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THE IMPACT OF SYSTEMATIC DISEASE ON EYES – A REVIEW

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ABSTRACT

The human body functions as an interconnected system, with systemic diseases significantly influencing ocular health. Various conditions such as diabetes, hypertension, autoimmune disorders, thyroid diseases, infectious diseases, kidney diseases, blood disorders, and neurological disorders contribute to ocular manifestations, sometimes serving as early indicators of these systemic illnesses. Understanding the relationship between systemic diseases and ocular changes is crucial for early diagnosis and treatment, preventing potential vision loss. This review highlights the mechanisms, clinical manifestations, and modern diagnostic and treatment approaches to systemic diseases affecting eye health. Clinicians must be vigilant in recognizing ocular symptoms to provide comprehensive care, improving patient outcomes.

INTRODUCTION

The human body is a complex network, and the state of one organ system can have a big impact on how another works. The eyes, which are the specialized organs for seeing, are especially susceptible to the effects of several systemic disorders. Even though many eye disorders are primarily ocular, many systemic diseases have a significant impact on ocular health and, if ignored, can result in blindness or vision impairment. These disorders, which impact the entire body, can damage the immune system, blood vessels, or nerves, upsetting the delicate equilibrium necessary for the best possible eye function.

Numerous eye conditions, including diabetic retinopathy, hypertensive retinopathy, dry eye syndromes, and uveitis, can be brought on by systemic diseases such diabetes, hypertension, autoimmune disorders, and thyroid disorders. Eye problems are frequently one of the initial indicators of underlying systemic problems, and identifying these ocular symptoms early on can be extremely helpful in identifying and treating the larger illness. For instance, inflammatory conditions like Sjögren's syndrome and rheumatoid arthritis can cause persistent dry eyes and damage to the surface of the eye, whereas alterations in the retina frequently show the consequences of diabetes and hypertension.

Improving patient care requires an understanding of how systemic disorders affect eye health. Clinicians can more successfully treat eye-related conditions and address the underlying problem early on by identifying the ocular symptoms of systemic diseases. The many systemic disorders that significantly impact ocular health are examined in this overview, along with their mechanisms of action, typical clinical manifestations, and contemporary methods of diagnosis and treatment. Khalsa college of engineering and technology.

Systematic Disease Cause Ocular Changes

Several systemic diseases can cause eye changes, affecting vision, eye structure, or function. These changes can sometimes serve as early indicators of an underlying condition. Here are some key systemic diseases and their associated eye manifestations:

1. Diabetes Mellitus

a) Ocular Surface: In any human group, diabetes mellitus is linked to high rates of illness and mortality. It is often known that diabetes causes chronic, progressive damage to major end organs, but it is not widely recognized that the cornea is the most visible and superficial organ impacted by the disease [1]. Dry eye, superficial punctate keratitis, recurrent corneal erosion syndrome, and persistent epithelial abnormalities are all more common in diabetic eyes [2],[3]. Being the initial layer of the eye, the corneal epithelium is always being worn down and needs to be renewed. Any procedure that alters the rate of epithelium regeneration or wound healing will have physiological effects and raise morbidity, such as redness and pain in the eyes [4],[5].

b) Diabetic Retinopathy: Diabetic retinopathy (DR) is a microangiopathy resulting from the chronic effects of diabetes mellitus (DM). It is the most common retinal vascular disease. DR affects three out of four people living with diabetes after 15 years of disease duration [6]. People with diabetes between the ages of 20 and 79 had an overall prevalence of 34.6% for any DR and 7.0% for proliferative DR (PDR), according to a recent meta-analysis. People with type 1 DM had a larger prevalence of any DR than those with type 2 DM (77.3% vs. 25.2%, respectively), and it was "lowest among Asians and highest among African Americans" [7].

c) Diabetic Macular Edema: The most frequent cause of vision loss in people with diabetic retinopathy is diabetic macular edema (DME), which is becoming more and more widespread worldwide. Depending on the type of diabetes and how long the condition has been present, the prevalence of DME in people with diabetic retinopathy ranges from 2.7% to 11% [8],[9]. After 25 years, it is roughly 30% for both types 1 and 2. Higher systolic blood pressure, higher haemoglobin A1C, and longer duration of diabetes are systemic variables linked to DME. The severity of diabetic retinopathy is the only

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ocular component linked to DME, as its prevalence rises with its severity [10],[11].

