

Ocular findings in metabolic syndrome: a review

Mário Lima-Fontes, MD, MSc^{a,b}, Pedro Barata, MD, PharmD, PhD^{c,d}, Manuel Falcão, MD, PhD^{a,e},
Ângela Carneiro, MD, PhD^{a,e}.

Abstract

Metabolic syndrome (MetS) has emerged as a worldwide health hazard of the modern lifestyle, representing a cluster of metabolic abnormalities and a risk factor for cardiovascular disease. Eye diseases, such as diabetic retinopathy, central retinal artery occlusion, cataract, age-related macular degeneration, glaucoma, and dry eye syndrome have been linked with many of MetS components. Their relationship with MetS itself is, however, a recent topic of investigation. This review aims to gather published evidence supporting associations between ocular findings and MetS and to explore the related physiopathological processes that congregate in this syndrome and lead to these diseases. Despite compiling interesting and compelling evidence, it raises awareness to the need of further studies in this field to keep solidifying these associations and unveiling the pathological processes that support them. It ultimately targets MetS patients as a population of individuals who are at increased risk of developing age-related eye diseases and vision loss.

Keywords: age-related macular degeneration, cataract, central retinal artery occlusion, diabetic retinopathy, dry eye disease, eye diseases, glaucoma, metabolic syndrome

Introduction

The metabolic syndrome (MetS), also known as syndrome X, is defined as a clustering of metabolic abnormalities that include central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced high-density lipoprotein (HDL)-cholesterol concentrations.^{1,2} It has been considered one of the most important risk factors for the epidemic of type 2 diabetes and cardiovascular disease (CVD) in the 21st century and it is associated with other comorbidities including the proinflammatory state, prothrombotic state, and nonalcoholic fatty liver disease.³ Most studies have found that the MetS is associated with an approximate doubling of CVD risk and a 5-fold increased risk for type 2 diabetes.³

MetS represents a worldwide epidemic and a major public health concern with its prevalence increasing all over the world. In the USA, it is estimated that approximately 25% American adults are affected by this cluster of findings.^{3,4} There is no significant data about the worldwide prevalence of MetS and the estimates vary, based on the criteria used for its definition.

However, since MetS is about 3 times more common than diabetes, the global prevalence can be estimated to be about 1 quarter of the world population.⁵ The PORMET study published in 2017 estimated the prevalence of MetS in Portuguese adults to be 36.5%, 49.6%, and 43.1%, using the Adult Treatment Panel III (NCEP-ATP III), International Diabetes Federation (IDF), and Joint Interim Statement (harmonizing criteria [HARM]) definitions, respectively.⁶

The 4 most popular definitions used for MetS are detailed in Table 1.⁷⁻¹⁰

Abdominal obesity and insulin resistance seem to play a central role in promoting the development of MetS.^{11,12} Therefore, lifestyle modification and weight loss should be considered to be the first step for preventing or treating MetS.^{13,14} In addition, other cardiac risk factors should be actively managed in individuals with MetS.¹⁵

The association of diabetes and hypertension with ocular conditions such as diabetic retinopathy (DR), cataract, and glaucoma has been established in the last years.¹⁶ These conditions account for most of the vision loss unrelated to refractive error, representing the leading causes of blindness around the world.¹⁷ However, few studies directly correlate MetS as a constellation of risk factors with ocular findings. This review summarizes current available evidence supporting associations between MetS and age-related eye diseases, including DR, cataract, central retinal artery occlusion (CRAO), age-related macular degeneration (AMD), glaucoma, and dry eye disease (DED).

Methods

A review of the association between MetS and ocular findings was conducted. Bibliographical search was performed in Medline database (PUBMED) up to June 2020 using the following terms: “Metabolic syndrome,” “eye diseases,” “diabetic retinopathy,” “central retinal artery occlusion,” “cataract,” “age-related macular degeneration,” “glaucoma,” and “dry eye.” Abstracts not written in English, Portuguese, or Spanish were excluded. Other

^aDepartment of Ophthalmology, Centro Hospitalar Universitário de São João,
^bDepartment of Biomedicine, Faculty of Medicine, ^ci3S, Institute for Research and Innovation in Health, University of Porto, ^dFaculty of Health Sciences, Fernando Pessoa University, ^eDepartment of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal.

Corresponding author. Department of Ophthalmology, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. E-mail address: mariofontes@gmail.com (Mário Lima Fontes).

Copyright © 2020 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of PBJ-Associação Porto Biomedical/Porto Biomedical Society. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Porto Biomed. J. (2020) 5:6(e104)

Received: 5 October 2020 / Accepted: 7 October 2020

<https://dx.doi.org/10.1097/j.pbj.000000000000104>

Table 1**Diagnostic criteria for metabolic syndrome**

Definition	WHO 1999 ⁷	NCEP-ATP III 2005 ⁸	IDF 2006 ⁹	HARM 2009: ¹⁰
Criteria	Presence of insulin resistance or glucose >6.1 mmol/L (110 mg/dL), 2 h glucose >7.8 mmol (140 mg/dL) (required) along with any 2 or more of the following: HDL cholesterol <0.9 mmol/L (35 mg/dl) in men, <1.0 mmol/L (40 mg/dL) in women. Triglycerides >1.7 mmol/L (150 mg/dL). Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI >30 kg/m ² . Blood pressure >140/90 mm Hg.	Presence of any 3 or more of the following: Blood glucose >5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose. HDL cholesterol <1.0 mmol/L (40 mg/dL) in men, <1.3 mmol/L (50 mg/dL) in women or drug treatment for low HDL-C. Blood triglycerides >1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides. Waist >102 cm (men) or >88 cm (women). Blood pressure >130/85 mm Hg or drug treatment for hypertension.	Waist >94 cm (men) or >80 cm (women) along with the presence of 2 or more of the following: Blood glucose >5.6 mmol/L (100 mg/dL) or diagnosed diabetes. HDL cholesterol <1.0 mmol/L (40 mg/dL) in men, <1.3 mmol/L (50 mg/dL) in women or drug treatment for low HDL-C. Blood triglycerides >1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides. Blood pressure >130/85 mm Hg or drug treatment for hypertension.	At least 3 (any) of the following characteristics: Fasting glucose ≥100 mg/dL or antidiabetic treatment. Blood pressure ≥130/85 mm Hg or antihypertensive medication. Triglycerides ≥150 mg/dL or specific treatment for this lipid abnormality. HDL-C <40 mg/dL in women and <30 mg/dL in men or specific treatment for this lipid abnormality. Waist ≥ 88 cm in women and ≥102 cm in men ("European" cut off points).

