To Editor,

Re: Response for manuscript 86099 "Advances in cardiovascular-related biomarkers to predict diabetic peripheral neuropathy"

June 23, 2023

Dear Editor,

Thanks for providing us with this great opportunity to submit a revised version of our manuscript. We appreciate the detailed and constructive comments provided by the reviewers. We have carefully revised the manuscript by incorporating all the suggestions by the review panel. **Revised portion are marked in green in the paper.** We hope you will consider this paper anew in light of the comments on the earlier version. If further modification is needed, please allow us the opportunity to respond.

Thank you in advance for your consideration.

Sincerely,

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Responses to the comments from Reviewer 1, 2.

Reply to Reviewer #1

Dear Reviewers,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

We appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. We hope the modification could express our idea more clearly.

Comment 1:

In the abstract section, the authors should add the main consolidate biomarkers to

predict diabetic peripheral neuropathy

Response 1:

Thanks for your great suggestion on improving the accessibility of our manuscript. We have added the main consolidate biomarkers to predict diabetic peripheral neuropathy.

In the page 2, line 49-51: In this review, we evaluate the association between major traditional and nontraditional cardiovascular-related biomarkers of DPN, such as cardiac troponin T (cTnT), B-type natriuretic peptide (BNP), C-reactive protein (CRP), myeloperoxidase (MPO), and homocysteine, and assess the evidence for early risk factor-based management strategies to reduce the incidence and slow the progression of DPN.

Comment 2:

In the page 3, line 66-68: please correct the phrase because it described results for the data 2021, but we are actually in 2023. "The International Diabetes Federation (IDF) estimates that approximately 536.6 million adults worldwide will have diabetes in 2021, and the number is predicted to increase to 783.2 million by 2045."

Response 2:

Thank you for the detailed review. I am sorry that the prevalence of diabetes in the review is for 2021 and not 2023, but we did not find updated data after reviewing the literature. We reviewed the literature and found recently published articles citing this same data. We are attaching two recently published articles that cite the prevalence of diabetes.

Int J Mol Sci. 2023 Apr; 24(8): 6978. PMCID: PMC10139109
Published online 2023 Apr 10. doi: 10.3390/ijms24086978 PMID: 37108143

The Pathogenesis of Diabetes

Huiqin Guo,[1,†] Haili Wu,[2,†] and Zhuoyu Li[1,*]

Antonio Lucacchini, Academic Editor

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Abstract Go to:

Diabetes is the most common metabolic disorder, with an extremely serious effect on health systems worldwide. It has become a severe, chronic, non-communicable disease after cardio-cerebrovascular diseases. Currently, 90% of diabetic patients suffer from type 2 diabetes. Hyperglycemia is the main hallmark of diabetes. The function of pancreatic cells gradually declines before the onset of clinical hyperglycemia. Understanding the molecular processes involved in the development of diabetes can provide clinical care with much-needed updates. This review provides the current global state of diabetes, the mechanisms involved in glucose homeostasis and diabetic insulin resistance, and the long-chain non-coding RNA (lncRNA) associated with diabetes.

Keywords: diabetes, signal pathway, insulin resistance, hyperglycemia, long-chain non-coding RNA (lncRNAs)

1. Status and Characteristics of Global Diabetes Go to:

According to the latest data released by the International Diabetes Federation (IDF) [1], the global prevalence of diabetes reached 10.5% in 2021. Of these cases, 537 million adults live with diabetes, which is an increase of 16% (74 million) from 2019. However, nearly half (44.7%) of adults have not yet been diagnosed. The IDF predicts that by 2045, 784 million adults will have diabetes, which is more than double the estimated population (20%) over the same period [1,2]. Diabetes is a chronic disease

frontiers in Endocrinology

Front Endocrinol (Lausanne). 2023; 14: 1118848. PMCID: PMC10033948
Published online 2023 Mar 9. doi: 10.3389/fendo.2023.1118848 PMID: 36967777

Pharmacological approaches to the prevention of type 2 diabetes mellitus

Priyanka Majety,[1] Faustina Alejandra Lozada Orquera,[1] Dinesh Edem,[2] and Osama Hamdy[1,3,*]

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Abstract Go to:

About 1 in 10 adults worldwide are estimated to have diabetes mellitus. They are at risk of developing life-threatening complications resulting in reduced quality of life, increased mortality and higher healthcare costs. The ability to prevent or delay type 2 diabetes mellitus (T2DM) by modifying some of its risk factors has been hypothesized for decades. The long and often gradual time-course of increasing dysglycemia prior to diabetes diagnosis suggests that interventions during that period could be effective in preventing T2DM. In addition to lifestyle modifications, certain drugs prevent or slow development of hyperglycemia. Recently, drugs used for obesity management were shown to prevent T2DM. In this review, we discuss various pharmacotherapeutic options for preventing T2DM.

