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Corrigendum: Look in or book in: The case for type 2 diabetes remission to prevent diabetic retinopathy

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In the published article (in the journal previously known as *Journal of Insulin Resistance*), Cripps J, Cucuzzella M. Look in or book in: The case for type 2 diabetes remission to prevent diabetic retinopathy. J Insul Resist. 2023;6(1):a79. https://doi.org/10.4102/jir.v6i1.79, on page 4 the following paragraphs are updated in the *Journal of Metabolic Health*, as it was incorrectly formulated:

The original incorrect wording:
Reducing overall carbohydrate intake for individuals with diabetes has demonstrated for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences.

The revised and updated wording:
Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences.

The original paragraph:
The trail was stopped early due to adverse outcomes, thus giving caution to this approach.

The revised and updated paragraph:
The trial was stopped early due to adverse outcomes, thus giving caution to this approach.

The authors apologise for this error. The correction does not change the study's findings of significance or overall interpretation of the study's results or the scientific conclusions of the article in any way.

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Background: Diabetic retinopathy (DR) remains the leading cause of legal blindness in 18- to 74-year-old Americans and in most developed nations. Screening for DR has increased minimally over four decades.

Aim: Primary care physicians are critical to improve both visual and systemic outcomes in patients with diabetes. Diabetic retinopathy screening affords clinicians the opportunity to discuss type 2 diabetes (T2D) remission with patients. Primary care is well positioned to manage, and lower risks, of the systemic-associated diseases predicted by DR. The goal of this review was to assess the current literature on DR, new technology to enhance primary care-based screening, and the science and practical application of diabetes remission. A two-pronged strategy, bringing attention to ophthalmologists the potential of diabetes remission, and family physicians, the importance of retinopathy screening, may reduce the prevalence of blindness in patients with diabetes.

Methods: Embase, PubMed, Google Scholar, AMED, and MEDLINE databases were searched using keywords 'diabetic retinopathy; diabetic retinopathy screening, diabetes remission, diabetes reversal, and AI and diabetic retinopathy'.

Results: Robust literature now exists on diabetes remission and international consensus panels are aligning on the strategies and the definition.

Conclusion: Diabetic retinopathy remains the leading cause of legal blindness. Novel primary care friendly imaging would benefit nearly half of Americans from earlier detection and treatment of DR still not receiving such care. The most powerful way a primary care clinician could impact DR would be assisting in making the T2D go into remission. Prevention or slowing of progression of DR would greatly improve both visual and systemic outcomes patients with diabetes.

Contribution: This article highlights the importance of addressing DR and metabolic health to reduce not only the eye effects of T2D but the multisystem complications.

Keywords: diabetic retinopathy; diabetic retinopathy screening; diabetes remission; diabetes reversal; AI and diabetic retinopathy.

Introduction

If one were to think about the most meaningful way a primary care clinician could impact diabetic retinopathy (DR), it would be assisting in making type 2 diabetes (T2D) go into remission. Diabetic retinopathy remains the leading cause of legal blindness in 18–74-year-old Americans and most developed nations.[1,2] Despite the fact that over 90% of blindness can be prevented with existing treatments,[3] screening for DR increased minimally over four decades and 40% – 45% of Americans who would benefit from earlier detection and treatment of retinopathy are still not receiving such care.[4] Screening, as per American Academy of Ophthalmology (AAO) 2019 guidelines, ranges from 34% to 65%, and vision-threatening diabetic retinopathy (VTDR) can be asymptomatic.[1,2,5] Diabetic retinopathy at the time of diagnosis in the United States (US) is estimated at 30%, including 3% VTDR, while in a large United Kingdom (UK) trial, rates of 35% – 39% were recorded.[6,7] Therefore, urgent measures are indicated to reduce the burden of disease and diminished quality of life (QOL) accompanying visual impairment and blindness.[1,2,8,9,10] Primary care physicians are an extremely valuable resource to improve both visual and systemic outcomes in patients with diabetes. Diabetic retinopathy screening affords primary care clinicians the opportunity to discuss the possibility of T2D remission with patients.