ATP-III = Adult Treatment Panel III; BMI = body mass index; HARM = harmonizing criteria; HDL = high-density lipoprotein; IDF = International Diabetes Federation; NCEP-ATP = National Cholesterol Education Program—Adult Treatment Panel; WHO = World Health Organization.

few relevant cited articles which were not present in the original search results were included.

Metabolic syndrome and eye diseases

Metabolic syndrome and retinal microvascular changes. The association of diabetes and hypertension with retinopathy and other microvascular changes is well known. Moreover, MetS in particular is associated with atherosclerosis affecting large vessels and simultaneously with inflammation and endothelial dysfunction of both large and small vessels.¹⁸

In a population-based cross-sectional study 11,265 individuals were participated. In the United States, patients with MetS were significantly more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, smaller retinal arteriolar diameters, and larger retinal venular diameters than people without the syndrome, independent of age, sex, race, education, cigarette smoking, and alcohol consumption.¹⁹ Zhao et al²⁰ reported very similar results in 2012 in Japanese individuals. Saito et al²¹ also found narrower retinal arterial diameters and wider retinal venular diameters in such patients. A similar finding was also reported in another study by Kawasaki et al²² in Japan.

Metabolic syndrome and diabetic retinopathy

DR is the most common microvascular complication in patients with diabetes and the leading cause of vision loss globally in working middle-aged adults.^{23,24}

Chronic hyperglycemia is the key promoter for the development and progression of DR due to its tissue-damaging effects. However, genetic factors may play a role in individual susceptibility to the effects of hyperglycemia and other clinical factors such as hypertension and dyslipidemia have also been implicated.^{23–25}

Oxidative stress has been proposed as a common element linking all of the hyperglycemia-induced biochemical and molecular pathways of DR pathophysiology, constituting a self-amplifying cycle in which the generation of superoxide drives metabolic dysfunction, which in turn drives more reactive oxygen species (ROS) production via a self-perpetuating positive feedback mechanism.^{26,27}

Superoxide causes an elevation in the levels of glyceraldehyde-3-phosphate by inhibiting its NAD⁺-dependent conversion to 1,3-bisphosphoglycerate via the inhibition of glyceraldehyde phosphate dehydrogenase activity. Glyceraldehyde-3-phosphate in turn upregulates the formation and deposition of advanced glycation end products by accelerating the addition of triose phosphates to methylglyoxal, the main advanced glycation end products precursor.

High levels of intracellular ROS cause irreversible cell damage through epigenetic changes, such as histone modifications, DNA methylation, and noncoding RNAs.²⁸ Hyperglycemia-derived ROS compromise function of the electron transport chain, leading to damages to mitochondrial DNA.²⁹

Chronic low-grade inflammation is a key driver of capillary occlusion and hypoxia that ultimately drives VEGF expression and concomitant hallmark vascular abnormalities that characterize DR.³⁰

Because hyperglycemia, oxidative stress, and inflammation are processes involved in MetS, several population studies evaluated its association with DR.

In 2016, Abdul-Ghani et al³¹ studied a population of Jewish patients with type 2 diabetes (270 with MetS according to NCEP-ATP III criteria and 145 without) and found that diabetic subjects with MetS had significantly higher frequency of microvascular-related complications than diabetic subjects without the syndrome (46.6% and 26.8% respectively, $P=.0005$). These

included microalbuminuria (41.5% vs 23.9%, $P=.013$), neuropathy (10.4% vs 7.5%, $P=.38$), retinopathy (9.6% vs 4.1%, $P=.046$), and leg ulcers (7.9% vs 2.8%, $P=.044$).

A multicentric study conducted in Italy and published in 2016 with a sample of 7859 type 2 diabetic patients reported an independent association of MetS diagnosed either via NCEP-ATP III criteria (1.41 times) or IDF criteria (1.49) with DR. This study also evaluated 638 type 1 diabetic patients and an association was found between MetS and DR, but it did not reach statistical significance.³²

Costa *et al*³³ reported in 2004 a higher prevalence of retinopathy in patients with MetS defined by WHO criteria (44% vs 20%), in a population of 548 European diabetic patients.

A cross-sectional study involving 1414 South Indian diabetic patients described a lower prevalence of DR in patients with MetS compared to those without (16.9% vs 21.3%). However, the prevalence of DR in subjects with MetS was higher in patients with duration of diabetes less than 10 years and in women with diabetes duration of 11 to 20 years.³⁴

A Finnish study published in 2001 failed to achieve an association between MetS and DR in a sample of 85 type 2 diabetic patients with MetS (by WHO criteria) and 85 without MetS. However, severe DR was more prevalent in type 2 diabetic patients with MetS than in those without.³⁵

A study published in 2018 with 1986 type 2 diabetic Asian patients reported a higher prevalence of retinopathy in patients with MetS defined by NCEP-ATP III (37.9% in T2D+MetS vs 28.6% T2D without MetS, $P < .001$).³⁶

In the Diabetes Control and Complications Trial, which involved 1337 type 1 diabetic Caucasian patients, no association was found between DR and MetS (defined by IDF criteria).³⁷

In 2018, Zhou *et al* published a meta-analysis compiling the results of 12 observational studies which addressed this relationship between MetS and retinopathy in diabetic patients (most of them are abovementioned). The authors reported no association between MetS and DR in type 1 or type 2 diabetic patients. Moreover, no correlation was found between isolated MetS components (body mass index [BMI]/waist circumference, blood pressure [BP], HDL, and triglyceride levels) and retinopathy.³⁸

