Review Article

Ocular associations of metabolic syndrome

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ABSTRACT

Metabolic syndrome is a cluster of diseases including central obesity, dyslipidemia, hyperglycemia, and high blood pressure. People with metabolic syndrome have been shown to be at an increased risk of developing cardiovascular disease, beyond the risk associated with individual components of the syndrome. The association of diabetes and hypertension with retinopathy, cataract, and raised intraocular pressure is well known. This review highlights the association of metabolic syndrome, including all its components, with various ocular conditions such as retinopathy, central retinal artery occlusion, cataracts, and raised intraocular pressure.

Key words: Cataract, central retinal artery occlusion, intraocular pressure, metabolic syndrome, retinopathy

Introduction

Almost all patients with diabetes/pre-diabetes and concomitant cardiovascular disease (CVD) risk factors of hypertension, obesity, and dyslipidemia also have insulin resistance.[1] The clustering of these risk factors in a single patient has been termed the metabolic syndrome. The components of metabolic syndrome include abdominal obesity, diabetes, glucose intolerance, dyslipidemia, high blood pressure, and hyperuricemia.[2] The association of diabetes and hypertension with ocular conditions such as retinopathy,[3] cataract,[4] and raised intraocular pressure (IOP)[5,6] is well known. Metabolic syndrome is increasingly being recognized as a distinct identity and this review is an attempt to highlight the association between metabolic syndrome and various ocular conditions such as non-diabetic retinopathy, cataract, and primary open angle glaucoma.

Diagnostic Criteria for Metabolic Syndrome

According to the National Cholesterol Education Program (NCEP) guidelines, the metabolic syndrome is based on the presence of three of the following five risk factors.[7]

- Abdominal obesity (waist circumference >40 inches in men, >35 inches in women)
- Plasma triglycerides 150 mg/dL
- Plasma high density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women
- Blood pressure 130/85 mmHg
- Fasting plasma glucose 110 mg/dL.

Epidemiology

The syndrome is increasingly being recognized as a distinct entity affecting a large proportion of US adult population.[8] The prevalence of metabolic syndrome as defined by the NCEP guidelines has been estimated using the National Health and Nutritional Examination Survey (NHANES) database.[8] Based on the data from NHANES collected between 1999 and 2002, the prevalence of metabolic syndrome is 34.5%.[9] The prevalence of metabolic syndrome in our country ranges from 20 to 55%. Much higher prevalence is seen among people in urban areas and those from higher socioeconomic strata.[10]

Ocular Associations of Metabolic Syndrome

Retinal microvascular signs

Persons with metabolic syndrome are known to be at risk of developing large vessel atherosclerotic disease.[11] Characteristics of large and small vessel disease such

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as inflammation and endothelial dysfunction have been reported to be associated with metabolic syndrome.[12] The association of diabetes and hypertension with retinopathy and other microvascular changes is well known.[3] Recent studies have shown that these retinal vascular signs are also associated with systemic markers of inflammation and endothelial dysfunction.[13] In a population-based cross-sectional study involving 11,265 persons, retinal photographs were taken and graded for the presence of retinal microvascular signs. The data showed that persons with metabolic syndrome 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, gender, race, education, cigarette smoking, and alcohol consumption. With the exception of retinopathy, most associations were significant even in people without diabetes or hypertension, suggesting that factors other than hyperglycemia and high blood pressure (i.e. dyslipidemia, obesity, and inflammation) may explain the occurrence of these retinal lesions.[14]

In another study conducted among Japanese adults, the various components of the metabolic syndrome were found to be associated with retinal microvascular signs: a larger waist circumference was associated with wider venular diameter and retinopathy lesions; a higher blood pressure level was associated with focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex, and narrower arteriolar diameter; and a higher triglyceride level was associated with enhanced arteriolar wall reflex. Overall, persons with the metabolic syndrome were more likely to have retinopathy (odds ratio 1.64, 95% CI: 1.02–2.64) and wider venular diameter of 4.69 μm (95% CI: 1.20–8.19 μm) than persons without the metabolic syndrome in this study.[15]

The association between metabolic syndrome and retinopathy was also studied in persons 40 years of age and older with gradable fundus photographs in the NHANES III. However, in this population-based cross-sectional study, there was no evidence of an association between the metabolic syndrome and retinopathy independent of diabetic status.[16] Thus, prospective studies are warranted to determine the casual link between metabolic syndrome and the risk of retinopathy and other microvascular changes.