In theory, access to artificial intelligence (AI) screening platforms in all primary care settings may be ideal. Novel primary care friendly imaging, when combined with information technology (IT)-based solutions and AI, can improve patient outcomes,[11,12] and reduce demands on physician's time.[1,2,11,12,13,14,15] The first US Food and Drug Administration (FDA) approved fully automated AI device in medicine was in 2018 for DR detection in primary care offices.[16] Lastly, diagnosis of DR also signals novel associations with cognitive impairment, structural brain abnormalities and cardiovascular (CV) risk factors.[17,18] Challenges to widespread AI implementation include financial barriers and the existence of pre-existing dedicated screening services reporting findings to primary care physicians in some settings. If primary care physicians are to perform non-AI assisted screening, then appropriate training in grading of retinal images would be required. Therefore, the low rates of screening are a testimony to the number of challenges.

Methods

The authors conducted a literature search using Embase, PubMed, Google Scholar, AMED and MEDLINE limited to human studies between 1990 and 2022 published in English. Relevant articles using keywords such as 'diabetic retinopathy', 'diabetic retinopathy screening', 'diabetes remission', 'diabetes reversal' and 'AI and diabetic retinopathy' were reviewed by each author separately followed by agreement by both authors on studies relevant to both primary care and ophthalmology practice. All types of articles were included in the study such as randomised controlled trials (RCTs), pilot studies, systematic reviews and literature reviews. The limitation of the method used was that quality analysis and risk of bias assessment were not carried out.

Results and discussion

Diabetic retinopathy

Diabetic retinopathy, the number one cause of blindness in working age Americans, requires early identification and treatment in high-risk eyes. Because T2D accounts for 90% – 95% of new cases of diabetes, the international diabetes federation predicts DR to increase significantly as one in nine adults may develop T2D by 2045.[19] Markers of poor cardiometabolic health, a risk factor for diabetes, CV disease, obesity and chronic diseases, was evident in 93.1% of the US adult population between 1999 and 2018.[20] Assisting T2D patients towards remission would be a powerful intervention.

Diabetic patients at greatest risk for development or progression of DR include type 1 diabetes (T1D) after 5 years, large hormonal swings such as puberty and pregnancy, uncontrolled hypertension, elevated haemoglobin A1c [HgA1c] levels, dyslipidaemia and large variations in blood glucose.[1,2,17] Primary care physicians are well positioned to manage, and lower risks, of the systemic associated diseases predicted by DR including neuropathy, nephropathy, CV disease, stroke and peripheral arterial disease.[18] Risk factors, duration of disease and diabetes type, T1D versus T2D, form the basis of screening recommendations as per the AAO outlined in Table 1.

Given the growing epidemic of T2D, increasing prevalence of DR is anticipated. Therefore, greater screening at the time of diagnosis may identify DR at earlier stages. The pathophysiology of DR suggests that both neural networks and microvasculature are under assault for years prior to identification of haemorrhages, exudates, new blood vessel growth or ischemic changes.[1] Specialised testing of the retinal cells, including electrophysiological testing, psychophysical tests, dark adaptation, contrast sensitivity, and visual fields reveals abnormalities years in advance of visible microangiopathy changes clearly associated with DR.[1] Early neurodegeneration in DR may contribute to microangiopathy[21]; therefore, the American Diabetes Association (ADA) statement of 2017 was modified to include this understanding: 'Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes'.[22] Hyperglycaemia has numerous pleiotropic effects leading to advanced glycation end products, glycocalyx damage, local activation of the renin-angiotensin system, protein kinase C, hexokinase and polyol pathways all adding to increased free radicals and oxidative stress.[23,24,25,26,27,28] Damage to neural retinal, supportive cells and endothelial microvasculature results in a breakdown of the blood-retinal barrier, a proinflammatory milieu, production of vascular endothelial growth factor (VEGF) and retinal dysfunction with apoptosis, haemorrhage, macular edema and retinal detachment.[29,30]

If screening determines retinopathy is present, a basic understanding of DR is helpful to guide patients in need of a referral. Although AI systems in primary care offices accurately determine the need for ophthalmological referral, discussion with the patient affords another opportunity to approach the topic of diabetes remission.[16] Stages of DR are outlined in Table 2, while DR pathophysiology with classical fundus changes is illustrated in Figure 1.