Keywords: type 2 diabetes mellitus, prevention, metformin, prediabetes, remission, pharmacotherapy

Introduction Go to:

The epidemic of diabetes mellitus and its complications pose major global health threat. The global prevalence of diabetes and impaired glucose tolerance (IGT) quadrupled in the past three decades. This pace of change in diabetes prevalence in many countries has been heightened by rapid urbanization (1, 2). The global prevalence of diabetes was estimated to be 463 million (9.3% of adults 20–79 years of age) and this estimate is projected to rise to 700 million by 2045 (3). Over 90% of diabetes mellitus

Comment 3:

Table 1 needs a figure legend with acronym definitions

Response 3:

Thanks for your great suggestion on improving the accessibility of our manuscript. We have added the figure legend with acronym definitions.

In the page 22, line 594-601:

Biomarker candidate	Sample source	Quantitative method	Role in human body	Change	Literature
hs-cTnT	Human serum /Plasma	ECLI	A marker of myocardial injury	↑	[27-28]
BNP/NT-proBNP	Human serum /Plasma	CLIA	Exclude the diagnosis of left ventricular heart failure	↑	[29-32,35]
hs-CRP	Huma	ELISA/LEIT	A nonspecific	↑	[39-42]

	n serum	A	inflammatory marker that can predict the early myocardial damage		
MPO	Human serum	ELISA	An inflammatory factor in coronary artery disease	↑	[47]
Hcy	Human plasma	FPIA/CLIA	Induction of vascular oxidative stress and endothelial cell damage	↑	[51-53]

hs-cTnT: high-sensitivity cardiac troponin; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal B-type natriuretic peptide; hs-CRP: high-sensitivity C-reactive protein; MPO: myeloperoxidase; Hcy: Homocysteine; ECLI: electrochemiluminescence immunoassays; CLIA: chemiluminescence analysis; ELISA: enzyme-linked immunosorbent assay; LEITA: latex-enhanced immunonephelometric assay; HPLC: high-performance liquid chromatography; FPIA: fluorescence polarization immunoassay; ↑: increased

Comment 4:

In the markers of myocardial injury section, I recommended the next reference (PMID: 32621046) related with myocardial damage-associated obesity, which express increased troponin I levels.

Response 4:

Thanks for your great suggestion on improving the accessibility of our manuscript. We have added the reference (PMID: 32621046) related with myocardial damage-associated obesity. The relevant contents are provided below as a screen dump for your quick reference.

In the page 6, line 152-153: It has been shown that increased troponin I levels can occur in obese mice with myocardial injury[1].

Comment 5:

The following phrase needs a reference at the end (page 5, line 132-134: "Troponin is a marker of myocardial injury, and its abnormal values indicate structural damage to the myocardium." Please also add if troponin is expressed with high or low levels in myocardial injury, because abnormal values are confusing.

Response 5:

I am sorry that this part was not clear in the original manuscript. I should have explained that troponin is expressed with high levels in myocardial injury. I have revised the contents of this part and add the reference at the end. In the page 6, line 151-152: Troponin is a marker of myocardial injury. In general, patients with myocardial injury may have elevated troponin levels in their bodies[2].

Comment 6:

In page 5, line 135-138: Simultaneously, microvascular circulation disorders may partly affect the blood supply to the myocardium, leading to myocardial damage, thereby affecting the content of troponin in the body. Please add the appropriate reference.

Response 6:

I have revised the contents of this part and add the reference at the end.

In the page 6, line 155-158: Simultaneously, microvascular circulation disorders may partly affect the blood supply to the myocardium, leading to myocardial damage, and changes in coronary microcirculation can lead to coronary microvascular disfunction, affecting the levels of troponin in the body[3].