Obesity, one of the major components of metabolic syndrome, has been shown to be associated with retinopathy signs in the general and non-diabetic population.[17] In the Hoorn Study in the Netherlands, waist–hip ratio was independently associated with a number of incident retinopathy signs including retinal hemorrhages, microaneurysms, hard exudates, and cotton wool spots in the non-diabetic general population, although the association with body mass index (BMI) failed to achieve a statistical significance.[18] Vasoproliferative factors such as vascular endothelial growth factor (VEGF) have been proposed to have a role in the pathogenesis of diabetic retinopathy.[19] The concentrations of serum angiogenic factors such as VEGF have been observed to be elevated in obese humans.[20] These findings provide a potential link between obesity and retinopathy. Moreover, oxidative stress also contributes to development of diabetic retinopathy by inducing overexpression of VEGF.[21] Obesity increases oxidative stress because of its associated hyperleptinemias.[22]

Central retinal artery occlusion

It is one of the most sudden and dramatic events seen by the ophthalmologist. Patients usually present with a sudden painless loss of vision. The appearance of a cherry-red spot in the fundus is the main characteristic. The cherry-red spot appears because soon after the obstruction of the blood flow to the inner retina, the normally transparent retina becomes opaque and blocks the brownish-red color from the underlying choroid, which is still supplied by blood. Because the retina overlying the foveola is relatively thin, however, the normal color of the choroid is still visible in this area.

Possible risk factors for the development of central retinal artery occlusion (CRAO) [Figure 1] are arteriosclerosis, chronic atrial fibrillation, congestive heart failure, cerebrovascular accident, systemic hypertension, myocardial infarction, diabetes mellitus, primary open angle glaucoma, and rheumatic heart disease.[23]

Our literature search reveals two case reports of CRAO wherein the patients met all the five NCEP criteria of

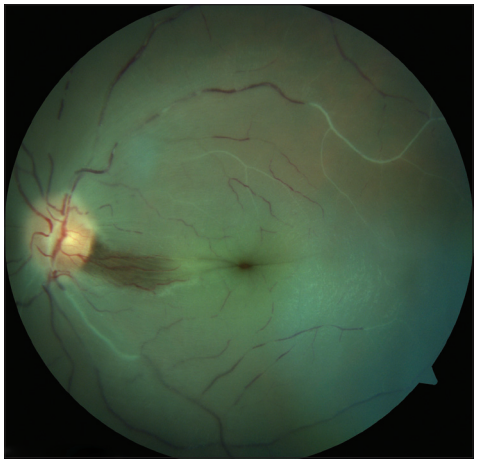

Figure 1: Central retinal artery occlusion

metabolic syndrome. The pro-inflammatory markers were found to be raised in both the cases.[24,25] 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.[26] Increased C-reactive protein (CRP) is associated with an increase risk of CVD. CRP may also be an important marker for complications of metabolic syndrome such as CRAO.[27] The most common risk factors for CRAO are present in metabolic syndrome. Thus, metabolic syndrome can result in CRAO causing profound visual loss. Other than these isolated case reports, our literature search did not reveal any prospective studies linking metabolic syndrome with CRAO. However, obesity has been recognized as a significant risk for retinal vein occlusion in few studies.[28] Moreover, retinal venous and arterial occlusions are known to be associated with hypertension, diabetes mellitus, and hyperviscosity syndromes.[29] There is evidence supporting association of obesity with diabetes, hypertension, and hypercoagulable disorders, thus providing a possible association between obesity and retinal occlusive diseases.[30]

