteria. Still, they do not report Ulcer duration, Ulcer size or depth, Wagner grade or University of Texas classification, Presence of osteomyelitis, Peripheral arterial disease status, or severity distribution of DFU cases. DFU represents a heterogeneous clinical condition, and patients with superficial ulcers cannot be directly compared with those having severe infected ulcers. The authors should provide additional information regarding ulcer severity and clinical characteristics.

Response: We sincerely thank the reviewer for this valuable comment. These information provided in Table 1.

3. Incorrect Description of Eligibility Criteria
The manuscript states:
"Criteria for inclusion were an incomplete medical record, diabetes mellitus type I, NYHA classes III/IV of heart failure..."
This appears to be an error. The listed conditions represent exclusion criteria, not inclusion criteria. This section should be revised accordingly to avoid confusion.

Response: Agreed, this was revised in the methodological part.

4. Matching Procedure
The authors state:
"The two groups were matched as closely as possible for age and sex."
However, the matching methodology is unclear.
The authors should clarify:
• Whether individual matching was performed.
• The matching ratio between cases and controls.
• The criteria used for matching.
If formal matching was performed, the statistical analysis should account for this (e.g., conditional logistic regression). If age and sex were only statistically adjusted, the term "matched" should be avoided.

Response: We thank the reviewer for this critical methodological observation. We clarify that individual (pair) matching was not performed, which explains the slight difference in sample sizes (102 cases and 98 controls; an approximate 1:1 overall ratio). Instead, frequency matching (group matching) was employed during the recruitment phase: controls with type 2 diabetes without foot ulceration were selected from the same clinical setting to balance the age (within 5-year intervals) and sex distribution of the case cohort.

5. Vitamin D Measurement Methodology
A major methodological concern is the lack of information regarding the measurement of serum 25(OH)D.

Response: Agreed, this was revised in the methodological part.

The manuscript should provide details regarding:
• The analytical method used (e.g., ELISA, chemiluminescent immunoassay, LC-MS/MS).
• The manufacturer and assay characteristics.
• Timing of blood sample collection.
Vitamin D levels are influenced by several factors, including:

• Seasonal variation
• Sun exposure
• Nutritional status
• Supplement use
Therefore, the methodology of vitamin D assessment should be clearly described.

Response: Thanks for your comment, since no information was available according to the listed variables, this was in the limitation part.

6. Control of Potential Confounding Factors
Although the authors mention the use of multivariable logistic regression, the manuscript does not specify which variables were included in the model.
The association between vitamin D deficiency and DFU may be influenced by multiple confounders, including:
• Age
• Sex
• Body mass index (BMI)
• Duration of diabetes
• Glycemic control (HbA1c)
• Smoking status
• Hypertension
• Renal function
• Insulin therapy
The authors should report:
• Variables included in the regression model.
• Criteria for selecting covariates.
• Adjusted odds ratios (ORs) with 95% confidence intervals.

Response: Agreed, this was revised in the methodological part

7. Absence of Glycemic Control Assessment
A major limitation is the lack of reporting of HbA1c levels. Glycemic control is one of the strongest determinants of diabetic foot complications and is also potentially associated with vitamin D status.
The authors should clarify whether HbA1c was measured and, if available, include it in the analysis. Failure to adjust for glycemic control may substantially affect the observed association between vitamin D levels and DFU.

Response: Thanks for your valuable comment. Information on glycemic measurements and treatments were missed, we add this in revised version. All methods, and results were updated.

8. Exclusion Criteria and Renal Function Findings
The authors excluded patients with:
"Severe renal and hepatic dysfunction."
However, the results indicate significantly higher creatinine and BUN levels among DFU patients.
The authors should clarify:
• How renal dysfunction was defined.
• Whether mild or moderate kidney impairment was allowed.
• Whether renal function was included as a covariate in regression analysis.
Because renal dysfunction can independently influence vitamin D metabolism, this issue requires careful consideration.

Response: Agreed, this was revised in the methodological part.

