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METABOLIC SYNDROME AND THE AGING RETINA: A SYSTEMATIC REVIEW

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Abstract

As we get older, we experience a progressive loss of visual function in our eyes. Changes in the structures of the ocular tissues, specifically the cornea, lens, retina, retinal pigment epithelium (RPE), choroid, and optic nerve, are the root cause of age-related macular degeneration, which leads to a loss of vision. Aging is linked to a wide variety of eye conditions, including Fuch's dystrophy, dry eye syndrome, cataracts, presbyopia, age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma, amongst others. Vision can be impaired as a result of these conditions in between 4 and 20 percent of people over the age of 65. The term "metabolic syndrome" (MetS) refers to a cluster of cardiometabolic components, some of which include abdominal obesity, hypertension, elevated glucose levels, and dyslipidemia. These components are highly predictive of type 2 diabetes mellitus and cardiovascular diseases (CVD), which eventually cause morbidity and mortality. The retinal age difference has proven itself as an innovative and reliable screening technique for metabolic syndrome and inflammation. When compared to earlier screening methods that were based on blood tests or anthropometric measurements, the retinal age gap is calculated using a deep learning model that automatically integrates all of the information from fundus images. This reduces the likelihood of making an error during manual assessment and eliminates the requirement for invasive testing. We discovered that there was a strong association between MetS and age gaps in the retina, as well as inflammation.

Keyword: *Aging; Metabolic syndrome; Retina; Retinopathy; Visual*

INTRODUCTION

The eye's visual function gradually declines as we age. This age-related vision loss is caused by structural changes in the ocular tissues, which include the cornea, lens, retina, retinal pigment epithelium (RPE), choroid, and optic nerve.[1] With age, there is a reduction in the number of corneal endothelial cells, and epithelium-derived glands, such as the lacrimal and meibomian glands, generate less tears to keep the cornea wet. The ability of the aging lens to alter shape, known as presbyopia, is probably caused by changes in the cortical fiber cells.[2]

The populations of neurons in the retina become less numerous as a person's visual acuity and sensitivity deteriorate. The macula, which is located in the middle of the retina and is densely packed with cone photoreceptors, also experiences a reduction in its microcirculation as one gets older.[3] There is a loss of melanin in the RPE, which is followed by the deposition of lipofuscin. Age causes a thickening of Bruch's membrane, which is the deepest layer of the choroid, as well as the formation of basal laminar and basal linear deposits. Along with that, there is a reduction in the number of axons in the optic nerve, but at the same time there is an increase in the number of elastic fibers.[4]

Aging is linked to a wide variety of eye conditions, including Fuch's dystrophy, dry eye syndrome, cataracts, presbyopia, age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma, amongst others. Vision can be impaired as a result of these conditions in between 4 and 20 percent of people over the age of 65.[3,4] Visual impairment greatly diminishes the quality of life and is a powerful predictor of mortality. The metabolic foundation of aging and age-related eye disorders remains unknown. Understanding the effects of aging on the eye should generate research with both fundamental and therapeutic relevance.[5]

The term "metabolic syndrome" (MetS) refers to a cluster of cardiometabolic components, some of which include abdominal obesity, hypertension, elevated glucose levels, and dyslipidemia. These components are highly predictive of type 2 diabetes mellitus and cardiovascular diseases (CVD), which eventually cause morbidity and mortality.[6,7] It has been observed that inflammation plays a critical role in the pathophysiology of MetS. As the population ages, the prevalence of MetS increases dramatically, placing a significant burden on people and families in an aging society.[8]

MetS detection and risk stratification are required to improve diabetes and CVD prevention and early intervention efforts. In an increasing number of research, possible screening techniques for the MetS, such as anthropometric measurements and blood tests, have been studied.[9] Noninvasive metrics such as body mass index, waist circumference, and blood pressure stand out among the proposed techniques. However, measurement problems and racial heterogeneity have hampered their continued use for screening large populations.[10–12] The purpose of this study is to present information that suggests a connection between metabolic syndrome and the deterioration of the retina with age.

METHODS

The standards for data collection, processing, and reporting for the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project have been satisfied. The decision to approve new restrictions was impacted by a number of reasons. This literature review investigates the relationship between metabolic syndrome and retinal aging. All written materials regarding the use of topical tretinoin to treat photoaging must be written in English, according to the study's primary findings. This systematic review investigated scholarly works published after 2015 that met the inclusion criteria of the study. The collection will eliminate editorials, entries lacking a DOI, reviews of previously published books, and too lengthy duplicate journal articles.

