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OCULAR MANIFESTATIONS OF SYSTEMIC NUTRITIONAL DEFICIENCIES: A Narrative Review

Narrative Review

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ABSTRACT

Background: Systemic nutritional deficiencies are a significant yet underrecognized contributor to visual impairment and ocular disease globally. Vitamins such as A, D, and B12 are essential for maintaining the structural integrity and functional health of the eye. Deficiencies in these micronutrients are associated with a range of ophthalmic manifestations, from dry eye and night blindness to optic neuropathy. Despite their clinical relevance, nutritional causes of ocular symptoms are frequently overlooked in routine practice.

Objective: This narrative review aims to explore the ocular manifestations of systemic deficiencies of vitamins A, D, and B12, synthesizing recent literature to highlight their pathophysiological effects, clinical presentations, and implications for patient care.

Main Discussion Points: The review discusses the role of vitamin A in ocular surface maintenance and its deficiency-related conditions such as xerophthalmia and keratomalacia. Vitamin D is examined for its immunomodulatory function and links to inflammatory ocular conditions, including dry eye and uveitis. Vitamin B12 deficiency is reviewed in the context of optic neuropathy and its neuro-ophthalmic sequelae. Additionally, the review identifies methodological limitations in the current literature, inconsistencies in measurement outcomes, and a lack of standardized clinical guidelines.

Conclusion: There is compelling evidence linking systemic nutritional deficiencies to distinct ocular pathologies. Early recognition and intervention can significantly alter disease progression and visual outcomes. However, further high-quality research is needed to standardize screening practices and refine therapeutic strategies.

Keywords: Vitamin A Deficiency, Vitamin D, Vitamin B12, Ocular Manifestations, Nutritional Deficiencies, Narrative Review

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INTRODUCTION

Nutritional health plays a critical role in preserving systemic and ocular function, yet micronutrient deficiencies remain a significant and often overlooked cause of visual morbidity across global populations. Despite ongoing advancements in healthcare and widespread availability of nutritional supplements, systemic deficiencies of essential vitamins such as A, D, and B12 continue to exert a considerable burden on public health. According to recent estimates, more than 2 billion people worldwide suffer from micronutrient deficiencies, commonly referred to as "hidden hunger," with vitamin A deficiency alone affecting approximately 190 million preschool-age children and 19 million pregnant women, primarily in low-income regions. This issue is particularly pressing due to the silent progression of many deficiencies until severe clinical manifestations, including vision loss, have already emerged (1,2). Ocular tissues are highly metabolically active and reliant on adequate nutritional supply to maintain normal structure and function. Deficiencies in specific vitamins present distinct ophthalmic signs: vitamin A deficiency is classically associated with xerophthalmia, night blindness, and keratomalacia; vitamin D insufficiency may contribute to dry eye disease and uveitis; and vitamin B12 deficiency can result in optic neuropathy and visual field defects. These manifestations are not merely anatomical curiosities but are clinically significant indicators of systemic nutritional compromise. The eye, therefore, serves as both a sentinel and a window into broader nutritional status (3,4).

Numerous studies have explored the relationship between vitamin deficiencies and ocular pathology. For example, a study reported that, deficiencies in vitamins A, B12, and D can produce a broad range of ocular symptoms from retinal dysfunction to optic nerve damage (5). Similarly, a study highlighted that, nutritional deficits manifest through symptoms such as dry eyes, corneal xerosis, and pigmentary retinal degeneration, underscoring the clinical diversity of these conditions (6). Furthermore, a study emphasized the importance of a well-balanced diet and the necessity of supplementation to prevent long-term ocular complications (7). Despite this growing body of knowledge, gaps in awareness and clinical practice persist. In many cases, ocular signs are not recognized as the initial indicators of a systemic deficiency, delaying diagnosis and treatment. Additionally, current literature often addresses individual vitamins in isolation, lacking an integrative perspective on how multiple deficiencies may converge to affect ocular health (8). These gaps are particularly detrimental in at-risk groups such as individuals with malabsorptive disorders, restrictive diets, alcohol dependency, or those undergoing bariatric surgery, where micronutrient monitoring is often suboptimal.