Metabolic syndrome and central retinal artery occlusion

CRAO is one of the most urgent and dramatic conditions in ophthalmology. It occurs when blockage in the central retinal artery develops within the optic nerve substance. The hallmark of retinal artery obstruction is abrupt and painless loss of vision.³⁹ The lack of arterial perfusion to the inner layers of the retina results in edema of the retinal nerve fiber layer and ganglion cell layer. The inner retina is multilayered throughout the posterior pole except at the fovea; thus, the retinal edema surrounds the fovea. In the fovea, the underlying choroid with intact retinal pigment epithelium (RPE) is visible and appears as a “cherry red spot” when compared to the cloudy, edematous retina adjacent to it.³⁹

Possible risk factors for the development of CRAO are arteriosclerosis, chronic atrial fibrillation, congestive heart failure, cerebrovascular accident, systemic hypertension, myocardial infarction, diabetes mellitus, primary open angle glaucoma (POAG), and rheumatic heart disease.⁴⁰

There are no prospective studies linking MetS with CRAO. However, there are 2 case reports of CRAO wherein the patients met all the 5 NCEP criteria of MetS.

The first one was published in 2005 and reported the case of a 52-year-old man with monocular and painless visual loss in his

right eye (no light perception). Fundoscopy showed signs compatible with CRAO and the laboratory investigation revealed raised erythrocyte sedimentation rate (105 mm/h) and C-reactive protein (CRP, 22 mg/L). Specific laboratory investigations and fluorescein angiography excluded the presence of vasculitis, collagen vascular diseases, hypercoagulable state, and antiphospholipid syndrome.³⁹

The second report was published in 2010 and described the case of a 64-year-old man who presented with abrupt, painless, and severe loss of vision in his left eye. Indirect ophthalmoscopy disclosed signs compatible with CRAO and laboratory investigations revealed erythrocyte sedimentation rate of 74 mm/h, CRP level of 21 mg/L, hyperglycemia, hyperuricemia, hypertriglyceridemia, and hypercholesterolemia. Fluorescein angiography and immunological studies excluded other systemic disorders.⁴¹

Both patients showed raised proinflammatory markers.^{39,41} Low-grade inflammation has been identified as a pivotal pathogenic factor for development of atherosclerosis and has been shown to predict myocardial infarction and stroke in patients with preexisting CVD.⁴² Increased CRP is associated with an increased risk of CVD. CRP may also be an important marker for complications of MetS such as CRAO.⁴³ The most common risk factors for CRAO are present in MetS. Thus, MetS can result in CRAO causing profound visual loss.¹⁶

In addition to these 2 case reports, there is evidence linking components of MetS with increased risk of CRAO. Obesity has been recognized as a significant risk for retinal vein occlusion in few studies.⁴⁴ Moreover, retinal venous and arterial occlusions are known to be associated with hypertension, diabetes mellitus, and hyperviscosity syndromes.⁴⁵ There is evidence supporting association of obesity with diabetes, hypertension, and hypercoagulable disorders, thus providing a possible association between obesity and retinal occlusive diseases.⁴⁶

Metabolic syndrome and cataract

A cataract is an opacification of the lens of the eye which leads to a decrease in vision. It represents a major public health problem, causing half of all cases of blindness and 33% of visual impairment worldwide.⁴⁷ Diabetes and hyperglycemia have long been recognized as risk factors for cataract.⁴⁷

The main mechanisms involved in the formation of cataract from MetS are oxidative stress, osmotic imbalance, and nonenzymatic protein glycation, physiopathological processes involved in MetS.⁴⁸

Hyperglycemia causes cataract via increasing nonenzymatic glycation of lens proteins, oxidative stress, and activation of polyol pathway with sorbitol accumulation.^{49–51} Oxidative stress was also found to have an effect on the rate of leucocyte telomere shortening, a marker of cataractogenesis.⁵²

Obesity was found to be linked to cataract via oxidative stress, inflammation, and endothelial dysfunction.⁵³ Inflammatory markers such as CRP, intracellular adhesion molecule-1, and interleukin-6 were found to be associated with cataract.^{54,55}

Serum lipids were also found to be associated with cataract formation. Large amount of adipose tissues causes hyperleptinemia and leptin resistance which facilitate formation of cataract.⁵⁶ Oxidative stress was also associated with high triglycerides and low HDL.⁵⁷ Diabetic rats induced by streptozotocin which were given cholesterol-rich diet led to earlier onset of cataract.⁵⁸

Association of hypertension with cataract is not well established. Animal studies found that cataract formation may

be linked to alterations in the protein structures of lens capsule, defective ion transport at the lens epithelium, and ciliary body and extracellular fluid volume state.⁵⁹⁻⁶¹

Most of the observational studies have shown an association between MetS and cataract.

In the Singapore Malay Eye Study, the prevalence of cataract rose with increasing number of MetS components in both men and women in a population-based sample of 3280 Malay adults aged 40 to 80 years. In this study, MetS and 2 of its principal components, diabetes, and high BP were significantly associated with cataract. Coexisting diabetes and high BP were associated with 4-fold higher odds of cataract. Serum triglycerides, HDL, and BMI were not found to be associated with cataract in this study. Among the subtypes, cortical cataract showed a positive association with MetS.⁶²

In the Blue Mountains Eye Study, a prospective cohort study of 3654 elderly Australian adults followed over 10 years, MetS was found to be associated with an increased risk of all subtypes of cataract including cortical, nuclear and posterior subcapsular cataract (PSC).⁶³ In the same population, Ghaem Maralani *et al*⁶⁴ reported changes in MetS to be associated with 5-year incidence of cortical cataract and posterior subcapsular cataract.