d) Cataracts: Numerous studies have looked at the risk of developing various kinds of cataracts in people with diabetes. Significant cortical, posterior subcapsular, and nuclear cataracts were found to be present in 65.5%, 42.5%, and 48.0% of people with type 2 diabetes, respectively, according to Olafsdottir et al [12]. The impact of diabetes on the lens also presents itself in accommodation disorders, leading to a decrease in its amplitude and the occurrence of presbyopia at a younger age in comparison to those without diabetes.

e) Glaucoma: The strength of the relationship between diabetes, diabetic retinopathy (DR), and glaucoma remains controversial. Although there is conflicting evidence, studies have indicated that diabetes and DR may raise the risk for glaucoma. Diabetes/DR may directly harm the optic nerve or indirectly (by raising intraocular pressure or causing vasculopathy) lead to glaucomatous optic neuropathy [13]. However, several aspects of diabetes may decrease the progression of glaucoma, and treating diabetes may also help control glaucoma. A major contributing factor to poor results following glaucoma surgery is diabetes. Numerous mechanistic connections have been established between the pathogenesis and treatment of diabetes, DR, and glaucoma, even though the relationship between these conditions is still debatable. Nonetheless, a more thorough comprehension of the factors that contribute to illness association is required.

2. Hypertension (High Blood Pressure): Several systemic diseases that result in significant morbidity and mortality are made more likely by hypertension. A systolic blood pressure of more than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg are considered hypertension by the World Health Organization, and an estimated 1.13 billion individuals worldwide suffer from this illness [14]. Several eye conditions, such as retinopathy, choroidopathy, and optic neuropathy, can be brought on by high blood pressure. Additionally, it is a risk factor for retinal artery microaneurysms, non-arteritic anterior ischemic optic neuropathy (NAION), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), branch retinal artery occlusion (BRAO), and central retinal artery occlusion (CRAO), among other vision-threatening eye conditions.

a) Hypertensive Retinopathy: Hypertensive retinopathy is a visual manifestation of the vascular alterations linked to systemic high blood pressure in the retina. Vasospasm-induced widespread constriction of the retinal arteriolar arteries and elevated vascular tone are early results. Intimal thickening and hyaline degeneration are two structural alterations in the arterial wall brought on by chronic hypertension. These appear like copper or silver wiring, which are focal or diffuse regions of vessel wall opacification [15,16]. Arteriovenous (AV) crossing, also known as nicking, is the compression of the venules where they cross due to thickening of the arterioles. Microaneurysms could develop. Cotton-wool spots are focal regions of ischemia of the retinal nerve fibre layer caused by severe hypertension. When the blood-retina barrier breaks down, lipids can exude as hard exudates, or blood can exude as retinal hemorrhages. Increased intracranial pressure from extremely severe hypertension can result in optic nerve ischemia and enlargement of the optic disc [17].

b) Choroidopathy: Younger patients who experience sudden increases in blood pressure are frequently found to have hypertension chorioretinopathy, also known as hypertensive choroidopathy, which is typically observed in conjunction with hypertensive retinopathy. The hallmarks of hypertensive choroidopathy are focal ischemia damage to the retinal pigment epithelium (RPE) and fibrinoid necrosis of choroidal arterioles, which results in non-perfusion of the choriocapillaris above [18]. Younger patients are thought to be more susceptible to hypertensive chorioretinopathy because of the flexibility of their blood vessels. The flexible choroidal arterioles first constrict in reaction to acute systemic hypertension, which prevents the choriocapillaris from being perfused. Furthermore, because the choroidal arteries supply the choriocapillaris at right angles, the choriocapillaris receives a more direct transmission of systemic blood pressure [19].

3. Autoimmune Diseases: Numerous eye conditions can be brought on by autoimmune illnesses. Inflammation and other difficulties arise when the immune system unintentionally targets healthy eye tissues. The following are a few prevalent autoimmune conditions that impact the eyes**:**

a) Rheumatoid Arthritis: Patients with chronic RA may experience ocular signs and symptoms of varying severity, which can occasionally be the disease's initial manifestation. The eye is a common extra-articular target of RA, as evidenced by a recent meta-analysis of ocular problems across the spectrum of rheumatic disorders, which found a prevalence of about 18% of patients with RA [20]. Grittiness, discomfort and redness, fluctuating pain, and visual abnormalities are the most prevalent ocular complaints. Studies on RA that have included an ophthalmological examination have revealed that the anterior region of the eye is more frequently affected by conditions such as anterior uveitis (AU), peripheral ulcerative keratitis (PUK), keratoconjunctivitis sicca (KCS), episcleritis, and scleritis [21]. with retinal vasculitis as a rare manifestation. Reports in the literature evidence the variable incidence and prevalence of these conditions, possibly depending on environmental factors as well as the ethnic and genetic characteristics of the patients, disease duration and stage, and the appropriateness of therapy [22,23,24]. Overall, it is likely that ocular manifestations of RA are overlooked and/or underdiagnosed to a significant extent.