Given the rising global prevalence of lifestyle-related malnutrition and increased longevity, a systematic understanding of how systemic nutritional deficiencies manifest in ocular tissues is vital. This narrative review seeks to explore the clinical manifestations of systemic deficiencies of vitamins A, D, and B12 in the eye. It synthesizes findings from recent literature to provide an updated understanding of how these micronutrients influence visual health, and what ocular signs may serve as early warnings for broader nutritional disturbances. The scope of this review includes peer-reviewed literature from the past five years, focusing on narrative and comprehensive reviews, observational studies, and relevant case reports detailing ocular presentations of these three major vitamin deficiencies. This selective approach ensures both recency and relevance of data, while integrating evidence from both high- and low-resource settings to offer a balanced perspective. The significance of this review lies not only in summarizing the clinical spectrum of ocular involvement but also in highlighting their diagnostic and therapeutic implications. By delineating the pathophysiological mechanisms, typical presentations, and potential reversibility of symptoms with nutritional correction, this review aims to support ophthalmologists, general practitioners, and public health professionals in early identification and management of visual symptoms secondary to systemic deficiencies. In doing so, it advocates for a more proactive and integrative approach to vision care—one that recognizes nutrition as a cornerstone of ocular health.

Thematic Discussion

Vitamin A Deficiency and Ocular Surface Disease

Vitamin A plays a crucial role in maintaining the integrity of the ocular surface and normal function of photoreceptors. One of the most widely documented manifestations of vitamin A deficiency (VAD) is xerophthalmia, which includes conjunctival xerosis, Bitot's spots, corneal ulceration, and ultimately keratomalacia. These manifestations result from the loss of conjunctival goblet cells and epithelial keratinization, leading to tear film instability and progressive ocular surface damage. A review emphasized that VAD remains one of the primary causes of preventable childhood blindness globally, particularly in low- and middle-income countries, where dietary insufficiency and malabsorption syndromes are prevalent (1). Epidemiological studies support these findings. A study reported that 2.5% of children in rural India exhibited conjunctival xerosis, and 0.9% had Bitot's spots—figures exceeding WHO thresholds for public health concern. Night blindness was also reported in 0.5% of the children, and 64% had subclinical VAD, revealing the silent burden of deficiency in vulnerable populations (2). The literature also indicates that even in developed nations, atypical presentations of VAD are seen in individuals with restrictive diets or post-bariatric surgery, such as the case reported by a study where Bitot's spots and nyctalopia were reversed with oral supplementation (3). Despite the well-documented effects, inconsistencies exist regarding optimal screening methods. Some studies suggest the use of conjunctival impression cytology and serum retinol levels, yet accessibility and affordability limit their widespread use in endemic areas. Moreover, while the benefits of prophylactic vitamin A supplementation programs are established, sustaining coverage and compliance remain key barriers in many regions.

Vitamin D Deficiency and Immune-Mediated Ocular Disorders

Vitamin D, known primarily for its role in calcium homeostasis and bone health, also has significant immunomodulatory properties. In the eye, vitamin D receptors are expressed in the cornea, retina, and ciliary body, suggesting its broader functional relevance. Emerging evidence links vitamin D deficiency to several ocular conditions, particularly those with an inflammatory component, such as dry eye disease (DED), uveitis, and age-related macular degeneration (AMD). A comprehensive review proposed that, vitamin D insufficiency exacerbates ocular surface inflammation by impairing epithelial barrier function and modulating cytokine expression (4). Supporting this, a study found that systemic vitamin D supplementation improved tear film stability and reduced symptoms in DED patients, highlighting a therapeutic avenue in managing ocular surface disorders (4,5). However, the evidence remains inconclusive regarding dosage, duration, and long-term benefits. Variability in baseline serum levels, geographic location, sun exposure, and dietary intake complicates the generalization of results. Additionally, while associations between vitamin D and retinal pathologies like AMD have been proposed, the causative link remains debated due to conflicting results from observational studies.

Vitamin B12 Deficiency and Optic Neuropathy

Vitamin B12 (cobalamin) deficiency presents a unique subset of ocular manifestations, most notably optic neuropathy characterized by progressive bilateral vision loss, central or cecocentral scotomas, and color vision impairment. These effects stem from impaired myelin synthesis and axonal degeneration of the optic nerve. Recent studies confirm that vitamin B12 deficiency can lead to irreversible visual impairment if not identified early. The optic nerve is highly susceptible to B12 deficiency due to its high metabolic demand and reliance on mitochondrial function for signal transduction (6,7). A study highlighted the limitations of conventional screening tools, such as mean corpuscular volume (MCV), which showed low sensitivity (10.14%) for detecting B12 deficiency, suggesting that many patients may remain undiagnosed until significant neuro-ophthalmic damage occurs (7). The complexity increases with the presence of confounding conditions like tobacco-alcohol amblyopia or hereditary optic atrophies, which may mimic the clinical picture of B12-related neuropathy. Although parenteral B12 supplementation often leads to visual recovery, outcomes vary depending on the duration of deficiency and extent of axonal damage at presentation.