The search for studies to be included in the systematic review was carried out from March, 30th 2023 using the PubMed and SagePub databases by inputting the words: “metabolic syndrome” and “aging retina”. Where *("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields]) AND ("aging"[MeSH Terms] OR "aging"[All Fields] OR "ageing"[All Fields]) AND ("retina"[MeSH Terms] OR "retina"[All Fields] OR "retinas"[All Fields] OR "retina s"[All Fields] OR "retinae"[All Fields])* is used as search keywords.

Abstracts and names of studies affected their acceptability. Therefore, they rely on historical documents. Due to the uniformity of study outcomes, unpublished English publications are necessary. Only studies meeting inclusion criteria were included in the systematic review. This restricts the search results to only match results. The evaluation method is described below. The study analyzed authors, publication dates, geographic regions, activities, and causes. After EndNote stored search results, the database deleted duplicate articles.

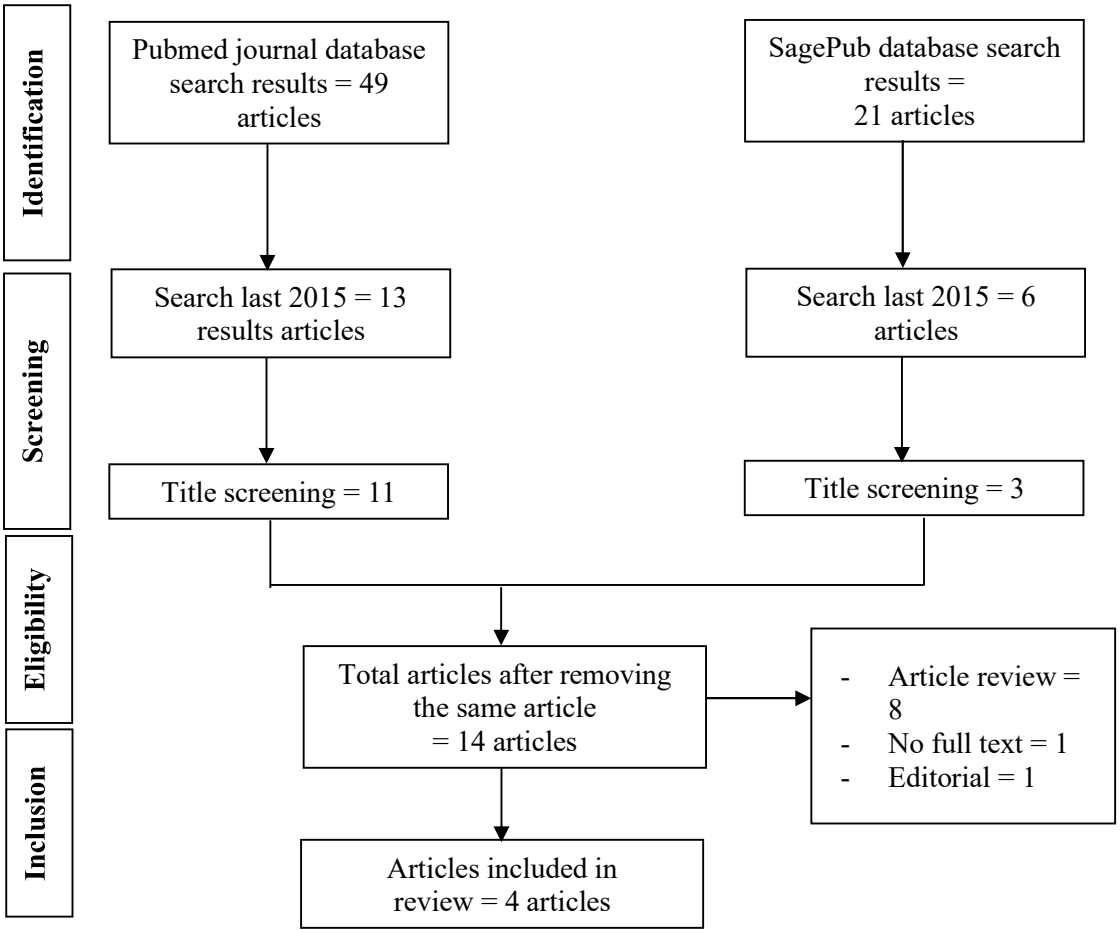

Figure 1. Article search flowchart

It was decided that two persons would look at the titles and abstracts. Every contributor read the article's abstract and title before making their choice about which article to discuss. Each and every manuscript that satisfies the review requirements will be scrutinized in great detail. After we have completed our investigation, we will go back and go at any pertinent scholarly articles. The criteria for document appraisal are outlined in this rule. In the future, it ought to be made simpler to identify objects that are subject to examination. Why was a particular study chosen to be included in the synthesis of the available literature?