b) Lupus (DLE): Discoid lupus erythematosus (DLE) is a chronic skin disease that may affect the eyelids. Unless suspected, these lid lesions may resemble chronic blepharitis and persist for years. SLE (Systemic Lupus Erythematosus - SLE) Can lead to **retinal vasculitis** (inflammation of the blood vessels in the retina), causing vision problems. Dry eye syndrome is also common in SLE. There are few articles available on lupus causes ocular manifestations.

c) Multiple Sclerosis (MS): Cognitive alterations and exhaustion are common and problematic symptoms in early-stage multiple sclerosis (MS) patients, likely associated with both anatomical and functional brain abnormalities. It is

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uncertain whether these symptoms are frequent in MS. Optic neuritis (ON) is common in patients with MS and can possibly interfere with pupillary measurements. It constitutes the first symptom of the disease for 25% of MS patients and occurs in the course of the disease in about 70% [25].

d) Sarcoidosis: Sarcoidosis can have a variety of ophthalmologic symptoms, affecting every aspect of the eyeball's anatomy. The most common and benign involvement is of the lacrimal glands and conjunctiva. About 20% of patients have uveitis. It evolves chronically and is generally torpid. Every patient with sarcoidosis should have their risk of uveitis regularly examined. Although rare, neuro-ophthalmologic involvement is severe. When isolated, it poses challenging diagnostic issues [26].

4. Thyroid Disorders (Graves' Disease - Hyperthyroidism)

a) Thyroid Eye Disease (TED): According to modern concepts, thyroid eye disease (TED) is an independent progressive autoimmune disease of the organ of vision, closely associated with the autoimmune pathology of the thyroid gland. The symptoms of thyroid eye disease (TED) can vary greatly and are typified by edema and inflammation of the orbital and periorbital structures. Diplopia, which is brought on by extraocular muscle constriction, or sight loss from exposure keratopathy or compressive optic neuropathy can all lead to visual dysfunction. With eye pain, photophobia, weeping, and cosmetic changes ranging from eyelid retraction to disfiguring proptosis, TED can negatively impact quality of life (QoL) even in cases where visual function is unaffected. The paucity of high-fidelity animal models and the difficulty of accessing target tissues have made it difficult to understand the pathophysiology of TED [27].

5. Infectious Diseases

a) Tuberculosis: Tuberculosis (TB) is considered a public health problem in several countries. This disease is classified as either pulmonary or extrapulmonary. Within the extrapulmonary disease, ocular involvement is uncommon, but it is important to recognize it because its incidence has been reported up to 1%. Ocular TB cases can be divided in primary and secondary. These manifestations can be caused by an active infection that invades the eye or by an immunologic reaction of delayed hypersensitivity in absence of the infectious agent. The most common clinical presentations are chronic anterior uveitis, choroiditis and sclerokeratitis. Despite the existence of highly sensitive molecular diagnostic techniques, the diagnosis of ocular tuberculosis continues to be presumptive, based upon clinical presentation, systemic evaluation and response to treatment. For the treatment we use four drugs during a two-month period (isoniazid, rifampin, pyrazinamide and ethambutol) and two drugs for four additional months [28].

b) Syphilis: One well-known condition that can be caused by an acquired or congenital infection is ocular syphilis. Ocular syphilis is one of the most prevalent forms of neurosyphilis, according to research conducted both recently and before the invention of antibiotics [29],[30]. Anterior uveitis is the most often seen ocular symptom in both early and late syphilis patients [31]. Although there is a lack of evidence, several case reports have indicated that posterior uveitis is more prevalent among HIV-positive individuals [32]. Early syphilis in the eye can present with a wide range of clinical symptoms, such as papulosquamous lesions of the lid skin, temporary eyebrow loss, diffuse papillary conjunctivitis, scleroconjunctivitis, interstitial keratitis, iritis, chorioretinitis, and optic neuritis. Research on ocular syphilis in people without HIV [33,[34].

