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Review

A Review of Peripheral Refraction in Myopia Research

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Abstract: Myopia has become a critical global public health issue, driven by the increasing prevalence of pathological myopia, which poses significant risks to visual health and leads to potential economic productivity losses. The theory of peripheral defocus affecting the visual feedback mechanism in emmetropization may play a role in the prediction and management of myopia. However, progress has been hindered by challenges, including the ambiguous definition and classification of peripheral defocus, as well as inconsistencies in clinical research findings. This review offers a comprehensive examination of peripheral refraction, encompassing its definition, measurement methodologies, characteristics across different refractive states, clinical applications, and underlying mechanisms. Additionally, it addresses current research limitations, such as the need to differentiate between intrinsic and extrinsic peripheral defocus and the absence of high-resolution measurement tools suitable for large-scale clinical studies. By advancing the understanding of peripheral refraction, this review aims to inform future researchers and clinical practitioners, paving the way for more effective strategies to prevent and manage myopia in children.

Keywords: peripheral refraction; peripheral defocus; refractive development; myopia progression

1. Introduction

Myopia has become a significant global public health concern, closely associated with urbanization and increasing educational pressures on children [1,2]. It is estimated that the global prevalence of myopia will rise from 1.5 billion individuals in 2000 to 4.8 billion by 2050, representing nearly half of the world's population [3]. This rapid increase poses a serious threat to vision health, with pathological myopia emerging as a leading cause of irreversible vision loss and blindness, particularly in Southeast Asia [3–7]. Beyond its impact on vision, refractive errors also impose substantial economic burdens. According to Smith et al., the global loss in purchasing power parity-adjusted gross domestic product (PPP-adjusted GDP) due to refractive errors is estimated to exceed $250 billion [8].

The development of myopia is multifactorial, involving an interplay of genetic and environmental factors, including family history, inheritance patterns, near-work activities, outdoor time, nutrition, educational pressures, and the visual feedback mechanism. Among these, the visual feedback mechanism has garnered significant attention from researchers in eye care, given its role in predicting and controlling myopia. The theory of peripheral defocus is central to the visual feedback mechanism, alongside other contributors such as higher-order aberrations (e.g., coma and spherical aberrations), astigmatism, retinal contrast, and spatial frequency. However, research on peripheral defocus remains contentious, largely due to the lack of accessible tools for quantifying high-resolution peripheral refraction and the ambiguous classification of peripheral defocus in clinical studies. This ambiguity has created confusion in the field. Despite these challenges, numerous clinical trials have demonstrated the effectiveness of myopia control strategies that involve modifying peripheral defocus.

This review seeks to clarify the concept of peripheral defocus, summarize the instruments used for its measurement, explore the characteristics of peripheral defocus in the human eye, discuss its applications in myopia control, examine its underlying mechanisms, and address the challenges and future directions in this field.

2. Definitions

2.1. Peripheral Defocus

Peripheral defocus refers to the focusing characteristics of the eye in the peripheral visual field. Based on the focal point position relative to the retina, it can be classified as peripheral myopic defocus (PMD), where light from the visual scene focuses in front of the retina, or peripheral hyperopic defocus (PHD), where light focuses behind the retina. In clinical studies, peripheral defocus is typically measured with accommodation relaxed. Peripheral refraction (PR) is another commonly used term often equated with peripheral defocus. For instance, peripheral myopic refraction corresponds to PMD, while peripheral hyperopic refraction corresponds to PHD. However, PR encompasses a broader set of optical characteristics, including astigmatism, higher-order aberrations, and image quality metrics, making it a more comprehensive term. In clinical applications, researchers frequently use terms like relatively peripheral myopic defocus (RPMD) and relatively peripheral hyperopic defocus (RPHD) to investigate the effects of relatively peripheral refraction (RPR) on myopia progression. RPR, a general term encompassing RPMD and RPHD, is calculated as the difference between peripheral refraction (PR) and central refraction (CR): RPR = PR − CR. This distinction is clinically relevant because central refraction correction is essential to ensure good visual acuity.

The prevailing consensus suggests that RPMD can slow the progression of myopia, while RPHD tends to promote it. However, inconsistent definitions and measurement methodologies for PR in clinical studies have led to controversial findings, underscoring the need for standardization in this area of research.

