Research Article Volume 01, Issue No. 02. 2025

The Indonesian Journal of Medicine and Public Health



Association of Metformin with the Development of Age-Related Macular Degeneration

[1,2] Marissa, [1,2] Lindawati
[1] Faculty of Medicine, Padjadjaran University, Bandung City, West Java, Indonesia
[2] Hasan Sadikin Central General Hospital, Bandung City, West Java, Indonesia
Correspondence : marissadokter293@gmail.com

Article History :
Received date : 2024/10/17
Revised date : 2024/11/04
Accepted date : 2024/12/23
Published date : 2025/01/12

Copyright: *© 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (https://creativecommons.org/licenses/by-nc/4.0/).*

ABSTRACT

Background: The literature surrounding the association of metformin with the development of age-related macular degeneration (AMD) has gained considerable attention in recent years, particularly as the aging population continues to grow. **Literature Review:** The exploration by (Hsu et al., 2021) highlights metformin's potential neuroprotective effects, suggesting that it may mitigate retinal cell damage through various mechanisms, including autophagy and oxidative stress regulation. This is further supported by (Hwang et al., 2023), which finds a significant association between metformin use and a reduced risk of developing AMD among diabetic patients. The robust methodology employed in their study enhances the reliability of these findings, although it does not establish causality. Furthermore, the review by (Moir et al., 2024) specifically addresses the relationship between metformin and new-onset geographic atrophy, a severe form of AMD, underlining the necessity for further investigation into this association. In addition to its implications for retinal health, the literature also discusses metformin's broader potential as a geroprotective agent, as noted by (M. C. Top et al., 2022). This perspective aligns with the increasing interest in interventions that can mitigate age-related decline and promote healthy aging. **Conclusion:** Overall, the literature presents a compelling case for the potential benefits of metformin in the context of age-related diseases, including AMD. While the evidence suggests a protective association, further research, particularly longitudinal and randomized controlled trials, is warranted to clarify the mechanisms involved and establish causality.

Keyword: Association, Metformin, Development, Age-Related Macular Degeneration

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

INTRODUCTION

The literature surrounding the association of metformin with the development of age-related macular degeneration (AMD) has gained considerable attention in recent years, particularly as the aging population continues to grow. In the systematic review by (Schlender et al., 2017), the authors provide a comprehensive analysis of metformin's efficacy and safety in managing type 2 diabetes mellitus (T2DM) among older adults. They highlight metformin's role as a first-line therapy, noting its potential benefits while emphasizing the need for cautious prescribing in the elderly due to the risk of gastrointestinal side effects and lactic acidosis.

Building on this foundation, (Hsu et al., 2021) explore the broader implications of metformin beyond glycemic control, particularly its effects on diabetic retinopathy and aging. The authors present evidence suggesting that metformin may mitigate retinal cell damage through mechanisms such as autophagy and oxidative stress regulation, thus hinting at its potential protective role against retinal diseases, including AMD.

Further investigating the neuroprotective aspects of metformin, (Liao et al., 2022) delve into its effects on Alzheimer's disease (AD). Their review indicates that metformin may lower the risk of AD in T2DM patients, potentially through improvements in macrovascular disorders. However, they also note the lack of significant cognitive benefits in patients with existing cognitive impairments, suggesting that while metformin presents promise, its therapeutic role in neurodegenerative diseases remains inconclusive.

(M. C. Top et al., 2022) expand the discussion by presenting metformin as a geroprotective agent with potential benefits for cardiovascular disease, cancer, and cognitive impairment. They argue for its repurposing in the context of age-related diseases, including AMD, based on its established safety profile and positive health outcomes in older populations.

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

(Hwang et al., 2023) contribute to the literature by examining diabetes-related risk factors for exudative AMD within a diabetic cohort. Their findings support the notion that metformin usage is associated with a reduced risk of developing AMD, aligning with previous observational studies that advocate for the protective effects of the drug against retinal degeneration.

(Esteves et al., 2023) further emphasize the importance of monitoring metformin's safety in elderly patients, given the heightened risk of adverse effects associated with aging and comorbidities. Their analysis highlights the necessity of ongoing pharmacovigilance to ensure that the benefits of metformin outweigh the risks, particularly in the context of age-related conditions.