TABLE 1: Recommended eye examinations for patients with diabetes and no diabetic retinopathy.

Diabetes type	Recommended initial evaluation	Recommended follow-up†
Type 1‡	5 Years after the diagnosis	Yearly
Type 2‡	At the time of diagnosis	Yearly
Pregnancy§ (type 1 or type 2)	Soon after conception and early in the first trimester	No retinopathy or mild to moderate NPDR: every 3–12 months Severe NPDR or worse: every 1–3 months

Source: Adapted from Table 2, page 83; Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern®. Ophthalmology. 2020;127(1):P66–P145. https://doi.org/10.1016/j.ophtha.2019.09.025.

NPDR, non-proliferative diabetic retinopathy.

†, Higher risk signs may require more frequent monitoring; ‡, Pubertal patients require increased vigilance due to increased risk of progression; §, Gestational diabetics do not require ophthalmological assessment as they do not appear to be at increased risk of retinopathy.

TABLE 2: Diabetic retinopathy severity scale: United States definition and treatment.

Disease severity level	Findings observable upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (CI-DME identified; usually, intravitreal anti-VEGF given)	Microaneurysms only
Moderate NPDR (CI-DME identified: usually intravitreal anti-VEGF given)	More than a few microaneurysms but less than severe NPDR
Severe NPDR (CI-DME identified: usually intravitreal anti-VEGF given)	Any of the following (4-2-1 rule) ant) no signs of proliferative retinopathy: • Severe intraretinal haemorrhages and microaneurysms in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants
PDR Non-high-risk PDR (CI-DME identified; usually intravitreal anti-VEGF given) High-risk PDR PRP (panretinal photocoagulation [scatter] laser) recommended (CI-DME identified; usually intravitreal anti-VEGF given)	One or both of the following: • Neovascularization • Vitreous preretinal haemorrhage

Source: Adapted from Table 1, page 81; Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern®. Ophthalmology. 2020;127(1):P66–P145. https://doi.org/10.1016/j.ophtha.2019.09.025.

Note: Additional treatment may be given in specific situations as determined by the ophthalmologist, including focal or grid laser.

CI-CME, center-involved diabetic macular edema; PDR, proliferative diabetic retinopathy; PRP, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

The case for type 2 diabetes remission to prevent diabetic retinopathy

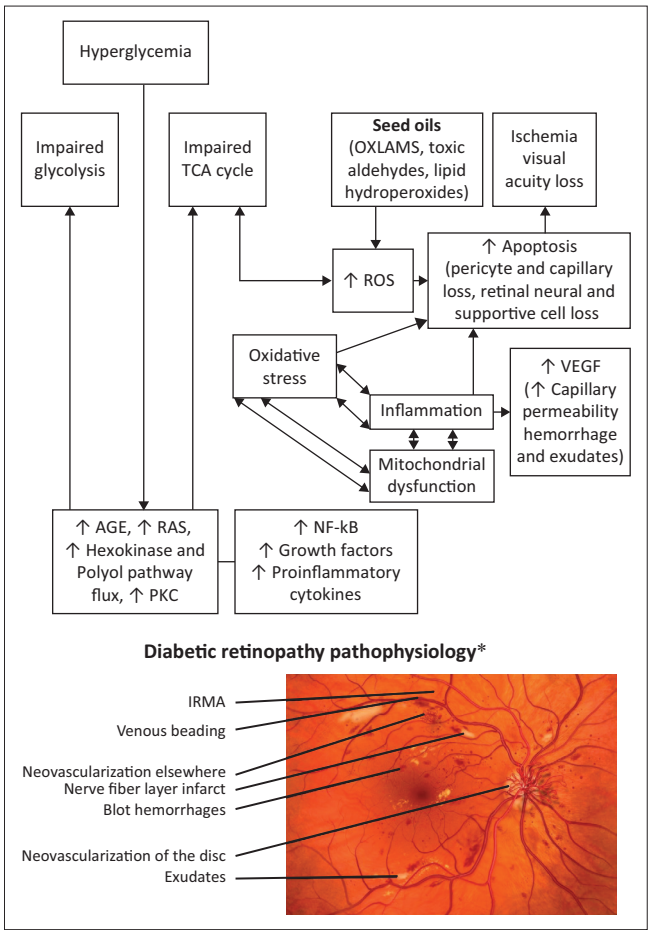
Because T2D has long been viewed as a chronic progressive disease, slowing or preventing DR through the mechanism of T2D remission was not considered until recently. Lifestyle-driven therapies to reduce the insulin resistance and hyperinsulinemia are now having global impact on how one can reframe T2D from a chronic progressive illness to one which can be placed into remission.