2.2. Eccentricity

Eccentricity, or the peripheral viewing angle, is a crucial concept in the study of peripheral refraction (PR). It is defined as the deviation of the measured angle relative to the line of sight (not visual axis). Traditional studies on peripheral refraction are typically limited to a maximum of the central 80° of the visual field (40° unilaterally in the horizontal direction) and slightly less in the vertical direction (30° unilaterally) due to anatomical constraints, such as the obstruction caused by eyelashes. The central visual field is generally defined as the central 10° in diameter [9]. From an anatomical perspective, the visual field corresponding to the macula can be subdivided into the foveola (central 1°), fovea (outer diameter of 5°), parafovea (8°), and perifovea (17°) [10]. Additionally, 1° of visual angle corresponds to approximately 0.33 mm on the human retina [11]. Understanding the relationship between visual angle and retinal anatomy is important for elucidating the mechanisms of PR. For example, animal studies have shown that imposed defocus beyond 20° from the fovea may not influence myopia development [12]. This underscores the importance of focusing on specific retinal regions when investigating peripheral refraction and its effects on myopia progression. However, it should be noted that retinal references are only approximate, as they are based on chief ray tracing using geometric optics. In reality, the actual projection of chief rays is influenced by various intraocular optical factors, including the cornea, entrance pupil, nodal point, crystalline lens, and fundus morphology. Therefore, for broader applicability in clinical research, it is recommended to describe eccentricity relative to the object space rather than the retinal reference.

2.3. Peripheral Defocus' Categories

A clear definition of peripheral defocus is essential for understanding its underlying mechanisms. Peripheral defocus can be broadly categorized into intrinsic peripheral defocus (IPD) and extrinsic peripheral defocus (EPD):

- Intrinsic Peripheral Defocus (IPD): IPD refers to the peripheral refraction measured directly within the eye using double-pass instruments. It includes peripheral refraction under active accommodation (IPD-A) and under relaxed accommodation (IPD-R). A special case arises when the subject is fitted with contact lenses, where the optics of the lens and the cornea are combined. Based on these conditions, IPD can be classified into four categories: IPD-R (refraction with relaxed accommodation), IPD-A (refraction with active accommodation), IPD-RC (refraction with relaxed accommodation while wearing contact lenses), and IPD-AC (refraction with active accommodation while wearing contact lenses).
- Extrinsic Peripheral Defocus (EPD): EPD refers to external factors that influence peripheral defocus. Depending on whether corrective lenses are provided, EPD can be categorized into two types: EPD-E

(without glasses, considering only the optical properties of the visual environment) and EPD-EG (with glasses, considering both the optics of the visual environment and the corrective lenses).

The combined effects of IPD and EPD are collectively referred to total peripheral defocus (TPD). In real-world conditions, TPD is represented as: TPD = IPD (A/R/AC/RC) + EPD (E/EG).

This value dynamically changes depending on the visual task and environmental context. The concept of the "retinocentric view", initially proposed by D.I. Flitcroft in 2012, integrates ocular refraction and environmental optical factors to explain how TPD may influence eye growth [13].

Despite its importance, practical limitations in simultaneously recording EPD and IPD-A/AC often led to studies focusing on only one of these aspects. Early clinical trials primarily investigated IPD, while EPD was more extensively studied in animal models. This fragmentation has posed challenges in comparative studies, as mixing these concepts without clear distinctions can result in conflicting conclusions.

3. Instruments for Peripheral Defocus

3.1. Instruments for IPD Studies (Intrinsic Peripheral Defocus)

3.1.1. Retinoscopy

Studies on peripheral refraction date back to the 19th century [14]. However, the first attempt to investigate the role of peripheral refraction in myopia research can be traced to 1971, when Rempt, Hoogerheide, and colleagues used retinoscopy to measure peripheral refraction [15,16]. Although retinoscopy allows for PR measurement, its accuracy and efficiency are highly dependent on the practitioner's expertise. Moreover, the procedure is time-consuming, requiring approximately 10 min to assess five eccentricities. Due to its low efficiency and poor repeatability, retinoscopy is not considered suitable for comprehensive PR studies. However, this has a significant historical importance.