Finally, (Moir et al., 2024) address the specific relationship between metformin use and new-onset geographic atrophy, a severe form of AMD. They underline the need for further investigation into this association, as previous studies have predominantly focused on the overall protective effects of metformin against AMD without isolating the impact on geographic atrophy.

Through this literature review, it becomes evident that while metformin is primarily recognized for its role in managing T2DM, emerging evidence points to its potential in mitigating risks associated with age-related diseases, including AMD. The interplay between metabolic health and retinal degeneration underscores the importance of continued research to clarify the mechanisms by which metformin may confer protective effects in aging populations.

LITERATURE REVIEW

The article "Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing" by (Schlender et al., 2017) provides a comprehensive examination of metformin as a first-line therapy for type 2 diabetes mellitus (DM2) in older adults. The systematic review synthesizes various studies to evaluate both the safety and efficacy of metformin, emphasizing its role within this specific demographic.

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

The authors present a clear rationale for their investigation, given the increasing prevalence of diabetes in older populations and the need for effective management strategies that minimize adverse effects. The systematic review method employed is robust, encompassing a wide range of studies that allow for a nuanced understanding of metformin's impact on older adults. This is particularly relevant as older patients often present with multiple comorbidities and may be at greater risk for medication-related complications.

One of the key insights from the article is the established efficacy of metformin in controlling blood glucose levels, which is critical for preventing complications associated with DM2. However, the review also highlights potential safety concerns, such as the risk of lactic acidosis, particularly in patients with renal impairment. This underscores the necessity for careful patient selection and monitoring, which is vital for ensuring the safe use of metformin among older adults.

Moreover, the authors discuss the implications of inappropriate prescribing practices, which can lead to unnecessary risks for this vulnerable population. The recommendations provided aim to guide clinicians in making informed prescribing decisions that align with the best evidence available. This aspect of the review is particularly valuable, as it addresses the gap between clinical guidelines and actual prescribing behaviors in practice.

The article "New Insight into the Effects of Metformin on Diabetic Retinopathy, Aging and Cancer: Nonapoptotic Cell Death, Immunosuppression, and Effects beyond the AMPK Pathway" by (Hsu et al., 2021) provides a comprehensive exploration of the multifaceted roles of metformin, particularly in the context of age-related diseases, including diabetic retinopathy (DR). The authors elucidate the primary action of metformin as a glucose-lowering agent in type 2 diabetes mellitus (T2DM), emphasizing its role in suppressing hepatic gluconeogenesis and enhancing insulin sensitivity. This foundational understanding sets the stage for a deeper investigation into metformin's potential benefits beyond its metabolic effects.

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

A significant contribution of the article is its examination of metformin's impact on aging and its potential neuroprotective and retinal protective effects. The authors argue that aging is a critical factor in the development of various diseases, including DR, and propose that metformin may mitigate some of these age-related effects. They highlight the drug's ability to modulate reactive oxygen species (ROS) and maintain protein homeostasis, primarily through the activation of AMP-activated protein kinase (AMPK) signaling pathways. This is particularly relevant given the oxidative stress associated with aging and its implications for retinal health.

Furthermore, the article critically evaluates metformin's mechanisms of action that extend beyond the AMPK pathway. The authors present evidence that metformin can prevent retinal cell abnormalities and apoptosis, which are pivotal in the progression of DR. By highlighting both AMPK-dependent and independent pathways, the authors suggest a complex interplay in which metformin may exert protective effects on retinal cells, thereby potentially reducing the risk of developing age-related macular degeneration.

In addition to its implications for retinal health, the article also touches upon the broader context of cancer risk in T2DM patients. The authors refer to systematic reviews indicating that metformin may lower the risk of cancer recurrence, thus positioning the drug as a multifaceted therapeutic agent that could address multiple health concerns in aging populations.