RESULT

Zhu, et al (2023)[13] showed the retinal age gap was found to be substantially linked with MetS and inflammation. Specifically, compared to participants with retinal age gaps in the lowest quartile, the risk of MetS increased by 10% and 14% for those with retinal age gaps in the third and fourth quartiles, respectively (odds ratio [OR] = 1.10; 95% confidence interval [CI] = 1.01,1.21;, p = 0.030; OR = 1.14, 95% CI = 1.03,1.26; p = 0.012, respectively). Similar patterns were discovered for the risk of inflammation and the combination of MetS and inflammation.

Zarei, et al (2017)[14] showed in the nasal superior (107.8 ± 19.5 μm) and temporal superior (135.7 ± 18.9 μm) sectors, RNFL thickness was thinner in the MetS group than in the control group (114.6 ± 22.4 μm, P = 0.013 and 140.7 ± 18.9 μm, P = 0.027, respectively). MetS was independently linked with a thinner retinal nerve fibre layer (RFNL) thickness in the nasal superior (β = 0.20, P = 0.009) and temporal superior (β = 0.14, P = 0.048) sectors following repeated adjustments for age, gender, and the studied eye side (right [OD]/left [OS]). Independent of age, gender, and examined eye side, persons with a greater number of metabolic disorders had a substantially thinner RNFL (P = 0.043).

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Conclusion
Zhu, 2023[13]	United Kingdom	Population-based cohort study	500,000 participants	This study discovered that there was a strong association between MetS and age gaps in the retina, as well as inflammation. The retinal age gap has significant potential to be utilized as a screening tool for MetS in large populations because it is both noninvasive and cost-efficient, and it is also effective.

Zarei, 2017[14]	Iran	Cross-sectional study	278 eyes from 139 participants	Our research demonstrates that metabolic syndrome is independently linked to lower RNFL thickness, which leads us to hypothesize that neurodegeneration may play a role in the etiology of metabolic syndrome.
Wang, 2016[15]	Australia	Cross-sectional study	1,680 participants	In people who are at high risk for coronary artery disease (CAD), having metabolic syndrome is independently related with having narrower retinal arterioles but not bigger retinal venules. Since the link between metabolic syndrome and narrower retinal arterioles is not significant in individuals who do not have hypertension or CAD, it is likely that the existence of these conditions in individuals who have metabolic syndrome is responsible for the significance of this association.
Haleh, 2015[16]	Iran	Prospective cohort study	2,218 participants at risk	It was found that having metabolic syndrome, being obese, having high glucose levels, and having high triglyceride levels were predictors of progression to late AMD. These findings offer new perspectives on the processes that contribute to the development of AMD.

Wang, et al (2016)[15] conducted a study with 979 people, they have information about components of MetS were included in cross-sectional analysis. After controlling for age, sex, smoking status, and fellow vessel calibre, those with metabolic syndrome exhibited narrower retinal arteriolar calibre (mean difference[MD] = 4.3 μm, $p < 0.0001$) than those without MetS. They noticed no significant differences in venular calibre ($p = 0.05$). This connection maintained among individuals without diabetes (mean arteriolar diameter difference = 4.4 μm, $p = 0.0006$), but not among those without CAD or hypertension.

Haleh, et al (2015)[16] counducted a study with 10-year follow-up. They showed 12% of participants at risk developed early AMD and 3% developed late AMD. MetS was linked with the incidence of late AMD in those younger than or equivalent to 70 years of age. During the 10-year follow-up, obesity, high glucose, and high triglyceride levels were related with an increased incidence of late AMD. There was no evidence that MetS and its components increased the likelihood of developing early AMD.