Comment 7:

In page 6, line 170-172: "Natriuretic peptides bind to receptors located in adipose tissue to induce lipolysis in adipocytes and regulate fat distribution while regulating oxygen and glucose uptake in adipocytes21,22". The authors should be clearer if natriuretic peptides increase or decrease oxygen and glucose uptake in adipocytes.

Response 7:

I am sorry that this part was not clear in the original manuscript. I should have explained that natriuretic peptides increase oxygen and glucose uptake in adipocytes.

In the page 7, line 190-193: Natriuretic peptides bind to receptors located in adipose tissue to induce lipolysis in adipocytes, regulate fat distribution, and promote the absorption of more oxygen and glucose by adipose tissue[4,5].

Comment 8:

Please add the necessary reference to the end of the following three phrases: page 7, line 186-188, "High-sensitivity C-reactive protein (hs-CRP) predicts the …… patients with acute coronary syndromes."

Page 8, line 211-212, "It is also an inflammatory factor in coronary artery disease."

Page 8, line 212-214, "It can promote the formation of lesions in acute coronary syndrome and affect the stability of atherosclerotic plaques."

Page 8, line 214-215, "Additionally, it can be used to predict the risk of recent myocardial infarction in patients with coronary heart disease."

Page 8, line 220-221, "thus aggravating oxidative stress and inflammation."

Response 8:

I am sorry that these parts were not cited relevant literature in the original manuscript. I have revised the contents of these parts and add the reference at the end.

In the page 8, line 206-209: High-sensitivity C-reactive protein (hs-CRP) predicts the risk of cardiac events in asymptomatic populations and can assess the outcome of patients with acute coronary syndromes[6,7].

In the page 9, line 231-234: It is also an inflammatory factor in coronary artery disease, and a study showed that elevated plasma MPO levels are associated with inflammatory status in patients who suffer from acute heart attacks[8].

In the page 9, line 234-235: MPO can promote the formation of lesions in acute coronary syndrome and affect the stability of atherosclerotic plaques[9].

In the page 9, line 235-237: Additionally, it can be used to predict the risk of recent myocardial infarction in patients with coronary heart disease[10].

In the page 9, line 240-243: Long-term hyperglycaemia can lead to increased nonenzymatic glycosylation end products and produce a large number of oxygen free radicals, thus aggravating oxidative stress and inflammation[11].

Comment 9:

In the next phrase (page 8-9, line 240-242: "The potential mechanism was associated with increased homocysteine-induced oxidative stress and vascular endothelial growth factor (VEGF) 31." The reference 31 does not have information on vascular endothelial growth factor (VEGF). Please add the appropriate reference.

Response 9:

I am sorry that this part was not cited relevant literature, I have revised the contents of these parts and add the reference at the end.

In the page 10, line 262-265: The potential mechanism involved increased homocysteine-induced oxidative stress and vascular endothelial growth factor (VEGF) [12,13]. Hcy can inhibit VEGF-induced vascular endothelial cell proliferation and migration.

Comment 10:

Please write Gonzalez R. et al. instead of Ricardo et al.34.

Response 10:

Thank you for the detailed review. We have carefully and thoroughly proofread the manuscript to correct all the grammar and formatting errors. We have corrected "Ricardo et al." to "Gonzalez R.et al." in the revised manuscript accordingly.

Comment 11:

In the conclusions section, the authors should add the main consolidate biomarkers to diagnostic diabetic peripheral neuropathy.

Response 11:

Thanks for your great suggestion on improving the accessibility of our manuscript. We have added the main consolidate biomarkers to diagnostic diabetic peripheral neuropathy in the conclusions section.

In the page 11, line 283-284: In this review, biomarkers of cardiovascular-related DPN have been summarized, including cTnT、BNP、CRP、MPO、Hcy.

Comment 12:

I suggest a figure related to the biomarkers considered in this manuscript that indicate their effects on biological processes and diabetic peripheral neuropathy.

Response 12:

Thanks for your suggestion of our manuscript. In order to make the narrative more visual, we have added a figure at the end.