Paunksnis *et al*⁶⁵ have also reported an association between cataract and MetS among middle-aged European men and women. Bojarskiene *et al*'s⁶⁶ study found a higher prevalence of cataract in people with MetS, but it was only significant in women.⁶⁶

Furthermore, MetS, its components, and their combination were found to be associated with an increased risk of cataract extraction in an Italian hospital population and among Swedish women younger than 65 years.^{67,68}

Metabolic syndrome and age-related macular degeneration

AMD is a leading cause of severe, irreversible vision impairment in developed countries.⁶⁹ Despite major geographical and lifestyle differences, its prevalence is rising all over the world, increasing sharply with age. This condition represents an acquired degeneration of the retina that causes significant central visual impairment through a combination of non-neovascular and neovascular derangement. The early and intermediate stages of AMD are characterized by the presence of pigmentary abnormalities and drusen in the macular area. Late AMD has 2 forms: geographic atrophy with major loss of the RPE and choriocapillaris; and neovascular AMD with newly formed blood vessels in the macular region that lead to leakage of blood and serum, causing an irreversible damage and progressive vision loss.⁶⁹

The exact pathophysiology of AMD is relatively poorly understood. As the RPE cells age, their metabolic and phagocytic functions decrease, leading to the accumulation of lipofuscin. Decreased RPE function and changes in the permeability of Bruch membrane also lead to deposition of material between the RPE and Bruch's membrane, accounting for the formation of drusen. Drusen physically impact RPE and photoreceptor layers and also seem to promote immune system activation, local inflammation, and oxidative stress. These processes stimulate a rise in vascular endothelial growth factors and can result in a breakdown of Bruch's membrane, leading to the growth of abnormal choroidal vessels toward the retina. The new vessels are associated with fluid leakage and hemorrhage, affecting retina structure and function. The end-stage of exudative AMD is the formation of a disciform scar in the macula that results in permanent loss of central vision.⁷⁰

The Age-Related Eye Disease Study has reported a cross-sectional association between higher BMI and more advanced AMD as documented from fundus photographs.⁷¹ Obesity increases systemic oxidative stress secondary to hyperleptinemia, and oxidative stress is known to play an important role in the pathogenesis of AMD.⁷²

Fitzgerald *et al*⁷³ in 2013 also hypothesized that elevated norepinephrine could be a common etiological factor for both AMD and MetS, leading to inflammation and immune system dysregulation.

There is only one study addressing the relationship between MetS and AMD. In this study no significant association was found between MetS and early AMD. However, in adults younger than 70 years, MetS was associated with an increased risk for late AMD. In the same study, among the individual components, obesity, high glucose, and high triglycerides blood levels were found to be associated with the progression of early to late AMD.⁷⁴

Some studies reported an association between AMD and obesity. Howard *et al*⁷⁵ found that obesity, measured in terms of BMI or waist circumference had an association with both early and late AMD in women who were nonsmokers. In a cross-sectional study involving adults aged 65 to 87 years in Norway, Erke *et al*⁷⁶ found an association of hypertension and obesity with late AMD only in women. However, Adams *et al* found that association between obesity and AMD was not consistent in a study involving 21,287 European adults. In fact, there was a negative association between all adiposity measures with early AMD in women.⁷⁷

Klein *et al*⁷⁸ in a pooled analysis involving 3 population-based cohorts found serum total cholesterol to be significantly associated with incident AMD.

In a retrospective study involving 10,449 Korean adults, Moon *et al*⁷⁹ found hyperlipidemia to be associated with early AMD. The same component was found to be associated with incident geographic atrophy but had an inverse relationship with incident neovascular AMD in a study by Tomany *et al*.⁸⁰

Metabolic syndrome and glaucoma

Glaucoma describes a group of conditions in which there is characteristic cupping of the optic disc with corresponding visual field defects, due to retinal ganglion cell loss. It is a progressive condition and is the most common cause of irreversible blindness worldwide. POAG is a subset defined by an open, normal appearing anterior chamber angle and raised intraocular pressure (IOP), with no other underlying disease. If there is an identifiable underlying cause for raised IOP, this is termed secondary glaucoma. If the IOP is within normal limits, this is termed normal tension glaucoma (NTG).⁸¹

Many cross-sectional and longitudinal epidemiological studies have reported association of elevated IOP with cardiometabolic risk factors such as type 2 diabetes mellitus, hypertension, and concurrent atherosclerotic disease, thereby suggesting a common underlying mechanism linking elevated IOP to various cardiometabolic factors.^{82,83} Chang *et al* analyzed the clinical data of 1112 patients undergoing health checkup and concluded that participants with MetS had significantly higher IOP than those without MetS. Each additional component of MetS was associated with a mean increase in IOP of 0.33 mm Hg.⁸⁴ Their findings were consistent with those reported by Oh *et al*⁸⁵ in the Korean population.

Jung et al in 2019 studied the incidence of POAG in metabolically healthy obese patients and metabolically unhealthy nonobese patients. Of the total 287,553 subjects included in the study, 4970 (1.3%) developed POAG. High fasting glucose, BP, and total cholesterol levels were all associated with increased risk of developing POAG. Regarding obesity level, people with BMI >30 kg/m² were more likely to develop POAG than those with normal BMI. Also, people with greater number of MetS components showed a greater POAG incidence. People who were metabolically unhealthy and obese (adjusted hazard ratio [HR], 1.574; 95% confidence interval [CI], 1.449–1.711) and those who were metabolically unhealthy nonobese (adjusted HR, 1.521; 95% CI, 1.405–1.645) but not those who were metabolically healthy obese (adjusted HR, 1.019; 95% CI, 0.907–1.144) had an increased hazard of developing POAG compared with metabolically healthy nonobese subjects.⁸⁶

A case-control study on 18,240 South Koreans, Kim et al found that MetS was not significantly associated with NTG. However, several studies have examined the association of individual components with glaucoma. Kim et al⁸⁷ found hypertension and impaired glucose tolerance to be associated with NTG.

The mechanism by which MetS is associated with IOP is currently unknown. Recent research has revealed some pathophysiological links such as sympathetic stimulation, endocannabinoid overactivity, and aquaporins.