Type 2 diabetes remission fact or fiction?

Type 2 diabetes remission is happening with frequency and, out of necessity to define T2D remission, three major societies recently published accurately and consistently on the topic. Diabetes Australia Position Paper T2 Diabetes Remission,[31] the ADA Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes,[32] and Diabetes UK Position Statement for Healthcare Professionals – Remission in Adults With Type 2 Diabetes[33] all have aligned to define 'remission' as the most appropriate descriptive term. Haemoglobin A1c (HbA1c) < 6.5% (48 mmol mol^{-1}) measured at least 3 months after cessation of glucose-lowering pharmacotherapy is defined as 'remission'.[31,32,33]

The three primary approaches to achieve this are bariatric surgery, very low calorie diets and significant carbohydrate reduction without intentional calorie restriction.[31,32,33] Active management of medications is essential with all approaches. The authors feel option three is the most sustainable and safest. The primary care physician is positioned to assist and direct this approach.

Detailed articles and reviews on the current landscape of T2D remission have been published by Hallberg et al.,[34]



Source: Retinopathy illustration courtesy of Mark A. Erickson, Proliferative diabetic retinopathy illustration | co3261 (https://eyeillustrations.com/eye-illustrations/eye-disease/retina-diseases/)

AGE, advanced glycation end-products; NF-kB, nuclear factor kappa B; OXLAMs, oxidised linoleic acid metabolites; RAS, local ocular renin-angiotensin system; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; VEGF, vascular endothelial growth factor; IRMA, intraretinal microvascular abnormality; PKC, Protein Kinase C.

FIGURE 1: Inflammation, oxidative stress and mitochondrial dysfunction contribute to diabetic retinopathy. Loss of retinal neural networks, supporting cells and capillaries, ischemic retinopathy and new vessel growth (neovascularisation) leads to macular edema, haemorrhage, exudate, retinal detachment and visual acuity loss.

Brown et al.[35] and Shabib et al.[36] A review of medication reduction with diet and lifestyle change was recently published by Cucuzzella, Riley, Isaacs and International Working Group on Remission of Type 2 Diabetes.[37] The clinical features best predicting remission in the three reviews[34,35,36] were younger age, early-stage disease, lower number of diabetes medications and greater sustained weight loss. Substantial weight loss of 15% is associated with reduced liver and pancreatic fat and with restoration β-cell insulin function.[38] A challenge to sustaining remission is the maintenance of weight loss and lifestyle change. Therefore, we make the case for reducing and eliminating insulin and sulfonylureas, which both promote weight gain.