Age-related maculopathy

The relationship between age-related maculopathy (ARM) and obesity has been investigated in several studies. The Age Related Eye Disease Study (AREDS) has reported a cross-sectional association between higher BMI and more advanced ARM as documented from fundus photographs.[31] Obesity increases systemic oxidative stress secondary to hyperleptinemia, and oxidative stress is known to play an important role in the pathogenesis of ARM.[22]

Age-related cataract

Cataract, a leading cause of blindness and poor vision, is a major public health problem worldwide, particularly in Asia, home to half of the world's population.[32] Diabetes and hyperglycemia have long been recognized as risk factors for cataract. Various studies conducted in the Western and Asian populations have shown an association between metabolic syndrome and cataract. In the Singapore Malay Eye Study,[33] the prevalence of cataract increased with increasing number of metabolic syndrome components in both men and women. In this study, metabolic syndrome and two of its principal components, diabetes and high BP, were significantly associated with cataract, assessed from lens photographs in a standardized manner. Coexisting diabetes and high BP were associated with fourfold higher odds of cataract. Serum triglycerides, HDL, and BMI were not found to be associated with cataract in this study. Mechanisms linking diabetes and hyperglycemia to cataract formation include advanced glycation of lens proteins and hyperosmotic effects of sorbitol on lens fibers formed through the aldose reductase pathway.[34] The mechanism linking hypertension and cataract is not clear. Inflammation and endothelial dysfunction could possibly play a role in the association between hypertension and cataract.[35]

Amongst the Western studies, Tan *et al*.[4] have shown that metabolic syndrome is associated with all the three types of cataract (nuclear, cortical, and posterior subcapsular) in an elderly cohort of Australians in the Blue Mountain Eye study. Paunksnis *et al*.[36] have also reported an association between cataract and metabolic syndrome among middle-aged European men and women. Further, metabolic syndrome, its components, and their combination were found to be associated with an increased risk of cataract extraction in an Italian hospital population[37] and among Swedish women aged <65 years.[38]

Obesity, an important component of metabolic syndrome, has been proposed to be a risk factor for cataract development, though the exact mechanisms are unclear. The Physicians Health Study, a randomized trial of 22,071 healthy male American physicians aged 40–84 years, reported both overall obesity, measured as BMI, and abdominal obesity as independent risk factors for cataract.[39] Prospective data from Framingham Eye Study also demonstrate an independent association between greater BMI and higher incidence of cortical cataract and posterior subcapsular opacities.[40] Several pathophysiological mechanisms have been proposed to explain the association of obesity and cataract. Leptin, a cytokine expressed and secreted mainly by adipocytes, is involved in the molecular mechanisms underlying cataract formation.[41] Individuals with obesity are likely to have hyperleptinemia and leptin resistance.[42] Thus, hyperleptinemia associated with obesity may promote cataract formation. These studies highlight the importance of tackling metabolic syndrome and its components for the prevention of cataract.

Primary open angle glaucoma

IOP is the only modifiable risk factor for primary open angle glaucoma.[43] IOP is determined by the balance between aqueous humor secretion and outflow.[44] 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.[45,46] Chang *et al*.[47] analyzed the clinical data of 1112 patients undergoing health checkup and concluded that participants with metabolic syndrome had significantly higher IOP than those without metabolic syndrome. Each additional component of metabolic syndrome was associated with

a mean increase in IOP of 0.33 mm Hg. Their findings were consistent with those reported by Oh *et al*.[48] in the Korean population.