Sympathetic hyperstimulation is a common feature of obesity, hypertension, and insulin resistance.⁸⁸ Stimulation of ocular sympathetic nerves also increases IOP.⁸⁹

Similarly, endocannabinoid overactivity contributes to the development of abdominal obesity, dyslipidemia, and hyperglycemia. In rodents, endocannabinoid receptors have been found in the trabecular meshwork where they regulate aqueous outflow and thus influence IOP.⁹⁰

Aquaporin is a family of small membrane proteins that transport water and small molecules. They are present in various human tissues including trabecular meshwork in the eye, adipose tissue, liver, and pancreas. Aquaporins have been shown to increase aqueous fluid secretion across ciliary epithelium and regulate IOP.⁹¹ Unexpectedly, aquaporin knockout mice were obese and developed severe insulin resistance, pointing toward another possible link between IOP and MetS.⁹²

Concerning MetS components, diabetes can either increase IOP or damage optic nerve's supplying vessels. Diabetes-induced autonomic dysfunction and corneal stiffening from glycation-induced corneal collagen cross-linking have been shown to increase IOP. Oxidative stress and vascular dysfunction associated to diabetes affect the small vessels supplying the optic nerve.⁹³ Atherosclerotic vessels that supply the optic nerve may also lead to glaucomatous changes.⁹⁴ Hypertension may increase ciliary artery perfusion and consequently increase aqueous production.^{95,96} There is no clear association between dyslipidemia and glaucoma. However, statins have been found to increase aqueous outflow and some studies have shown that individuals treated for hyperlipidemia have a reduced risk of OAG.^{49,50,97} The excessive orbital fat and increased blood viscosity seen in diabetes may increase episcleral venous pressure and reduce aqueous outflow, consequently raising IOP.¹⁷

Population-based data from several studies have demonstrated independent cross-sectional association between obesity and ocular hypertension. The Beaver Dam Eye Study reported a significantly positive association of IOP with several factors including BMI.⁹⁸ Obesity exerts an effect on IOP by causing excessive intraorbital adipose tissue, increased blood viscosity,

increased episcleral venous pressure, and impairment of aqueous outflow facility.⁹⁶ Also, obesity has been shown to cause vascular endothelial dysfunction and autonomic dysfunction.⁹⁹ This may cause abnormal ocular blood flow and perfusion instability leading to impaired vascular supply to the optic nerve head and glaucomatous changes.¹⁰⁰ Hyperleptinemia can also lead to oxidative stress and may affect the function of the trabecular meshwork.^{101,102}

Metabolic syndrome and dry eye disease. DED is increasingly recognized as a serious, worldwide public health concern.¹⁰³ DED may result from reduced aqueous tear flow or increased tear evaporation.¹⁰⁴ A disrupted ocular surface may also disturb tear film homeostasis, causing DED.¹⁰⁴ Regardless of the initiating etiology, inflammation is usually a key factor in the development of DED.¹⁰⁵ MetS is also a well-known chronic and systemic low-grade inflammatory condition, which could explain a link with DED.¹⁰⁶

There are only 4 published studies addressing this possible association:

- A 2014 study done on 672 Japanese by Kawashima et al¹⁰⁷ showed that tear volume was significantly reduced in patients with MetS.
- Park and Park in 2016 studied a sample of 15,294 adults from the Korea National Health and Nutrition Examination Survey V and reported no significant association between MetS and DED in men and women. However, a significant association was observed between DED and hypertriglyceridemia in women (OR, 1.13; 95% CI, 1.01–1.29).¹⁰³
- Serefoglu Cabuk et al in 2016 evaluated the prevalence of DED in 44 Turkish patients with MetS and 43 healthy controls. No statistically significant difference was found in tear osmolarity, tear film break-up time and symptoms questionnaire scores between MetS and control group. However, tear volume assessed by Schirmer test was significantly lower in MetS group (14.8 ± 9.4 vs 20.4 ± 9.4 mm, $P = .007$). In women subgroup, tear osmolarity was significantly higher in MetS group compared to the normal group (309.4 ± 13.1 vs 301.2 ± 8.7 mOsm/L, $P = .012$).¹⁰⁸
- Another study in Turkish patients by Erdur et al in 2017 compared 64 patients with MetS and 55 healthy controls and found higher levels of tear osmolarity and symptoms questionnaire scores and lower values in Schirmer test and tear film break-up time in the first group. There was also significant correlation between tear osmolarity and waist circumference or fasting blood glucose.¹⁰⁹

CONCLUSION

Noncommunicable diseases have replaced infections as the new health hazards of the modern world. MetS represents the epitome of western lifestyle and a risk factor for many diseases. Eye diseases associated with visual loss and diminished quality of life, such as DR, CRAO, cataract, AMD, glaucoma, and DED are linked with many of MetS components and with the whole cluster of metabolic derangements, as shown in this review. From the gathered evidence, we show a consistent association between MetS and retinopathy in patients with type 2 diabetes, cataract, increased IOP, and DED. There is, however, a paucity of evidence linking MetS with increased risk of CRAO and AMD, even though these associations seem very plausible. The relationship between MetS and retinopathy in type 1 diabetic also needs

additional investigation. Because there is increasing evidence that individual components of MetS are related to different eye diseases, further studies are required to evaluate the relationship between MetS and these diseases. Exploring this interaction, both in populational and animal studies, is crucial to solidify association and causality between MetS and ocular findings and to unveil the pathological pathways that ultimately lead to disease. MetS has become a new target to control age-related eye diseases and prevent vision loss.

ACKNOWLEDGMENTS

Financial support and sponsorship

None.

Conflicts of interest

None.