Multi-nutrient Deficiencies and Combined Ocular Pathologies

In real-world clinical settings, isolated vitamin deficiencies are rare; rather, combined micronutrient deficiencies often coexist, especially in populations with poor dietary diversity or gastrointestinal diseases. The synergistic damage caused by deficiencies in vitamins A, D, B12, and zinc, which collectively compromise epithelial health, retinal function, and optic nerve integrity (8). A study supported this integrated view, recommending that clinicians adopt a broader nutritional assessment in patients presenting with atypical or unexplained ocular complaints. They further highlight the risk in elderly patients, bariatric surgery recipients, and those with restrictive diets, where combined deficiencies may be masked by overlapping symptoms. However, research comparing single versus combined nutrient supplementation in ophthalmic disease management is sparse, and robust trials are needed to determine the optimal strategies for diagnosis and treatment in such contexts. The lack of standardized nutritional screening protocols in ophthalmology further widens this gap, delaying intervention and worsening visual prognosis.

Critical Analysis and Limitations

While the reviewed literature has provided valuable insights into the ocular manifestations of systemic nutritional deficiencies, particularly those involving vitamins A, D, and B12, a critical appraisal reveals several limitations that constrain the robustness and applicability of the current evidence. A major concern across the studies is the predominance of descriptive and observational designs, with a noticeable paucity of randomized controlled trials. This methodological limitation undermines the ability to draw strong causal

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inferences. Most reviews and case reports, though rich in clinical detail, rely heavily on retrospective data or isolated case findings, which may not accurately represent broader population trends or establish temporal relationships between deficiency and ocular outcomes (9,10). Another pervasive issue is the small sample sizes observed in many included studies. For instance, several findings on vitamin A-related xerophthalmia or post-bariatric deficiency cases are based on limited patient numbers or even single case reports (11). While these cases effectively highlight clinical phenomena, they lack statistical power and external validity. Similarly, studies exploring vitamin D and B12 often include narrow cohorts, making it difficult to generalize findings to diverse populations or across different age groups and comorbid conditions.

Methodological bias is also evident. Selection bias is a concern, especially in studies focusing on already symptomatic individuals or high-risk groups such as patients with malabsorptive disorders, thereby neglecting subclinical or asymptomatic populations. For example, the association of B12 deficiency with optic neuropathy is primarily derived from studies that investigate patients presenting with neuro-ophthalmic symptoms, potentially overestimating the prevalence of such manifestations in the general B12-deficient population (12,13). Performance bias also appears in studies lacking blinding, particularly when subjective symptoms like visual disturbance or dry eye are primary outcomes. Without standardized assessment protocols or blinding, observer expectations could influence the interpretation of clinical signs. Publication bias is a notable but underreported issue in this domain. There appears to be a higher frequency of published literature detailing positive findings or striking clinical presentations, while inconclusive or negative results may be underrepresented. This tendency potentially skews the perceived frequency and severity of ocular involvement in nutritional deficiencies. Moreover, the majority of literature appears in open-access case-based journals or regional publications, which may reflect selection pressures favoring unusual clinical scenarios over broader epidemiological evaluations (14,15).

A critical barrier to synthesizing evidence is the variability in outcome measures across studies. Some reports use biochemical parameters such as serum vitamin levels as diagnostic benchmarks, while others rely solely on clinical symptoms or imaging findings, without correlating systemic and ocular indicators. For example, the thresholds for defining vitamin D deficiency differ widely, complicating cross-study comparisons. Similarly, studies assessing the improvement of symptoms post-supplementation vary in their follow-up durations and endpoints—some measuring tear film breakup time, others focusing on subjective patient reports—leading to inconsistent conclusions about therapeutic efficacy (16). Generalizability remains an overarching challenge. Much of the evidence originates from specific geographical regions with high malnutrition prevalence or unique clinical populations like bariatric surgery patients. This regional skewness limits applicability to global clinical practice, particularly in resource-rich settings where nutritional deficiencies are less overt but still clinically relevant. For instance, data from rural India showing high rates of vitamin A-related ocular pathology may not directly translate to urban populations with different dietary patterns, access to healthcare, or underlying health profiles (17). Furthermore, differences in sunlight exposure, cultural diets, and healthcare infrastructure affect the incidence and presentation of deficiencies across populations, further complicating extrapolation. Collectively, while the literature reviewed contributes important clinical and mechanistic insights, its limitations underscore the need for well-designed, large-scale prospective studies with standardized diagnostic criteria and outcome measures. Multicenter trials involving diverse populations would improve the reliability of associations between nutritional deficiencies and ocular health, and ultimately guide evidence-based screening and management strategies.