Published literature in support of diabetes remission

The data on bariatric surgery and T2D remission is heterogeneous depending on the type of procedure and the patient population. An international consensus statement

endorsed by 45 international diabetes associations including the ADA cited numerous RCTs with postoperative follow-up ranging between 1 and 5 years have consistently documented diabetes remission in 30% – 63% of patients.[39]

The UK DiRECT study used a low-calorie meal replacement (about 825 kcal/day) for 3–5 months followed by a stepped food reintroduction with supportive follow by primary care. The remission rates were 46% after a year and 36% after 2 years.[40] Remission in the control group was 4% and 3%, respectively. An informative subset was 1 year remission rate of 86% in participants who lost 15 kg or more.[41]

The primary care-based DIADEM-1 study from Qatar which replicated the DiRECT approach with an intensive lifestyle therapy in people with T2D achieved 61% diabetes remission after a year compared with 12% for the control.[42] The study was a cohort of Middle Eastern and North African origin mostly male and younger than the DiRECT participants.

There is a growing body of published literature discussing the clinical application of a low carbohydrate diet (LCD) for T2D. An RCT comparing a low carb Mediterranean diet to a low fat diet reported a remission rate of 15% after a year and 4% at 6 years follow-up compared to 1% and 0% at year one and year six in the low-fat diet group.[43]

Virta Health (https://www.virtahealth.com/) implements a digitally monitored continuous care intervention (CCI) aiming for nutritional ketosis through an LCD and active management of medication reduction. The non-randomised study of 349 patients with T2D were enrolled, with 262 self-selecting the ketogenic diet, reported T2D remission rates of 25% at year one and 18% at year two.[44,45] Virta Health protocol is to recommend continuing metformin for those patients who can tolerate it, even when remission criteria are otherwise achieved. When including the participants taking no diabetes medication or only Metformin, 60.3% (123/204) of participants achieved HbA1c below 48 mmol mol^{-1} (< 6.5%) at 1 year with 54% of completers maintaining HbA1c below 6.5% at 2 years. Adherence to the protocol was good. One hundred ninety-four participants (74% of 262) remained enrolled in the CCI at 2 years as did 68 in the usual care group (78% of 87).

David Unwin published data from an audit of over 6 years in his primary care cohort in the United Kingdom.[46] This study reflects a real-world practice and therefore is not randomised and does not have a control group but provides important insights into what is possible in primary care when T2D remission options are given to patients and when results are tracked on an ongoing basis. Important findings from the study include: (1) for those choosing an LCD approach nearly half achieved drug-free T2D remission as well as improvements in weight, blood pressure and lipid profiles; (2) an LCD approach reduced HbA1c to below prediabetes threshold in 93% who presented with that condition and (3) patients with the highest HbA1c saw the greatest improvements in their T2D control.

Recent Phase 3 trials show promise that high dose GLP-1 analogues (i.e. semaglutide)[47] or GLP-1/GIP dual analogues (i.e. tirzepatide)[48] can be powerful assists in type 2 diabetes mellitus (T2DM) reversal and weight loss although not meeting the definition as stated above by the three consensus groups because this is, of course, added medication. When titrated up to the maximum doses, these medications can promote weight loss and A1c reductions to the levels of bariatric surgery. The question remains though if these medications can ever be removed.[49]

A case for carbohydrate reduction

For many years the ADA has been somewhat silent on carbohydrate reduction often suggesting 'individualized therapy'. But in 2021, their standards of care document clearly made the case for carbohydrate reduction:

> For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns, in particular, have been found to reduce HemoglobinA1C (HbA1c) and the need for antihyperglycemic medications. These eating patterns are among the most studied eating patterns for type 2 diabetes.[50] (p. 736)

The report builds on their Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report 2019 which states:

> Reducing overall carbohydrate intake for individuals with diabetes has demonstrated for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences. For individuals with type 2 diabetes not meeting glycemic targets or for whom reducing glucose-lowering drugs is a priority, reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option.[51] (p. 736)

The European Association for the Study of Diabetes (EASD)[52] and Diabetes Canada[53] have also acknowledged carbohydrate reduction as a powerful method in diabetes care.