In the page 23, line 619-631:

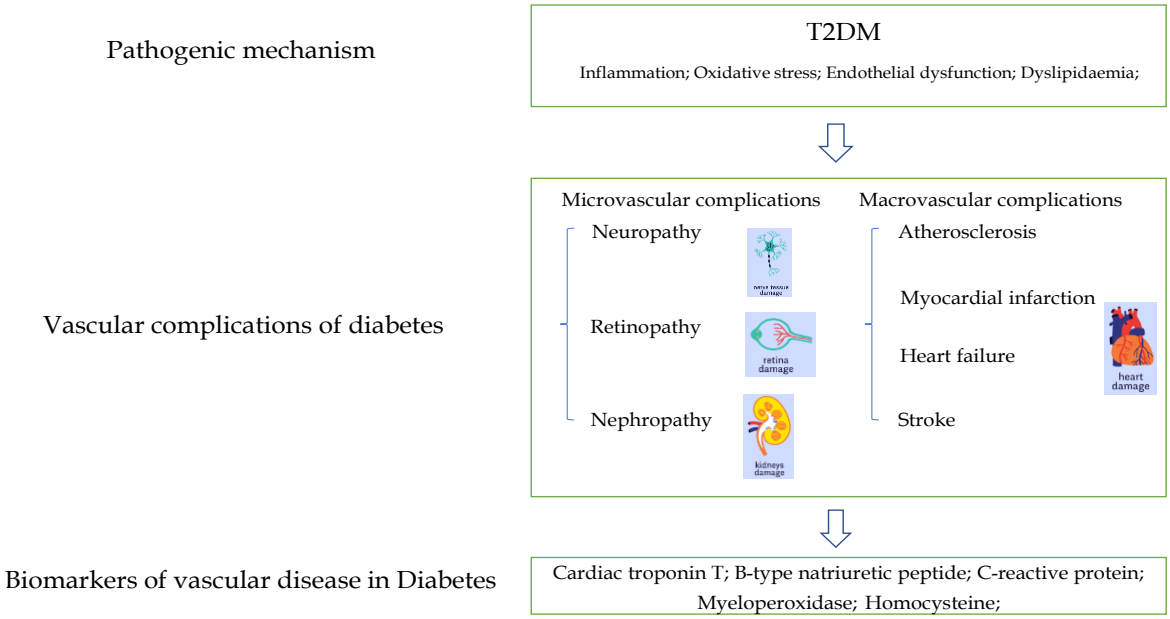

Figure 1. A brief introduction to vascular-related complications of diabetes and their common diagnostic markers. Common pathogenic mechanisms for macrovascular and microvascular complications include inflammation, oxidative stress, abnormal lipid metabolism and endothelial dysfunction. Cardiac troponin T is a marker of impaired microvascular circulation, which can affect myocardial blood supply and vascular endothelial cell function, resulting in the release of large amounts of troponin in the blood. B-type natriuretic peptide regulates blood pressure, blood volume, sodium balance, and glucose and fat metabolism. C-reactive protein is a marker of early myocardial injury and nonspecific inflammation. Myeloperoxidase is involved in the regulation of inflammatory response and oxidative stress in vivo and can induce acute coronary syndrome. Homocysteine is a marker of impaired neurons and vascular endothelial cells that induces oxidative stress and excessive proliferation of vascular endothelial cells.

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We hope you will find this revised version satisfactory.

Reply to Reviewer #2

Dear Reviewers,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

Comments:

"In this paper, the authors review the association between major traditional and nontraditional cardiovascular-related biomarkers and diabetic peripheral neuropathy (DPN) and assess the evidence for early risk factor-based."

We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. We hope the modification could express our idea more clearly.

Comment 1:

Line 64, Page 3, In the introduction section, the authors need to explain the urgency of clinical study for investigated disease.

Response 1:

Thanks for your great suggestion on improving the accessibility of our manuscript. In order to emphasize the urgency of clinical study for investigated disease, we add the latest data on the prevalence of diabetic peripheral neuropathy, which is more than one in four. The annual cost of treating diabetic peripheral neuropathy between $4.6 and $13.7 billion. As well as the damage to a woman's immune system from DPN, which can also affect the neurological development of the baby during pregnancy, leading to congenital autism. Therefore, there is an urgent need to find an easy and sensitive way to diagnose DPN.

In the page 3, line 74-77: A survey of patients with type 2 diabetes in 14 countries showed that the overall prevalence of DPN was 26.71%, indicating that more than a

quarter of patients with type 2 diabetes in these 14 countries had diabetic peripheral neuropathy as a complication[14].