The mechanism by which metabolic syndrome 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.[49] Stimulation of ocular sympathetic nerve also increases IOP.[50] 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.[51] 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.[52] Unexpectedly, aquaporin knockout mice were obese and developed severe insulin resistance, pointing toward another possible link between IOP and metabolic syndrome.[53]

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.[54] Obesity exerts an effect on IOP by causing excessive intraorbital adipose

Table 1: Associations of metabolic syndrome with eye disorders

Author	Study, year	Title	Inference
Metabolic syndrome and retinopathy			
Wong *et al*.	2004	Associations between the metabolic syndrome and retinal microvascular signs	Individuals with metabolic syndrome were significantly more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, smaller retinal arteriolar diameters, and larger retinal venular diameters
Kawasaki *et al*.	The Funagata Study, 2008	The metabolic syndrome and retinal microvascular signs in a Japanese population	Metabolic syndrome was found to be associated with retinal microvascular signs like focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex and narrower arteriolar diameter
Keenan *et al*.	2009	Retinopathy in non-diabetic persons with the metabolic syndrome	There was no evidence of an association between the metabolic syndrome and retinopathy independent of diabetic status
Van leiden *et al*.	Hoorn Study, 2003	Risk factors for incident retinopathy in a diabetic and non-diabetic population	Waist–hip ratio is associated with incident retinopathy signs
	Age Related Eye Disease Study, 2001	Risk factors associated with macular degeneration	Higher BMI is associated with more advanced age-related maculopathy
Metabolic syndrome and cataract			
Sabanayagam *et al*.	Singapore Malay Eye Study, 2011	Metabolic syndrome components and age-related cataract	Metabolic syndrome is significantly associated with age-related cataract
Tan *et al*.	Blue Mountain Eye Study, 2008	Influence of diabetes and cardiovascular disease on long-term incidence of cataract	Metabolic syndrome is associated with all three type of cataract – nuclear, cortical, and posterior subcapsular
Paunksnis *et al*.	2007	Relationship between cataract and metabolic syndrome in middle-aged European men and women	Metabolic syndrome and its components are associated with metabolic syndrome
Galeone *et al*.	2010	Metabolic syndrome and age-related cataract extraction: A case–control study in Italy	Metabolic syndrome is associated with increased risk of cataract extraction
Metabolic syndrome and primary open angle glaucoma			
Chang *et al*.	2010	Association of intraocular pressure with metabolic syndrome and novel cardiometabolic risk factors	Participants with metabolic syndrome had significantly higher IOP than those without metabolic syndrome
Oh *et al*.	2005	Elevated intraocular pressure is associated with insulin resistance and metabolic syndrome	Elevated intraocular pressure is associated with metabolic syndrome in Korean population

tissue, increased blood viscosity, increased episcleral venous pressure, and impairment of aqueous outflow facility.[55] Also, obesity has been shown to cause vascular endothelial dysfunction and autonomic dysfunction.[56] This may cause abnormal ocular blood flow and perfusion instability leading to impaired vascular supply to the optic nerve head and glaucomatous changes.[57] Data from various studies is summarized in Table 1.

Miscellaneous

Obesity has also found to be related to oculomotor nerve palsy and recurrent lower lid entropion.[58,59] Obstructive sleep apnea syndrome, a comorbid condition related to obesity, which has been associated with papilledema,[60] and floppy eyelid syndrome.[61]

Conclusion

The prevalence of metabolic syndrome is rapidly increasing worldwide due to the sedentary lifestyles. Its association with various ocular manifestations such as non-diabetic retinopathy, CRAO, cataract, and primary open angle glaucoma suggests that an epidemic of metabolic syndrome can have far-fetched ocular consequences as well. Amelioration of metabolic syndrome may have a therapeutic role in preventing these ocular conditions. However, most of the studies done in this regard were cross-sectional studies, and thus a causal relationship cannot be proven. Prospective, interventional studies are required to determine the causal association between metabolic syndrome, its components, and various ocular manifestations such as retinal microvascular signs, cataract, and primary open angle glaucoma.

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