The article "Deciphering the Roles of Metformin in Alzheimer’s Disease: A Snapshot" by (Liao et al., 2022) provides a comprehensive overview of the implications of metformin use in the context of Alzheimer's Disease (AD), particularly focusing on individuals with Type 2 Diabetes Mellitus (T2DM). The authors present a nuanced discussion on the dual aspects of metformin's efficacy: its potential neuroprotective role and the limitations observed in clinical settings.

A key insight from the article is the suggestion that metformin may lower the risk of developing AD among T2DM patients, a finding that underscores the drug's potential beyond glycemic control. This is particularly relevant given the increasing prevalence of both T2DM and AD in aging populations. The authors

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

emphasize that while animal studies have indicated a neuroprotective effect of metformin, clinical studies have not consistently demonstrated significant cognitive benefits in subjects already experiencing cognitive impairment due to AD. This discrepancy raises important questions about the translational applicability of preclinical findings to clinical outcomes.

Furthermore, the article highlights the interaction between metformin and ApoE carrier status, suggesting that genetic factors may play a crucial role in determining the protective effects of metformin against AD. This aspect is particularly critical as it points to the need for personalized approaches in treatment strategies, where patient characteristics could influence therapeutic outcomes.

The authors also discuss the pharmacokinetic challenges associated with metformin, including poor oral absorption and gastrointestinal side effects, which limit its clinical application. The exploration of prodrugs with enhanced lipophilicity to improve permeability represents a promising avenue for future research. Moreover, the article notes that the delivery of metformin to the central nervous system (CNS) is contingent upon cerebral blood flow and the integrity of the blood-brain barrier (BBB), both of which are compromised in early AD pathology. This connection between AD progression and drug efficacy is a critical area that warrants further investigation.

The article titled "Metformin: A Narrative Review of Its Potential Benefits for Cardiovascular Disease, Cancer and Dementia" by (M. C. Top et al., 2022) provides a comprehensive overview of the multifaceted benefits of metformin beyond its primary use as an antidiabetic medication. The authors trace the historical context of metformin, highlighting its introduction to the European market in 1958 and subsequent approval in the United States in 1995, emphasizing the drug's established safety profile following the withdrawal of phenformin due to lactic acidosis concerns.

A critical evaluation of the article reveals that the authors effectively synthesize existing literature to support their claims regarding metformin's potential benefits for various age-related diseases, including cardiovascular disease, cancer, and cognitive decline. The inclusion of findings from the UK Prospective Diabetes

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study (UKPDS) underscores metformin's role in reducing cardiovascular mortality among obese patients with type 2 diabetes mellitus (T2DM), which is a significant contribution to the understanding of the drug's broader implications for health in aging populations.

Furthermore, the article discusses the emerging perspective of metformin as a geroprotective agent, suggesting that it may promote healthy aging and extend lifespan. This notion is particularly relevant in the context of increasing interest in gerontology and the search for interventions that can mitigate age-related decline. The authors' mention of the ongoing debate surrounding metformin's position in diabetes treatment, especially in light of newer drug classes with strong cardiovascular protective properties, adds depth to the discussion and invites further research into the comparative effectiveness of these therapies.

However, while the article presents a thorough narrative review, it would benefit from a more detailed exploration of the mechanisms by which metformin may exert its potential protective effects against age-related diseases. Additionally, the authors could enhance their argument by including more recent studies that specifically investigate the association between metformin and the development of age-related macular degeneration, as this is a critical area of interest within the broader topic of aging and metabolic health.

The article "Diabetes-Related Risk Factors for Exudative Age-Related Macular Degeneration: A Nationwide Cohort Study of a Diabetic Population" by (Hwang et al., 2023) presents a significant exploration into the relationship between diabetes, specifically the use of metformin, and the incidence of age-related macular degeneration (AMD). The authors conducted a comprehensive case-control study that highlights metformin's potential protective effects against the development of AMD, a condition that poses a substantial risk to vision in older adults.

The study's methodology is robust, utilizing a nationwide cohort to ensure a diverse and representative sample of the diabetic population. This approach enhances the reliability of the findings, as it minimizes selection bias and allows for a more generalized understanding of the relationship between metformin use and

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

AMD. The authors meticulously detail the criteria for participant selection, which strengthens the validity of their conclusions.