9. Statistical Analysis
The statistical methods are generally appropriate; however, several details require clarification.
The authors should specify:
Normality assessment:
Which statistical test was used to determine normality?
(e.g., Shapiro–Wilk test)
Multiple comparisons:
A large number of clinical and laboratory variables were compared. The authors should clarify whether any correction for multiple testing was applied.
Regression analysis:
The logistic regression model requires more detailed reporting, including:
• Dependent variable definition
• Independent variables included
• Model selection strategy

Response: Agreed, this was revised in the methodological part.

Minor Concerns

1. The study period is reported as 2024–2026. The authors should clarify whether data collection was completed before manuscript submission.

Response: Agreed, this was revised in the methodological part.

2. The manuscript should clarify whether laboratory measurements were performed at admission or during hospitalization.

Response: Agreed, this was revised in the methodological part.

3. The timing between DFU diagnosis and vitamin D measurement should be reported.

Response: Thanks for the comment, this information was not available. This was mentioned in the limitation part.

4. Medication history, particularly insulin therapy and vitamin D supplementation, should be clearly described.

Response: Agreed, this was revised in the methodological part.

Results section:
The Results section provides useful descriptive comparisons between patients with and without DFU; however, the interpretation of the association between vitamin D levels and DFU is limited by insufficient adjustment for important clinical confounders. The groups differ significantly in BMI, renal function, smoking status, and treatment regimen, all of which may influence vitamin D status and DFU risk. A detailed multivariable analysis including diabetes duration, HbA1c, renal function, smoking, and metabolic parameters is essential. Furthermore, DFU severity characteristics and diabetes-related complications should be reported to better understand the clinical relevance of the findings.
• Avoid repeating information already provided in Table 1. The text should summarize the most important findings rather than reproduce all values.

Response: Agreed, this was revised in the result part.

• The phrase: "The mean age was 63.6 ± 3.5 years (range 56–70)" is unnecessary if Table 1 already provides this information.

Response: Agreed, this was revised in the result part.

• The term "case group" and "control group" should be used consistently throughout the manuscript.

Response: Agreed, this was revised in the result part.

• The authors should report the number of missing data, if any.

Response: Thanks for valuable comment, those with complete information were included. This was mentioned in the method part.

• The manuscript states: BUN levels were significantly elevated in the case group compared to the control group: 23.81 mg/dL [range: 20–28] vs. 18.12 [range: 15–201]. The control group range appears to contain a typographical error: 15–201. This should be corrected.

Response: Agreed, this was revised in the result part.

• The authors stated: "no statistically significant difference was found in the distribution of comorbidities." However, the text describes differences in hypertension, ischemic heart disease, and chronic kidney disease. The authors should provide:
o exact numbers
o percentages
o p-values
and avoid descriptive statements that are not supported by statistical testing.

Response: Agreed, this was revised in the result part.

Discussion section:
The Discussion provides a plausible biological rationale linking vitamin D status with diabetic foot ulcer; however, it requires substantial condensation and refinement. The authors should avoid causal interpretations given the observational design and should emphasize that the findings demonstrate association rather than proof of therapeutic benefit. The molecular discussion is relevant to the journal's scope but should be more focused on VDR signaling, inflammatory pathways, oxidative stress, immune modulation, and tissue repair mechanisms. The Conclusion should be tempered, and a clear limitations section should be added before clinical recommendations are made
The Discussion provides a comprehensive interpretation of the association between vitamin D status and diabetic foot ulcer (DFU). However, it is too repetitive, overly lengthy, and occasionally overstates causal relationships beyond what can be supported by the case-control design. The discussion should be more concise and should better distinguish between association and causality.
The Discussion should be shortened by combining repetitive paragraphs and focusing on:
• Main findings,
• Comparison with previous studies,
• Possible mechanisms,

• Clinical implications and limitations.

Response: Agreed. Discussion section was remarkably modified.

Causal interpretation should be avoided. The authors should use more cautious language, such as:
• "was associated with"
• "may be involved in"
• "could represent a marker of disease severity"
rather than implying a causal effect.

Response: Agreed. Discussion section was remarkably modified.