3.1.2. Open-View Autorefractors

The WAM5500 (Grand Seiko Co., Japan)) and NVision-K 5001 (Rexxam Co., Japan) are among the most commonly used devices in the clinic for peripheral refraction studies. However, these instruments require subjects to rotate their eyes, with each capture corresponding to a single eccentricity, making it difficult to obtain high-resolution peripheral refraction maps. An alternative is the Voptica Peripheral Refraction (VPR) system, which enables faster PR scanning [17,18]. The VPR utilizes a Hartmann-Shack wavefront sensor (Voptica SL, Spain) to estimate refraction and features a rotating optical arm to adjust the measured horizontal visual field. While VPR significantly enhances measurement speed compared to other commercial devices, subjects must still rotate their eyes vertically. Generating a 2D refraction map for a 60° × 36° visual field takes approximately 10 min per subject.

3.1.3. Closed-View Autorefractors

Closed-view autorefractors designed specifically for PR measurement include devices such as the BHVI-EyeMapper (Brien Holden Vision Institute, Australia) [19], Multispectral Refractive Topography (MRT) [20], and Ultra-wide-angle Peripheral Refraction (UPER, the second generation of VPR) [21,22]. BHVI-EyeMapper uses multiple beam splitters for different horizontal eccentricities, along with a scanning mirror that shifts the optical path among these angles. Its principle is based on the Hartmann-Shack aberrometer. UPER replaces multiple beam splitters with a single composite eyepiece and a two-axis scanning mirror to measure eccentricities in a 2D manner. UPER can produce a radial symmetry refraction map within a central 50° visual field (diameter) using 88 points. Impressively, it completes the 2D mapping in less than 3 s. MRT estimates PR by linking the local blurred fundus image to optical defocus. However, MRT only provides a rough estimation of defocus (spherical equivalent refraction, SER). Additionally, the calibration protocol and algorithms for peripheral refraction are not publicly accessible yet, limiting the validation of the reported results. Figure 1 summarizes some of these instruments.