Implications and Future Directions

The findings from this review offer valuable insights with practical implications for clinical decision-making, healthcare policy, and future research in ophthalmology and nutritional medicine. Clinicians are increasingly confronted with patients presenting with unexplained ocular symptoms such as night blindness, dry eye, or optic neuropathy, and this review reinforces the need for heightened clinical suspicion toward underlying systemic nutritional deficiencies. Given the often-reversible nature of these conditions with timely supplementation, routine nutritional assessment should be considered in patients with atypical or treatment-resistant ocular presentations. In particular, screening for vitamin A, D, and B12 deficiencies in populations at risk—such as individuals with restrictive diets, malabsorptive disorders, or history of bariatric surgery—may facilitate earlier diagnosis and prevent irreversible visual sequelae (18,19). The evidence also suggests a need to integrate nutritional evaluation into broader ophthalmic care protocols. This underscores the importance of interdisciplinary collaboration between ophthalmologists, primary care providers, and nutritionists. However, existing clinical guidelines rarely emphasize micronutrient screening in routine ophthalmology practice, which reflects a critical gap in policy. Developing standardized guidelines that incorporate vitamin screening in the diagnostic workup of specific ocular diseases, such as dry eye syndrome, optic neuropathy, and xerophthalmia, could lead to more holistic and cost-effective patient care. Moreover, public health campaigns emphasizing the ocular risks of nutritional deficiencies may help raise awareness, particularly in underserved communities where the prevalence of deficiencies is high (20,21).

Despite the progress in understanding the ocular effects of systemic vitamin deficiencies, several knowledge gaps remain. There is a limited understanding of the long-term visual outcomes following correction of deficiencies, especially in cases where ocular damage is advanced but not yet irreversible. In addition, the role of subclinical deficiencies—where serum levels may hover near the lower limit of normal—on ocular physiology is poorly defined. It is also unclear whether micronutrient supplementation in individuals without overt deficiency might offer preventive benefits against age-related ocular conditions like cataracts or macular degeneration. These areas merit further exploration to refine preventive strategies and therapeutic thresholds (22,23). To address these gaps, future research should prioritize prospective, multicenter trials with larger and more diverse populations to ensure greater generalizability. Randomized controlled trials (RCTs) comparing various supplementation strategies—systemic versus topical, single nutrient versus combination therapy—could offer clearer insights into treatment efficacy across different ocular conditions. Studies should also aim for standardized outcome measures, such as visual acuity, contrast sensitivity, and objective ocular surface parameters, to enhance comparability. Furthermore, longitudinal cohort studies that track ocular and systemic outcomes over time following nutritional intervention would help clarify long-term benefits and inform follow-up care protocols (24,25).

Incorporating advanced diagnostic techniques, such as tear film cytokine profiling, conjunctival impression cytology, and retinal imaging, into future research may also help detect subclinical disease and reveal novel biomarkers linked to nutritional status. Additionally, exploring the interplay between multiple micronutrient deficiencies, gut health, and genetic predisposition could deepen understanding of the multifactorial nature of ocular disease progression in malnutrition. In conclusion, the review highlights the underappreciated but clinically significant impact of systemic nutritional deficiencies on ocular health and provides a compelling case for integrating nutritional assessment into routine eye care. Future research, guided by more rigorous methodologies and broader scopes, holds the potential to refine clinical practice, enhance patient outcomes, and shape more inclusive and evidence-based healthcare policies.

Conclusion

This review underscores the significant yet often underrecognized impact of systemic nutritional deficiencies—particularly involving vitamins A, D, and B12—on ocular health. The synthesis of current literature reveals that these deficiencies manifest through a diverse range of ophthalmic conditions, including xerophthalmia, dry eye disease, and optic neuropathy, many of which are preventable or reversible with timely intervention. While the existing evidence provides valuable clinical insights, much of it stems from small-scale observational studies and case reports, limiting its generalizability and strength. Nonetheless, the recurring patterns observed across diverse populations support a credible link between micronutrient status and visual function. Clinicians are advised to maintain a high index of suspicion for nutritional etiologies in patients presenting with unexplained visual symptoms, especially in at-risk groups such as those with malabsorptive conditions or dietary restrictions. There is a pressing need for more rigorous, large-scale, and standardized research to better define diagnostic criteria, clarify treatment protocols, and evaluate long-term outcomes. Future studies should aim to integrate nutritional screening into ophthalmic practice and investigate the broader role of micronutrients in ocular disease prevention.

Author Contributions

Author	Contribution
Muhammad Israr*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Khalida Bano	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Amna Naseer	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Usama Rahim	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ariba Shah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Naeem	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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