The molecular mechanisms should be better integrated but not overstated
The lower vitamin D levels observed in DFU patients may reflect:
• reduced mobility and sunlight exposure,
• poorer nutritional status,
• longer diabetes duration,
• renal dysfunction,
• systemic inflammation.
The Discussion should acknowledge that vitamin D deficiency may be a consequence or marker of advanced disease, rather than an independent cause.

Response: Agreed. Discussion section was remarkably modified.

Because vitamin D metabolism is strongly affected by kidney function, the higher creatinine and BUN levels in the DFU group are important. The authors should discuss whether reduced vitamin D levels may partly reflect renal impairment rather than DFU itself.

Response: Agreed. Discussion section was remarkably modified.

#Reviewer 2

- Abstract:
• Structured abstract formatting (Background, Methods, Results, Conclusion) should conform to the Journal's Instructions for Authors.

Response: Thanks, this was checked.

- Introduction:
•Several sentences are overly long and should be divided for readability.

Response: Thanks. Long sentences were paraphrased.

•The hypothesis and primary objective should be stated more explicitly at the end of the Introduction.

Response: Thanks, this was included in the introduction part.

-**Materials and Methods :**
1. Inclusion/Exclusion criteria: The authors must define:
o Diagnostic criteria for DFU (e.g., Wagner/Meggitt or University of Texas grade, and which grades were included);
o Criteria for the control group (T2DM patients without DFU — how were they screened and confirmed?);
o Exclusion of conditions that independently alter 25(OH)D levels or wound healing (chronic kidney disease stage, parathyroid disorders, malabsorption, medications such as corticosteroids or anticonvulsants, pregnancy).

Response: Agreed, this was revised in the methodological part.

2. Sampling and matching: The authors state the groups were matched for age and sex, yet Table 1 shows significant between-group differences in BMI, systolic blood pressure, duration of diabetes, renal function, insulin use, and smoking.

Response: Agreed, this was revised in the methodological part.

3. The authors must clarify:
o Whether matching or frequency-matching was performed, and how controls were selected (medical records and hospital information system — with what safeguards against selection

bias?);
o Exactly which covariates were entered into the multivariable model and whether BMI, diabetes duration, eGFR/creatinine, insulin use, and smoking were adjusted for. Without this, the reported association may be substantially confounded.

Response: Agreed, this was revised in the methodological part.

4. Vitamin D measurement: Specify the assay method

Response: Agreed, this was revised in the methodological part.

5. . Also define the vitamin D deficiency/insufficiency thresholds used (e.g., IOM vs. Endocrine Society cutoffs), since these differ and affect interpretation.

Response: Agreed, this was revised in the methodological part.

6. Data source and quality: Since data were collected retrospectively from medical records/HIS, describe missing-data handling and any quality-control measures.

Response: Agreed, this was revised in the methodological part.

-Results:
1. Table 1 (p. 19) — critical error: In the “Duration of diabetes” column, the figures appear to be duplicated from the BMI column. This is a data-integrity issue; please correct it and verify against the source data.

Response: Agreed, this was revised in the results part.

2. Table 1 formatting: Data should be consistently presented as mean ± SD or median (IQR) as appropriate to the distribution, with the statistical test used specified in the footnote (t-test vs. Mann–Whitney U; χ^2 vs. Fisher’s exact test).

Response: Agreed, this was revised in the methodological part.

3. Consider a dose-response or subgroup analysis (e.g., DFU risk by vitamin D category: deficient/insufficient/sufficient), which would strengthen the biological interpretation.

Response: Agreed, this was revised in the results part.

-Discussion

• Patients with DFU are more likely to be hospitalized, less mobile, and less physically exposed to sunlight, which could lower their 25(OH)D independent of a causal effect. It should be discussed and explained more

Response: Agreed. Discussion section was remarkably modified.

-Limitations
There is no dedicated “Limitations” section. The authors must add their limitations

Response: Agreed. Limitations section was added.

-References

• Verify all citations for accuracy of author names, journal abbreviations, and page numbers per the Journal’s Vancouver-style requirements.

Response: Agreed. Modifications were made.

2 Revision 1

1 comment · 25 Oct 2026

Editor-in-Chief

ACCEPT 25 Oct 2026

Dear authors
Thank you for the revision. The revised version is now appropriate for publication.