The often cited UK Prospective Diabetes Study (UKPDS) demonstrated higher HbA1c is associated with more diabetes complications, morbidity and mortality.[54] Yet globally we are failing to achieve these goals even with new and often expensive medications. An important trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) was initiated with a goal of intense pharmacologic therapy to lower HbA1C. The trail was stopped early due to adverse outcomes, thus giving caution to this approach. Intensive medical treatment carried an increased risk of all-cause mortality, a 35% increased risk of CV mortality, and a greater risk of hypoglycaemic events and weight gain of 10 kg compared to those on standard insulin therapy.[55]

The ACCORD is not alone. Other high-quality large trials using medications to achieve tight glycaemic targets did not

demonstrate reductions in heart disease or in overall mortality.[56,57,58,59,60,61] These consistent findings from highly funded and well-conducted trials make the case for an alternative approach to treating people with T2D with a focus on addressing insulin resistance.

Type 2 diabetes is, by definition, an inability to tolerate carbohydrate. The literature and clinical experience support therapeutic carbohydrate reduction; lifestyle changes to include exercise, stress reduction and sleep; and accompanying medication reduction. Large practice gaps exist in bringing the science and the experience to clinicians and diabetes educators. Expert panel reports such as the recent Lancet Commission on Diabetes do not make effort to close the gaps as the only mention of carbohydrate in the 63-page report has to do with dosing insulin.[62] Primary care physicians must bridge this gap.

Defining LCDs has also been an ongoing challenge as described in the article *Adapting Medication for Type 2 Diabetes to a Low Carbohydrate Diet*:[37]

> The Low Carbohydrate Diet (LCD) has lacked a consistent definition and has been used to refer to carbohydrate intake levels that are low only in relation to population averages, often measured as a percentage of kcals, but do not reach the therapeutic levels of restriction necessary to reverse insulin resistance and T2D. (n.p.)

In some reported studies, an LCD has included up to 45% of daily calories from carbohydrates. For an individual consuming 2500 calories a day, this would be 280 g of carbohydrates. An LCD by some definitions comprises less than 130 g of digestible carbohydrates per day which is less than 50% of the average daily intake in the United Kingdom and the United States. To fully address insulin resistance and promote T2D remission reduction to levels below 50 g of digestible carbohydrates a day are often needed. Digestible carbohydrate is defined as simple sugars and complex carbohydrates such as starch, which is digested to glucose; this contrasts with fibre, which is a carbohydrate that is not digested or is only partly digested with the aid of intestinal bacteria. Recommended food choices on a lower carbohydrate meal plan include (1) non-starchy vegetables, (2) protein-containing foods such as fish, meat, poultry and eggs, (3) natural fats such as olive oil and butter and (4) foods that naturally contain fats, fibre and/or protein such as nuts, olives, and avocado. Sugar and refined, starchy carbohydrates should be eliminated.

Conclusion

Diabetic retinopathy remains the leading cause of legal blindness in 18–74-year-old Americans. Novel primary care friendly imaging would benefit 40% – 45% of Americans from earlier detection and treatment of retinopathy still not receiving such care. The most impactful way a primary care clinician could impact DR would be assisting in making the T2D go into remission. Current evidence is for delaying or slowing progression of DR. A two-pronged strategy, bringing attention to ophthalmologists the potential of diabetes remission, and family physicians, the importance of retinopathy screening, may reduce the prevalence of blindness in patients with diabetes. Hopefully, future studies can demonstrate the reversal of existing DR with T2D remission which would greatly improve both visual and systemic outcomes in patients with diabetes. There is a need for randomised controlled clinical trials demonstrating reversal of DR in patients showing remission from T2D whilst adopting a LCD.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

J.C. conceptualised the idea of reviewing diabetic retinopathy (DR) in the context of primary care. A literature search was conducted to determine the latest DR pathophysiology and how artificial intelligence (AI), combined with user-friendly imaging, could enhance screening in primary care offices. Given the association of hyperglycaemia with DR, and potential remission of type 2 diabetes (T2D) with low carbohydrate diets, M.C. reviewed the latest evidence on why T2D remission might be the best approach to prevent or treat pre-existing DR.

Ethical considerations

This article followed all ethical standards for research without direct contact with human or animal subjects.

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Data availability

All figures and tables are included in the article. No additional raw data were utilised.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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