In the page 4, line 87-94: According to statistics, the annual cost of treating diabetic peripheral neuropathy and its complications in the United States is estimated to be between 4.6 and 13.7 billion US dollars, and DPN treatment accounts for 27% of total diabetes treatment expenditures each year[15]. DPN can suppress the immune function of the body[16], and this damage can also affect the neurological development of the next generation during pregnancy and induce congenital autism[17]. Therefore, it is essential to develop convenient diagnostic methods with high sensitivity.

Comment 2:

Line 68, page 3, other relevant statistic data in encouraged to support the statement.

Response 2:

we add the latest data on the prevalence of diabetic peripheral neuropathy.

In the page 3, line 74-77: A survey of patients with type 2 diabetes in 14 countries showed that the overall prevalence of DPN was 26.71%, indicating that more than a quarter of patients with type 2 diabetes in these 14 countries had diabetic peripheral neuropathy as a complication[14].

Comment 3:

Line 122, page 4, please reprhase the literature objective to become more easily understood.

Response 3:

In response to the difficulty of diagnosing diabetic peripheral neuropathy, it is important to find diagnostic markers to improve the efficiency of diagnosis. In this review, we list the cardiovascular-related markers that can be used to screen for DPN.

In the page 5, line 133-134: Finding the delicate and precise biomarkers has been a top priority in order to reduce the negative effects and financial burden of DPN.

In the page 6, line 144-145: We hope to provide a new direction for the clinical diagnosis of DPN to protect against this common and cruel disease.

Comment 4:

It is unclear whether the author's something new in this work. According to the evaluation, several published literature by other researchers in the past adequately explain the issues you made in the present paper. Please be careful to highlight in the introduction section anything really innovative in this work.

Response 4:

In recent years, there have been many studies on biomarkers of diabetic peripheral neuropathy, but there is a lack of biomarkers exploring cardiovascular-related diabetic peripheral neuropathy. This is the first summary of cardiovascular-related markers that can be used to diagnose diabetic peripheral neuropathy.

In the page 6, line 141-144: Therefore, this is the first summary of cardiovascular-related markers that can be used to diagnose diabetic peripheral neuropathy, such as cardiac troponin C and B-type natriuretic peptide (BNP)[18] (错误!未找到引用源。), and the underlying pathological mechanisms (Figure 1) are briefly described in the review. Meanwhile, we will assess the evidence for early risk factor-based management strategies to reduce the incidence and slow the progression of DPN.

Comment 5:

To underline the submitted article gaps that the newest works tries to fill, it is crucial to explain the merits, novelty, and limits of earlier studies in the introduction.

Response 5:

We highly appreciated your important suggestions. We add the merits, novelty, and limits of earlier studies in the introduction.

In the page 5, line134-140: Other excellent reviews have summarized markers of diabetic peripheral neuropathy. There are numerous biomarkers that can be utilized to diagnose DPN, such as inflammatory markers[19], nerve tissue damage factors[20], and oxidative stress markers[21]. Some researchers have used machine learning techniques combined with novel biomarkers to diagnose DPN, which can effectively improve the efficiency of physicians[22]. However, there is still no single marker that

can be widely used for clinical diagnosis.

Comment 6:

The authors urged readers to discuss future research that might use in silico or computer simulation. When opposed to clinical/in or ex testing, which was used in the current study, it offers various advantages, including reduced cost and quicker findings.

Response 6:

Thanks for your great suggestion on improving the accessibility of our manuscript. We add the discussion of using computer simulation in the conclusion.

In the page 11, line291-293: Computer simulation technology is widely used in medical research[23], not only to improve the efficiency of researchers but also to reduce costs.

Comment 7:

In keeping with earlier remarks, in silico/computational simulation would serve as a preliminary investigation before conducting an in vivo investigation or as evidence for an in vivo investigation's findings.

Response 7:

Thanks for your suggestion. Performing computer simulations as a preliminary investigation before conducting in vivo experiments can be effective in improving efficiency and reducing error rates. We have added the relevant literature at the end.

In the page 11, line293-296: In recent years, many researchers have conducted preliminary studies using computer simulation techniques before conducting in vivo investigation[24]. Future studies will use machine learning technology to screen biomarkers in combination with artificial intelligence[25].

Reference

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10.1186/s12872-022-02953-7]

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10.3390/biom13010039]

Revision reviewer

Comments: i am recommending the manuscript for publication.

Thanks for your comments.