A critical evaluation of the findings reveals that metformin appears to significantly lower the odds of developing AMD among diabetic patients. This aligns with existing literature suggesting that metformin may have neuroprotective and anti-inflammatory properties that could contribute to retinal health. The authors provide a thorough analysis of the data, employing appropriate statistical methods to support their claims. However, it is essential to note that while the association is evident, the study does not establish causality. Future research should focus on longitudinal studies to further elucidate the mechanisms through which metformin may influence AMD development.

Moreover, the authors discuss potential confounding factors, such as the duration of diabetes and the presence of other comorbidities, which could influence the results. This acknowledgment adds depth to the study, as it emphasizes the complexity of the relationship between diabetes management and eye health. However, the article could benefit from a more detailed exploration of these confounding variables and their potential impact on the findings.

The article titled "Analysis of Reports Sent to the Portuguese Pharmacovigilance System and Published Literature Regarding the Safety of Metformin in the Elderly" by (Esteves et al., 2023) provides a comprehensive examination of the safety profile of metformin, particularly among older patients. The authors focus on the implications of using metformin in this demographic, highlighting both the potential benefits and the risks associated with its use.

One of the key insights presented in the article is that metformin carries a minimal risk of hypoglycemia compared to other antidiabetic medications. However, the authors emphasize that the drug is associated with a higher incidence of gastrointestinal side effects and lactic acidosis, particularly in patients with compromised renal function. The article underscores the importance of adhering to the FDA guidelines, which contraindicate metformin use in patients with glomerular filtration rates (GFR) below 30 mL/min. This is particularly relevant for

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

older adults, as renal function typically declines with age, necessitating closer monitoring of renal parameters in this population.

The authors also discuss the implications of comorbid conditions such as heart failure and impaired liver function, which can exacerbate the risk of lactic acidosis when using metformin. This aspect of the article is crucial, as it highlights the need for a tailored approach to prescribing metformin in elderly patients, taking into account their overall health status and potential for adverse drug reactions (ADRs).

Furthermore, the article calls for ongoing surveillance of metformin's safety in the elderly, advocating for the collection of real-world data to better understand the incidence of serious ADRs and the effects of concomitant medications. This recommendation is significant, as it addresses the gap in current knowledge regarding the long-term safety of metformin in older adults, which is essential for informed clinical decision-making.

The article "The Association Between Metformin Use and New-Onset ICD Coding of Geographic Atrophy" by (Moir et al., 2024) delves into the relationship between metformin usage and the onset of geographic atrophy (GA), a severe form of age-related macular degeneration (AMD). This investigation is particularly pertinent given the growing body of observational studies suggesting that metformin may offer protective benefits against AMD, yet there remains a gap in understanding its specific impact on GA.

The authors begin by contextualizing the significance of GA within the spectrum of AMD, emphasizing its debilitating nature and the lack of effective treatments. They highlight that while previous studies have indicated a potential protective role of metformin against the broader category of AMD, the specific association with GA had not been thoroughly explored prior to their research. This gap in literature sets the stage for their analysis, which aims to clarify whether metformin use correlates with a reduced incidence of GA as indicated by new-onset ICD coding.

In their methodology, Moir et al. employ a robust observational study design, utilizing a large dataset to assess the incidence of GA among metformin

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

users compared to non-users. This methodological rigor is commendable, as it strengthens the validity of their findings. The authors meticulously detail their statistical analyses, which include adjustments for confounding variables, thereby enhancing the reliability of their conclusions.

The results presented indicate a noteworthy association between metformin use and a lower incidence of GA. This finding is significant, as it not only adds to the existing literature on metformin's potential protective effects against AMD but also raises important questions regarding its mechanism of action. The authors suggest that the anti-inflammatory and neuroprotective properties of metformin could play a role in mitigating the progression of retinal degeneration associated with GA.

However, the article does acknowledge certain limitations inherent in observational studies, such as the potential for residual confounding and the challenges in establishing causation. While the authors make a compelling case for the association, they also call for further research, particularly randomized controlled trials, to establish a clearer causal relationship and to explore the underlying mechanisms that could explain the observed protective effect of metformin on GA.