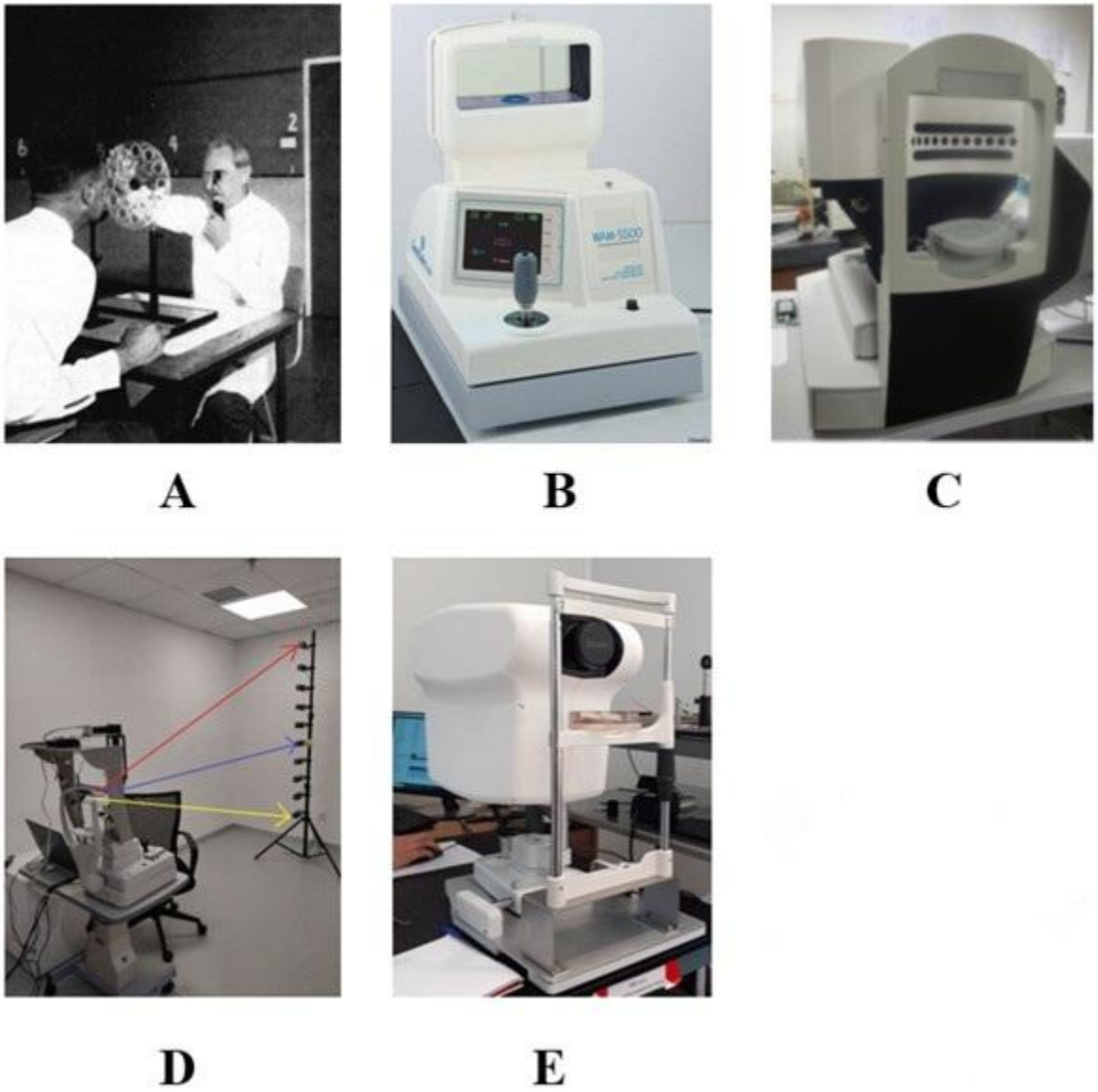

Figure 1. Approaches for peripheral refraction. (**A**) Retinoscopy [15,16]. (**B**) Open-view refractor WAM5500 [23]. (**C**) Close-view auto-refraction BHVI-EyeMapper [19]. (**D**) Open-view refractor VPR [17,18,24]. (**E**) Closed-view auto-refractor UPER [21,22].

3.2. Instruments for EPD Studies (Extrinsic Peripheral Defocus)

3.2.1. EPD-E (Extrinsic Peripheral Defocus-Environment)

The optical power of the visual environment can be calculated as the reciprocal of the distance between an object's surface and the eye's entrance pupil. 3D virtual reconstruction provides a convenient and non-invasive method to study EPD-EG in specific tasks. For example, Flitcroft [13] used simulations to analyze dioptric maps during desk reading tasks. The study found that the greatest relative peripheral hyperopia occurred at 18 degrees in the inferior visual field (corresponding to 18 degrees superiorly on the retina). This refractive pattern is consistent with 2D peripheral refraction maps observed in rapidly progressing emmetropic children [25] and is further supported by findings of asymmetric peripheral refraction in bird species, when viewed from a ground perspective [26–28]. Figure 2 shows examples of dioptric error maps.