References

- [1] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
- [2] Samson SL, Garber AJ. Metabolic syndrome. *Endocrinol Metab Clin North Am*. 2014;43:1–23.
- [3] Wang HH, Lee DK, Liu M, Portincasa P, Wang DQ. Novel insights into the pathogenesis and management of the metabolic syndrome. *Pediatr Gastroenterol Hepatol Nutr*. 2020;23:189–230.
- [4] McCullough AJ. Epidemiology of the metabolic syndrome in the USA. *J Dig Dis*. 2011;12:333–340.
- [5] Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20:12.
- [6] Raposo L, Severo M, Barros H, Santos AC. The prevalence of the metabolic syndrome in Portugal: the PORMETS study. *BMC Public Health*. 2017;17:555.
- [7] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
- [8] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol Rev*. 2005;13:322–327.
- [9] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469–480.
- [10] Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
- [11] Genser L, Casella Mariolo JR, Castagneto-Gissey L, Panagiotopoulos S, Rubino F. Obesity, type 2 diabetes, and the metabolic syndrome: pathophysiologic relationships and guidelines for surgical intervention. *Surg Clin North Am*. 2016;96:681–701.
- [12] Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome. *Lancet*. 2005;366:1921–1922. author reply 3–4.
- [13] Young DR, Hivert MF, Alhassan S, et al. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279.
- [14] Ekelund U, Ward HA, Norat T, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr*. 2015;101:613–621.
- [15] Bozkurt B, Aguilar D, Deswal A, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e535–e578.
- [16] Chopra R, Chander A, Jacob JJ. Ocular associations of metabolic syndrome. *Indian J Endocrinol Metab*. 2012;16 (suppl 1):S6–S11.
- [17] Poh S, Mohamed Abdul RB, Lamoureux EL, Wong TY, Sabanayagam C. Metabolic syndrome and eye diseases. *Diabetes Res Clin Pract*. 2016;113:86–100.
- [18] Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol*. 2001;46:59–80.
- [19] Wong TY, Duncan BB, Golden SH, et al. Associations of the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. *Invest Ophthalmol Vis Sci*. 2004;45:2949–2954.
- [20] Zhao Y, Yang K, Wang F, et al. Associations between metabolic syndrome and syndrome components and retinal microvascular signs in a rural Chinese population: the Handan Eye Study. *Graefes Arch Clin Exp Ophthalmol*. 2012;50:1755–1763.
- [21] Saito K, Nagao Y, Yamashita H, Kawasaki R. Screening for retinal vessel caliber and its association with metabolic syndrome in Japanese adults. *Metab Syndr Relat Disord*. 2011;9:427–432.
- [22] Kawasaki R, Tielsch JM, Wang JJ, et al. The metabolic syndrome and retinal microvascular signs in a Japanese population: the Funagata study. *Br J Ophthalmol*. 2008;92:161–166.
- [23] Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology*. 2018;125:1608–1622.
- [24] Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40:412–418.
- [25] Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556–564.
- [26] Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci U S A*. 2000;97:12222–12226.
- [27] Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature*. 2000;404:787–790.
- [28] Reddy MA, Zhang E, Natarajan R. Epigenetic mechanisms in diabetic complications and metabolic memory. *Diabetologia*. 2015;58:443–455.
- [29] Roy S, Trudeau K, Roy S, Tien T, Barrette KF. Mitochondrial dysfunction and endoplasmic reticulum stress in diabetic retinopathy: mechanistic insights into high glucose-induced retinal cell death. *Curr Clin Pharmacol*. 2013;8:278–284.
- [30] Yuuki T, Kanda T, Kimura Y, et al. Inflammatory cytokines in vitreous fluid and serum of patients with diabetic vitreoretinopathy. *J Diabetes Complications*. 2001;15:257–259.
- [31] Abdul-Ghani M, Nawaf G, Nawaf F, Itzhak B, Minuchin O, Vardi P. Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome. *Isr Med Assoc J*. 2006;8:378–382.
- [32] Bonadonna R, Cucinotta D, Fedele D, Riccardi G, Tiengo A. The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: results from Metascreen, a multicenter diabetes clinic-based survey. *Diabetes Care*. 2006;29:2701–2707.
- [33] Costa LA, Canani LH, Lisboa HR, Tres GS, Gross JL. Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in Type 2 diabetes. *Diabet Med*. 2004;21:252–255.
- [34] Raman R, Gupta A, Pal SS, et al. Prevalence of metabolic syndrome and its influence on microvascular complications in the Indian population with type 2 diabetes mellitus. *Sankara Nethralaya Diabetic Retinopathy Epidemiology And Molecular Genetic Study (SN-DREAMS, report 14)*. *Diabetol Metab Syndr*. 2010;2:67.
- [35] Isomaa B, Henricsson M, Almgren P, Tuomi T, Taskinen MR, Groop L. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. *Diabetologia*. 2001;44:1148–1154.
- [36] Lee MY, Hsiao PJ, Huang JC, Hsu WH, Chen SC, Shin SJ. Association between metabolic syndrome and microvascular and macrovascular disease in type 2 diabetic mellitus. *Am J Med Sci*. 2018;355:342–349.
- [37] Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: “double diabetes” in the Diabetes Control and Complications Trial. *Diabetes Care*. 2007;30:707–712.