c) HIV/AIDS: Cotton-wool spots and, less frequently, intraretinal haemorrhages, microaneurysms, and telangiectatic vessels are the hallmarks of HIV retinopathy, the most prevalent ocular disease observed in AIDS patients. The degree of immunodeficiency is positively correlated with the presence of retinopathy. Retinopathy was observed in 66% of patients with category C disease, 40% of patients with category B disease, 1% of patients with category A disease, and 0% of HIV-negative homosexual men in a group of HIV-positive patients [35]. These results supported research by Freeman and colleagues that found a correlation between HIV retinopathy and decreased CD4+ T cell numbers [36]. HIV retinopathy shares a clinical picture with collagen vascular disorders, diabetes mellitus, and malignant hypertension. A thorough history and physical examination are typically sufficient to distinguish HIV retinopathy from other causes. Lesions from early CMV retinitis can sometimes seem like cotton-wool patches. In these situations, the diagnosis is made after careful monitoring over a few weeks since cotton-wool patches vanish while CMV retinitis enlarges [37].

6. Kidney Disease: Chronic kidney disease is an emerging health problem worldwide. The eye shares striking structural, developmental, and genetic pathways with the kidney, suggesting that kidney disease and ocular disease may be closely linked. A growing number of studies have found associations of chronic kidney disease with age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract. In addition, retinal microvascular parameters have been shown to be predictive of chronic kidney disease. Chronic kidney disease shares common vascular risk factors including diabetes, hypertension, smoking, and obesity, and pathogenetic mechanisms including inflammation, oxidative stress, endothelial dysfunction, and microvascular dysfunction, with ocular diseases supporting the 'Common Soil Hypothesis.

Risk Factors of CKD	Associated Eye Diseases
Age	Cataract, AMD, DR, Glaucoma, Retinal Vascular Damage
Smoking	AMD, Cataract
Diabetes Mellitus	Cataract, DR, AMD, Glaucoma, Retinal Vascular Damage
Hypertension	AMD, DR, Retinal Vascular Damage, Glaucoma
Obesity	AMD, DR, Cataract
Hyperlipidemia	AMD, DR

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Although age and smoking are established risk factors for AMD [38], hypertension, diabetes [39], elevated serum cholesterol [40], and obesity have also been associated with AMD recently [41]. Obesity, diabetes, hypertension [42], and hyperlipidemia [43] are risk factors for DR [44] and retinal microvascular changes. Glaucoma has been associated with diabetes [45] and hypertension [46], whereas age, smoking, diabetes, and obesity [47], have all been found to be risk factors for cataract [48].

7. Blood Disorders

a) Sickle Cell Disease: Sickle cell disease (SCD) is a disorder that causes red blood cells to become sticky and rigid. Sickle cells can block blood flow in small blood vessels depriving the eye of oxygen and cause damage. This is called sickle retinopathy that can progress to severe proliferative sickle cell retinopathy, bleeding into the eye, detachment of the retina or even loss of vision. Patients are often asymptomatic until complications arise as vitreous haemorrhage and retinal detachment. Some studies report that the incidence and prevalence rates of all ocular complications in SCD increase with age and that proliferative retinopathy progresses rapidly during adolescence, justifying the routine screening of children [49].

b) Leukemia: Chronic myeloid leukemia (CML) can appear in a variety of ways, depending on the stage of the illness. Numerous symptoms and indicators may be present; at the time of diagnosis, leukemia patients have been known to have ocular involvement. We characterize ocular signs as a CML patient's first presentation. Between 1971 and 2020, we found 38 papers that described CML's ocular symptoms. Neoplastic cell infiltration, either direct or indirect, or secondary reasons, might result in ocular issues. The most common clinical symptom is leukemic retinopathy, though almost all ocular structures may be impacted. Other conditions include exudative/serous retinal detachment, hypopyon, anterior uveitis, iris infiltration, and optic nerve infiltration [50].

c) Anemia: Iron-deficiency anemia (IDA) is a public health issue that primarily causes several health issues in underdeveloped nations and affects both pregnant women and children. [51] Between 4 and 5 million people are impacted by IDA annually [52]. One of the main causes of anemia in wealthy nations is IDA. Inadequate dietary iron intake or circumstances that cause bleeding and impaired iron absorption are the etiological reasons for the development of IDA [53]. Excessive menstrual bleeding during pregnancy, especially in women in the reproductive age range, increases the need for iron. Chronic gastrointestinal bleeding, renal illness, persistent infections, and inflammations are common causes in the aged population. In addition to aiding in the synthesis of red blood cells, iron is essential for the healthy operation of the circulatory system. Haemoglobin, which transports oxygen-rich blood to every organ, is rich in iron. [54] Retinal hypoxia has been linked to the development of glaucomatous optic nerve injury, diabetic retinopathy, and retinal vascular occlusions.