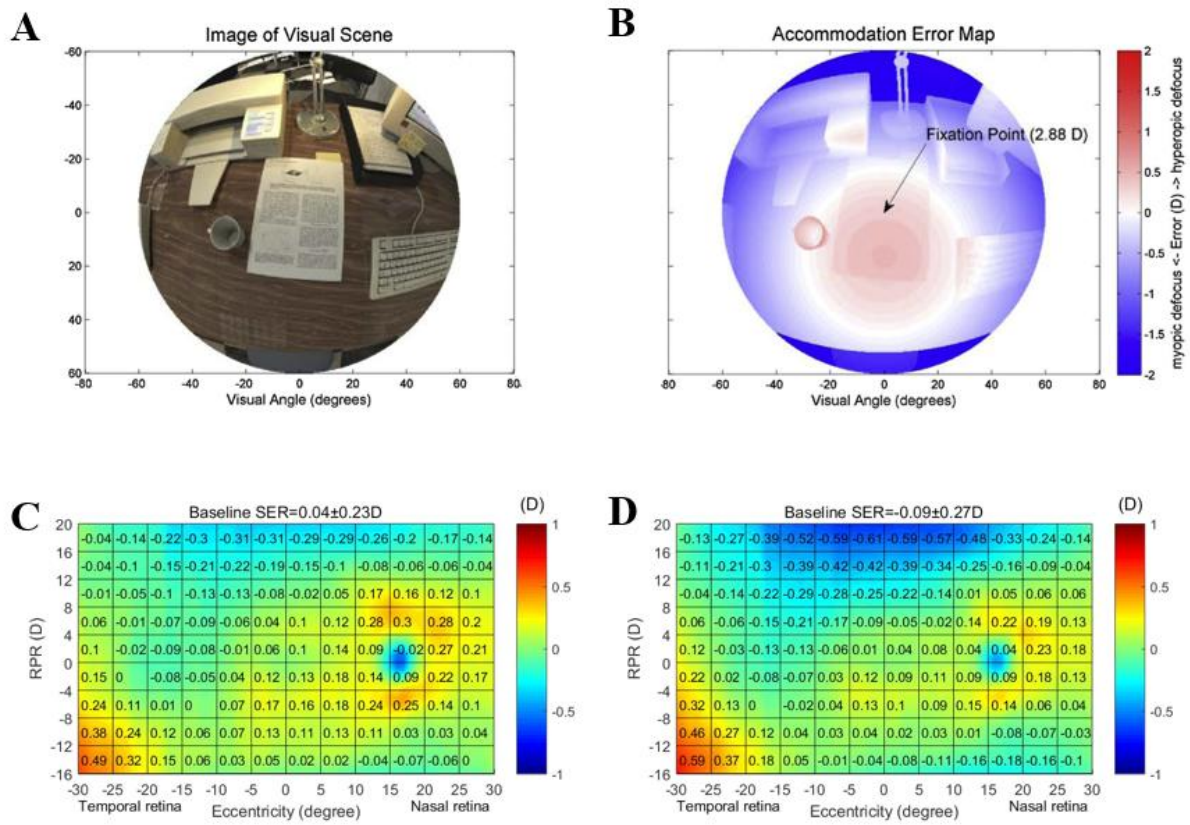

Figure 2. Dioptric error maps from Flitcroft, D.I. (Fig. 2A & 2B, 2012, Prog Retin Eye Res) and Lin Z. (Fig. 2C & 2D, 2023, IOVS). (**A**) A scenario of indoor environment. (**B**) The dioptric map of the indoor scenario with near visual behaviour. (**C**) The RPR retinal map of emmetropic children with low risk of developing myopia. (**D**) The RPR retinal map of emmetropic children with high risk of developing myopia.

Choi et al. [29,30] utilized Kinect-for-Windows to capture 3D images of study environments in children's homes. Their research demonstrated that the dioptric map, which reflects total defocus and variability within the scene, is associated with refractive development and may serve as a risk factor for myopia. A significant peak in peripheral hyperopia was identified at 15 degrees in the lower visual field, which was attributed to the habitual head orientation of the subjects during tasks.

To gain a more comprehensive understanding, researchers aim to record dioptric environments in real-life daily activities, particularly in subjects with varied indoor routines or significant outdoor exposure. Gibaldi et al. [31] developed a helmet-based device that combines a spectrometer and depth camera to evaluate visual environments. Read et al. introduced a novel wearable eye tracker designed to measure gaze distance and dioptric environments. This device incorporates two pupil cameras and one depth camera to quantify the visual field. Their study revealed that peripheral defocus within a 20° field is strongly associated with reading tasks, offering valuable insights into the relationship between environmental optical properties and refractive development [32].

3.2.2. EPD-G (Extrinsic Peripheral Defocus-Glasses)

Numerous myopia control spectacles have been developed to modify peripheral refraction (EPD-G). These optical solutions demonstrated some efficacy in preventing myopia progression. Representative products include DIMS (Hoya) [33], Stellest (Essilor) [34], and MyoCare (ZEISS) [35]. Understanding the mechanisms by which these glasses influence peripheral retinal refraction requires precise measurement of their optical characteristics. In general, two approaches are used to evaluate the optical effects of these lenses. The first involves on high-resolution commercial testing devices, such as Optocraft (Optocraft GmbH, Germany) [36] and ClearWave (Lumetrics Inc., USA) [37], or through-focus instruments [38], are commonly used. The resulting data can then be integrated into optical design software like Zemax, OpticsStudio to simulate total retinal refraction. The second relies on double-pass ophthalmic instruments that can measure the comprehensive effects of the lenses and IPD, minimizing errors in total refraction estimation. Nevertheless, lens reflections may limit the applicability of this

method. Through-focus-based double-pass instruments may offer additional benefits by mitigating these reflection issues [39].