- [38] Zhou Y, Wang C, Shi K, Yin X. Relation of metabolic syndrome and its components with risk of diabetic retinopathy: a meta-analysis of observational studies. *Medicine (Baltimore)*. 2018;97:e12433.
- [39] Kosanović-Jaković N, Petrović L, Risić D, Milenković S, Matić D. Metabolic syndrome and central retinal artery occlusion. *Vojnosanit Pregl*. 2005;62:935–938.
- [40] Mangat HS. Retinal artery occlusion. *Surv Ophthalmol*. 1995;40:145–156.
- [41] Cekić SP, Petković T, Stanković-Babić GL, Mršić JM. Central retinal artery occlusion in a patient with metabolic syndrome x. *J Ophthalmic Vis Res*. 2010;5:57–60.
- [42] Alexander RW. Inflammation and coronary artery disease. *N Engl J Med*. 1994;331:468–469.
- [43] Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet*. 1997;349:462–466.
- [44] Backhouse O, Parapia L, Mahomed I, Lee D. Familial thrombophilia and retinal vein occlusion. *Eye (Lond)*. 2000;14 (pt 1):13–17.
- [45] Lahey JM, Kearney JJ, Tunc M. Hypercoagulable states and central retinal vein occlusion. *Curr Opin Pulm Med*. 2003;9:385–392.
- [46] Abramson N, Abramson S. Hypercoagulability: clinical assessment and treatment. *South Med J*. 2001;94:1013–1020.
- [47] Kiziltoprak H, Tekin K, Inanc M, Goker YS. Cataract in diabetes mellitus. *World J Diabetes*. 2019;10:140–153.
- [48] Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. *Panminerva Med*. 2005;47:201–210.
- [49] Perejda AJ, Uitto J. Nonenzymatic glycosylation of collagen and other proteins: relationship to development of diabetic complications. *Coll Relat Res*. 1982;2:81–88.
- [50] Reddy PY, Giridharan NV, Reddy GB. Activation of sorbitol pathway in metabolic syndrome and increased susceptibility to cataract in Wistar-Obe rats. *Mol Vis*. 2012;18:495–503.
- [51] Suryanarayana P, Patil MA, Reddy GB. Insulin resistance mediated biochemical alterations in eye lens of neonatal streptozotocin-induced diabetic rat. *Indian J Exp Biol*. 2011;49:749–755.
- [52] Sanders JL, Iannaccone A, Boudreau RM, et al. The association of cataract with leukocyte telomere length in older adults: defining a new marker of aging. *J Gerontol A Biol Sci Med Sci*. 2011;66:639–645.
- [53] Abraham AG, Condon NG, West Gower E. The new epidemiology of cataract. *Ophthalmol Clin North Am*. 2006;19:415–425.
- [54] Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. *Ann Epidemiol*. 1999;9:166–171.
- [55] Klein BE, Klein R, Lee KE, Knudtson MD, Tsai MY. Markers of inflammation, vascular endothelial dysfunction, and age-related cataract. *Am J Ophthalmol*. 2006;141:116–122.
- [56] Gómez-Ambrosi J, Salvador J, Frühbeck G. Is hyperleptinemia involved in the development of age-related lens opacities? *Am J Clin Nutr*. 2004;79:888–889. author reply 9.
- [57] Katsuki A, Sumida Y, Urakawa H, et al. Increased oxidative stress is associated with serum levels of triglyceride, insulin resistance, and hyperinsulinemia in Japanese metabolically obese, normal-weight men. *Diabetes Care*. 2004;27:631–632.
- [58] Tsutsumi K, Inoue Y, Yoshida C. Acceleration of development of diabetic cataract by hyperlipidemia and low high-density lipoprotein in rats. *Biol Pharm Bull*. 1999;22:37–41.
- [59] Lee SM, Lin SY, Li MJ, Liang RC. Possible mechanism of exacerbating cataract formation in cataractous human lens capsules induced by systemic hypertension or glaucoma. *Ophthalmic Res*. 1997;29:83–90.
- [60] Rodríguez-Sargent C, Cangiano JL, Berrios Cabán G, Marrero E, Martínez-Maldonado M. Cataracts and hypertension in salt-sensitive rats. A possible ion transport defect. *Hypertension*. 1987;9:304–308.
- [61] Rodríguez-Sargent C, Berrios G, Irizarry JE, Estapé ES, Cangiano JL, Martínez-Maldonado M. Prevention and reversal of cataracts in genetically hypertensive rats through sodium restriction. *Invest Ophthalmol Vis Sci*. 1989;30:2356–2360.
- [62] Sabanayagam C, Wang JJ, Mitchell P, et al. Metabolic syndrome components and age-related cataract: the Singapore Malay eye study. *Invest Ophthalmol Vis Sci*. 2011;52:2397–2404.
- [63] Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008;15:317–327.
- [64] Ghaem Maralani H, Tai BC, Wong TY, et al. Metabolic syndrome and risk of age-related cataract over time: an analysis of interval-censored data using a random-effects model. *Invest Ophthalmol Vis Sci*. 2013;54:641–646.
- [65] Paunksnis A, Bojarskiene F, Cimbalas A, Cerniauskiene LR, Luksiene DI, Tamosiunas A. Relation between cataract and metabolic syndrome and its components. *Eur J Ophthalmol*. 2007;17:605–614.
- [66] Bojarskiene F, Cerniauskiene LR, Paunksnis A, Luksiene DI. Association of metabolic syndrome components with cataract. *Medicina (Kaunas)*. 2006;42:115–122.
- [67] Galeone C, Petracchi E, Pelucchi C, Zucchetto A, La Vecchia C, Tavani A. Metabolic syndrome, its components and risk of age-related cataract extraction: a case-control study in Italy. *Ann Epidemiol*. 2010;20:380–384.
- [68] Lindblad BE, Håkansson N, Philipson B, Wolk A. Metabolic syndrome components in relation to risk of cataract extraction: a prospective cohort study of women. *Ophthalmology*. 2008;115:1687–1692.
- [69] Carneiro Á, Andrade JP. Nutritional and lifestyle interventions for age-related macular degeneration: a review. *Oxid Med Cell Longev*. 2017;2017:6469138.
- [70] Nowak JZ. Age-related macular degeneration (AMD): pathogenesis and therapy. *Pharmacol Rep*. 2006;58:353–363.
- [71] Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: age-related eye disease study report number 3. *Ophthalmology*. 2000;107:2224–2232.
- [72] Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. *Faseb j*. 1999;13:1231–1238.
- [73] Fitzgerald PJ. Elevated norepinephrine may be an etiological factor in a wide range of diseases: age-related macular degeneration, systemic lupus erythematosus, atrial fibrillation, metabolic syndrome. *Med Hypotheses*. 2013;80:558–563.
- [74] Ghaem Maralani H, Tai BC, Wong TY, et al. Metabolic syndrome and risk of age-related macular degeneration. *Retina*. 2015;35:459–466.
- [75] Howard KP, Klein BE, Lee KE, Klein R. Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*. 2014;55:2592–2598.
- [76] Erke MG, Bertelsen G, Peto T, Sjølie AK, Lindekleiv H, Njølstad I. Cardiovascular risk factors associated with age-related macular degeneration: the Tromsø Study. *Acta Ophthalmol*. 2014;92:662–669.
- [77] Adams MK, Simpson JA, Aung KZ, et al. Abdominal obesity and age-related macular degeneration. *Am J Epidemiol*. 2011;173:1246–1255.
- [78] Klein R, Myers CE, Buitendijk GH, et al. Lipids, lipid genes, and incident age-related macular degeneration: the three continent age-related macular degeneration consortium. *Am J Ophthalmol*. 2014;158:513.e3–524.e3.
- [79] Moon BG, Joe SG, Hwang JU, Kim HK, Choe J, Yoon YH. Prevalence and risk factors of early-stage age-related macular degeneration in patients examined at a health promotion center in Korea. *J Korean Med Sci*. 2012;27:537–541.
- [80] Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology*. 2004;111:1280–1287.
- [81] European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th edition—chapter 2: classification and terminology supported by the EGS Foundation. *Br J Ophthalmol*. 2017;101:73–127.
- [82] Lee JS, Lee SH, Oum BS, Chung JS, Cho BM, Hong JW. Relationship between intraocular pressure and systemic health parameters in a Korean population. *Clin Exp Ophthalmol*. 2002;30:237–241.
- [83] Memarzadeh F, Ying-Lai M, Azen SP, Varma R. Associations with intraocular pressure in Latinos: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2008;146:69–76.
- [84] Chang YC, Lin JW, Wang LC, Chen HM, Hwang JJ, Chuang LM. Association of intraocular pressure with the metabolic syndrome and novel cardiometabolic risk factors. *Eye (Lond)*. 2010;24:1037–1043.
- [85] Oh SW, Lee S, Park C, Kim DJ. Elevated intraocular pressure is associated with insulin resistance and metabolic syndrome. *Diabetes Metab Res Rev*. 2005;21:434–440.
- [86] Jung Y, Han K, Park HYL, Lee SH, Park CK. Metabolic health, obesity, and the risk of developing open-angle glaucoma: metabolically healthy obese patients versus metabolically unhealthy but normal weight patients. *Diabetes Metab J*. 2019;44:414–425.
- [87] Kim M, Jeoung JW, Park KH, Oh WH, Choi HJ, Kim DM. Metabolic syndrome as a risk factor in normal-tension glaucoma. *Acta Ophthalmol*. 2014;92:e637–e643.
- [88] Mancia G, Bousquet P, Elghozi JL, et al. The sympathetic nervous system and the metabolic syndrome. *J Hypertens*. 2007;25:909–920.