8. Neurological Disorders

a) Brain Tumors: Brain tumors have long been considered one of the most prevalent causes of potentially reversible cognitive impairment. An accurate underlying cause of cognitive impairment due to brain tumor needs to be evaluated pragmatically. Patterns of cognitive impairment associated with brain tumors depend mainly on their location, lateralization, pathological classification and secondary effects of the treatment, as well as the structural plasticity and diaschisis. Hence, it is not rare that lesions with different locations and histologist may manifest with a similar pattern of cognitive impairment due to the complex interplay of determinants. Either a distant, unrelated region or a crucial site may be affected by brain tumors, resulting in frontal dysexecutive syndrome. Although they have different effects, they can cause similar cognitive deficits and even dementia. This disease is very similar to known psychiatric conditions. One of the most basic and useful methods for identifying the underlying medical condition may be associated supranuclear abnormalities in eye movement. Examining the motor and cranial nerves requires pragmatism because a precise diagnosis is more difficult due to the vast range of involvement types [55].

b) Myasthenia Gravis: Although diplopia and ptosis frequently present problematic issues with daily living activities and quality of life, OMG is generally considered a moderate condition and is not life-threatening. There is no proven proof that patients with OMG are treated any differently from those with gMG. One Furthermore, information regarding clinical procedures and results in OMG patients has rarely been recorded. Few randomized clinical trials (RCTs) have been conducted for OMG, even though RCTs are suitable for demonstrating the effectiveness of conventional immunosuppressive treatments. OMG is a rare disease, therefore it can be challenging to get enough people to participate in scientific trials. As a result, there aren't enough established evidence-based therapy choices [56].

9. Vitamin Deficiencies

a) Vitamin A Deficiency: Medical personnel usually dismissed this complaint as malingering and failed to investigate or recognize a dietary basis for nutritional night blindness, a prevalent issue among troops forced to survive on nutritionally inadequate meals during the American Civil War. Due to insufficient data for black soldiers and POWs, many of the more than 8,000 cases of night blindness that were reported among Union forces were not counted. Similar data were available for both whites and blacks between 1864 and 1865. The average yearly cumulative incidence of night blindness for whites was 4.3 per 1,000 troops, but for blacks it was 11.0 per 1,000 troops. Affected patients had dilated pupils that were poorly responsive to candlelight. Approximately 30 cases of keratomalacia were also reported among severely malnourished and emaciated soldiers with chronic diarrhoea, generally within 2 weeks before death. The reported clinical manifestations are characteristic of the full range of vitamin A deficiency eye disease from night blindness to corneal ulceration and perforation. Although medical officers typically accused affected soldiers of malingering, malingering cannot account for either the observed abnormalities of pupillary reflexes, or

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the corneal epithelial pathology and mortality recorded in severe cases [57].

b) Vitamin B12 Deficiency: Vitamin B_{12} deficiency is a worldwide problem. It affects all ages, including children. It is one of the most common nutritional disorders and can cause harmful effects on the nervous system. A deficiency in vitamin B_{12}, elsewhere it is important for the development of the central nervous system, is associated with a reduction in the thickness of the superior RNFL [58].

CONCLUSION

Systemic diseases have profound effects on ocular health, often leading to severe complications, including vision impairment or blindness if left untreated. Recognizing ocular manifestations as early indicators of systemic disorders can facilitate timely medical intervention, reducing morbidity and improving overall patient care. Comprehensive management requires collaboration between ophthalmologists and other healthcare providers to address both the ocular and systemic aspects of disease. Further research and advancements in diagnostic techniques will enhance the ability to detect and treat these conditions effectively, preserving vision and overall health in affected individuals. Systemic diseases have profound effects on ocular health, often leading to severe complications, including vision impairment or blindness if left untreated. Recognizing ocular manifestations as early indicators of systemic disorders can facilitate timely medical intervention, reducing morbidity and improving overall patient care. Comprehensive management requires collaboration between ophthalmologists and other healthcare providers to address both the ocular and systemic aspects of disease. Further research and advancements in diagnostic techniques will enhance the ability to detect and treat these conditions effectively, preserving vision and overall health in affected individuals.

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