DISCUSSION

The metabolic syndrome is characterized by a cluster of risk factors, the most prominent of which are central obesity, hypertriglyceridemia, insulin resistance, dyslipidemia, and hypertension, as well as hyperglycemia during fasting. In addition, the development of insulin resistance syndrome and cardiovascular disease are both partially influenced by central obesity as well as the excess adipose tissue that is present in obese patients. It is possible that metabolic syndrome and endocrine malfunction of adipose tissue both played a significant role in the evolution of retinopathy and the development of retinal lesions.[17]

People who are obese have a markedly higher risk of developing metabolic syndrome; however, the underlying mechanism that underlies this link is not yet totally known. As a consequence of obesity, there will be an increase in the production of reactive oxygen species (ROS) in the circulation as well as in the adipose cells, which will then be followed by an acceleration of the fat-burning metabolic process. The disruption of the equilibrium of oxidation-reduction reactions (redox) can be caused when there is an increase in reactive oxygen species (ROS) in adipose cells. This can result in a reduced concentration of antioxidant enzymes in the bloodstream.[18]

Oxidative stress is the name given to this condition. An increase in oxidative stress is the first step in the pathophysiology of metabolic syndrome (SM), hypertension, and atherosclerosis. This step induces dysregulation of adipose tissue. Oxidative stress is frequently linked to the pathogenesis of a wide variety of diseases, including type 2 diabetes and atherosclerosis. It is typical for there to be an increase in oxidative stress in people who have diabetes mellitus type 2, and this is primarily because of hyperglycemia.[18]

Oxidative stress is considered as one of the causes of endothelial dysfunction-diabetic angiopathy, and the center of all diabetic angiopathy is hyperglycemia which induces oxidative stress through 3 pathways, namely; increase in the polyol pathway, increase in glucose auto-oxidation and increase in protein glycosylates. In diabetes, oxidative stress inhibits glucose uptake in muscle cells and fat cells and reduces insulin secretion by pancreatic β-cells.[18]

Study looked at a wide group of adults ranging in age from middle age to older adults and discovered that there was a substantial association between the retinal age gap and both MetS and inflammation. To be more specific, when compared to people with retinal age gaps in the lowest quartile, those in the third and fourth quartiles showed a considerably elevated risk of MetS, with a ten percent and fourteen percent increase, respectively, compared to those in the lowest quartile. Similar tendencies were found for the risk of inflammation as well as the combined risk of metS and inflammation.[13]

In the course of our investigations into the links between retinal age gaps, MetS, and inflammation, we have been able to make use of some very valuable suggestions that were provided to us by earlier research that had been conducted. First, alterations in the structural makeup of the retina were found in patients who suffered from both MetS and inflammation. These patients had both conditions at the same time.[19] For instance, the OCT segmentation analysis revealed that people who had MetS and high levels of CRP had thinner layers of photoreceptors and smaller inner retinal layers.[14,20]

There were signs of retinal microvascular dysfunction found in the fundus images of patients with MetS. On the basis of retinal images, a population-based investigation revealed that MetS was related with retinal microvascular symptoms such as microaneurysms, retinal hemorrhages, arteriovenous nicking, and focal arteriolar narrowing.[15] In addition, the MetS and its components, in addition to CRP, which is a marker of inflammation, have been linked to retinal illnesses such as age-related macular degeneration, retinopathy, and glaucoma, which has led to large increases in morbidity and mortality.[16,17]

Obesity, hypertension, hyperlipidemias, and insulin resistance are low-grade systemic inflammatory diseases, hence the inflammatory pathway is crucial to metabolic syndrome retinopathy.[21] After infiltrating adipose tissue, immune cells such macrophages, lymphocytes, and leukocytes release pro-inflammatory cytokines, contributing to inflammation. The pro-inflammatory cytokines secreted by adipose tissue include interleukins (ILs), notably IL-1β, IL-6, and tumor necrosis factor alpha. These cytokines impact glucose homeostasis, insulin signaling, insulin resistance, and cardiovascular problems such retinopathy.[22]

The retinal age difference has established a novel and dependable tool for screening for MetS and inflammation. Compared to prior screening techniques based on blood tests or anthropometric measurements, the retinal age gap is calculated using a deep learning model that automatically integrates all information from fundus images, thereby minimizing manual assessment error and eliminating the need for intrusive testing.[23]

In light of its noninvasiveness, dependability, and objectivity, it offers considerable promise for application as a diagnostic biomarker. This ensures its continued use in screening for MetS and inflammation in large populations. In addition, early diagnosis and risk stratification of MetS and inflammation could contribute to the promotion of preventative and intervention methods for chronic diseases such as diabetes and CVDs, hence reducing the societal economic burden.[23]

CONCLUSION

We discovered that there was a strong association between MetS and age gaps in the retina, as well as inflammation.

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