- [89] Belmonte C, Bartels SP, Liu JH, Neufeld AH. Effects of stimulation of the ocular sympathetic nerves on IOP and aqueous humor flow. *Invest Ophthalmol Vis Sci.* 1987;28:1649–1654.
- [90] Järvinen T, Pate DW, Laine K. Cannabinoids in the treatment of glaucoma. *Pharmacol Ther.* 2002;95:203–220.
- [91] Verkman AS. Role of aquaporin water channels in eye function. *Exp Eye Res.* 2003;76:137–143.
- [92] MacDougald OA, Burant CF. Obesity and metabolic perturbations after loss of aquaporin 7, the adipose glycerol transporter. *Proc Natl Acad Sci U S A.* 2005;102:10759–10760.
- [93] Szaflik JP, Rusin P, Zaleska-Zmijewska A, Kowalski M, Majsterek I, Szaflik J. Reactive oxygen species promote localized DNA damage in glaucoma-iris tissues of elderly patients vulnerable to diabetic injury. *Mutat Res.* 2010;697:19–23.
- [94] Wolf S, Arend O, Sponsel WE, Schulte K, Cantor LB, Reim M. Retinal hemodynamics using scanning laser ophthalmoscopy and hemorheology in chronic open-angle glaucoma. *Ophthalmology.* 1993;100:1561–1566.
- [95] Bulpitt CJ, Hodes C, Everitt MG. Intraocular pressure and systemic blood pressure in the elderly. *Br J Ophthalmol.* 1975;59:717–720.
- [96] Shiose Y, Kawase Y. A new approach to stratified normal intraocular pressure in a general population. *Am J Ophthalmol.* 1986;101:714–721.
- [97] De Castro DK, Punjabi OS, Bostrom AG, et al. Effect of statin drugs and aspirin on progression in open-angle glaucoma suspects using confocal scanning laser ophthalmoscopy. *Clin Exp Ophthalmol.* 2007;35:506–513.
- [98] Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci.* 1992;33:2224–2228.
- [99] Głowińska B, Urban M, Hryniewicz A, Peczyńska J, Florys B, Al-Hwish M. Endothelin-1 plasma concentration in children and adolescents with atherogenic risk factors. *Kardiol Pol.* 2004;61:329–338.
- [100] Broadway DC, Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol.* 1998;82:862–870.
- [101] Izzotti A, Saccà SC, Cartiglia C, De Flora S. Oxidative deoxyribonucleic acid damage in the eyes of glaucoma patients. *Am J Med.* 2003;114:638–646.
- [102] Saccà SC, Pascotto A, Camicione P, Capris P, Izzotti A. Oxidative DNA damage in the human trabecular meshwork: clinical correlation in patients with primary open-angle glaucoma. *Arch Ophthalmol.* 2005;123:458–463.
- [103] Park HW, Park JW. The association between symptoms of dry eye syndrome and metabolic outcome in a general population in Korea. *J Korean Med Sci.* 2016;31:1121–1126.
- [104] The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf.* 2007;5:75–92.
- [105] Miljanović B, Trivedi KA, Dana MR, Gilbert JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. *Am J Clin Nutr.* 2005;82:887–893.
- [106] Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444:860–867.
- [107] Kawashima M, Uchino M, Yokoi N, et al. Decreased tear volume in patients with metabolic syndrome: the Osaka study. *Br J Ophthalmol.* 2014;98:418–420.
- [108] Serefoglu Cabuk K, Cakir İ, Kirgiz A, Atalay K, Taskapili M. Dry eye disease in patients with metabolic syndrome. *Saudi Med J.* 2016;37:1334–1338.
- [109] Erdur SK, Aydin R, Ozsutcu M, et al. The relationship between metabolic syndrome, its components, and dry eye: a cross-sectional study. *Curr Eye Res.* 2017;42:1115–1117.