CONCLUSION

The review of the literature surrounding metformin's association with age-related macular degeneration (AMD) illustrates a growing body of evidence suggesting its potential protective effects beyond its primary role in glycemic control for type 2 diabetes mellitus (T2DM). The systematic review by (Schlender et al., 2017) establishes metformin as a first-line therapy, while emphasizing the importance of careful prescribing practices in older adults due to associated risks. This foundational understanding sets the stage for further exploration of metformin's broader implications, particularly in relation to retinal health.

The exploration by (Hsu et al., 2021) highlights metformin's potential neuroprotective effects, suggesting that it may mitigate retinal cell damage through various mechanisms, including autophagy and oxidative stress regulation. This is

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

further supported by (Hwang et al., 2023), which finds a significant association between metformin use and a reduced risk of developing AMD among diabetic patients. The robust methodology employed in their study enhances the reliability of these findings, although it does not establish causality.

Furthermore, the review by (Moir et al., 2024) specifically addresses the relationship between metformin and new-onset geographic atrophy, a severe form of AMD, underlining the necessity for further investigation into this association. The findings suggest that metformin may confer protective benefits against this debilitating condition, reinforcing the need for ongoing research into its mechanisms of action.

In addition to its implications for retinal health, the literature also discusses metformin's broader potential as a geroprotective agent, as noted by (M. C. Top et al., 2022). This perspective aligns with the increasing interest in interventions that can mitigate age-related decline and promote healthy aging. However, concerns regarding the safety profile of metformin in older populations, as highlighted by (Esteves et al., 2023), emphasize the importance of ongoing pharmacovigilance.

Overall, the literature presents a compelling case for the potential benefits of metformin in the context of age-related diseases, including AMD. While the evidence suggests a protective association, further research, particularly longitudinal and randomized controlled trials, is warranted to clarify the mechanisms involved and establish causality.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved

REFERENCES

1. Schlender, L., V. Martinez, Y., Adeniji, C., Reeves, D., Faller, B., Sommerauer, C., Al Qur'an, T., Woodham, A., Kunnamo, I., Sönnichsen, A., & Renom-Guiteras, A., 2017. Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. ncbi.nlm.nih.gov
2. Hsu, S. K., Cheng, K. C., Oluebube Mgbeahuruike, M., Lin, Y. H., Wu, C. Y., David Wang, H. M., Yen, C. H., Chiu, C. C., & Sheu, S. J., 2021. New Insight into the Effects of Metformin on Diabetic Retinopathy, Aging and Cancer: Nonapoptotic Cell Death, Immunosuppression, and Effects beyond the AMPK Pathway. ncbi.nlm.nih.gov
3. Liao, W., Xu, J., Li, B., Ruan, Y., Li, T., & Liu, J., 2022. Deciphering the Roles of Metformin in Alzheimer's Disease: A Snapshot. ncbi.nlm.nih.gov
4. M. C. Top, W., Kooy, A., & D. A. Stehouwer, C., 2022. Metformin: A Narrative Review of Its Potential Benefits for Cardiovascular Disease, Cancer and Dementia. ncbi.nlm.nih.gov
5. Hwang, S., Woong Kang, S., Jin Kim, S., Na Lee, K., Han, K., & Hui Lim, D., 2023. Diabetes-Related Risk Factors for Exudative Age-Related Macular Degeneration: A Nationwide Cohort Study of a Diabetic Population. ncbi.nlm.nih.gov
6. Esteves, B., Monteiro, C., & Paula Coelho Duarte, A., 2023. Analysis of Reports Sent to the Portuguese Pharmacovigilance System and Published Literature Regarding the Safety of Metformin in the Elderly. ncbi.nlm.nih.gov
7. Moir, J., J. Hyman, M., Gonnah, R., Flores, A., M. Hariprasad, S., & Skondra, D., 2024. The Association Between Metformin Use and New-Onset ICD Coding of Geographic Atrophy. ncbi.nlm.nih.gov

Downloaded from The Indonesian Journal of Medicine and Public Health
Copyright © International Medical Journal Corp. Ltd. All rights reserved