In certain cases, contact lenses also provide additional peripheral defocus. In these situations, the overall optical effect within the eye can be considered a form of intrinsic peripheral defocus, as the contact lens integrates closely with the eye. Nonetheless, the optical characteristics of the contact lens per se remain categorized under EPD-G.

4. The Theory of Peripheral Defocus in Myopia Progression

4.1. Early Peripheral Defocus Studies

The study of peripheral refraction in myopia research can be traced back to 1971 (while the measurement of PR can be even earlier), when Rempt and Hoogerheide conducted an observational study on a group of pilots [15,16]. Peripheral refraction was categorized into five patterns based on relative peripheral defocus: bilateral hyperopia (type-1), slightly bilateral hyperopia (type-2), asymmetric peripheral refraction (type-3; hyperopia in the nasal field with a flat temporal side), flat peripheral refraction (type-4), and bilateral myopia (type-5). Over time, the researchers found that type-1 was most strongly associated with myopia progression, whereas individuals with type-4 showed little to no refractive development. This marked the beginning of peripheral defocus research aimed at myopia prevention. However, it is worth noting that this classification relied solely on horizontal meridians with limited eccentricities. Moreover, approximately 70% of the population fell into type-4, raising concerns about unbalanced sample distribution and its impact on the study's conclusions. Some researchers have also questioned whether the study was conducted after, rather than before, the onset of myopia, which could diminish its significance in the historical context of myopia research [40].

4.2. Establishment of Defocus Theory

The defocus theory, which suggests compensatory ocular growth in response to the plane of retinal defocus, was first proposed by Schaeffel et al. in 1988. Their research demonstrated a significant correlation between axial elongation and the power of induced lenses, although they noted that the compensatory growth appeared incomplete [41]. Irving et al. extended these findings in chicks, concluding that the mechanisms driving compensatory growth differed from those underlying form deprivation myopia. Their results showed that the retinal response to myopic defocus (positive power) was stronger than the response to hyperopic defocus (negative power) within a ±10 diopter range [42,43]. Diether and Schaeffel (1997) later demonstrated localized retinal responses to defocus, even in the presence of active accommodation [44]. Compensatory effects were also observed in higher primates fitted with full-field lenses, further cementing defocus theory as a foundational concept in myopia research [45].

4.3. Transition from Central to Peripheral Refraction

In 2009, Smith et al. demonstrated that foveal ablation did not prevent the development of central refractive errors when hyperopic defocus was introduced in the periphery [46]. This finding significantly shifted the focus of research, encouraging clinicians and vision scientists to develop optical solutions that specifically target peripheral retinal optics for myopia control. Their following study also suggested that central vision is not necessarily involved in normal refractive development [47], further emphasizing the role of peripheral defocus in myopia progression.

4.4. Application of Peripheral Defocus Theory

Several optical solutions have been developed with potential involvement in the peripheral defocus theory, including progressive addition lenses (PALs), specialized progressive lenses, bifocal spectacles, orthokeratology, and various contact lenses. These options preceded the widespread adoption of multiple-segment peripheral defocus-based spectacles. However, earlier designs often demonstrated limited efficacy in controlling myopia [48,49]. For example, bifocals and PALs include additional optical power in the lower portion of the lenses to support near vision. Their myopia treatment effects showed slight improvements compared to single-vision glasses, with the most success observed in children exhibiting significant accommodative lag [50,51]. The limited effectiveness of these lenses can be explained by the "retinocentric view". While these spectacles may induce additional myopic defocus in the superior retina, this effect requires wearers to use the lens's optical center for distant vision, typically occurring during outdoor activities. In outdoor environments, the dioptric landscape is

relatively uniform with minimal peripheral defocus, rendering the additional defocus provided by the glasses less impactful for myopia control. Conversely, during near-work tasks, the eyes must rotate to use the optical center in the lower portion of the lenses, but the additional power is effectively neutralized by the dioptric distance of near objects. As a result, the expected peripheral defocus from bifocals and PALs contributes minimally to myopia prevention.

However, it should be noted that the explanation above is based purely on the theory of peripheral refraction. The purpose of using bifocals is primarily aimed at reducing accommodative lag instead of adding peripheral myopic defocus. Nevertheless, these lenses still exhibit some ability to slow myopia progression. In addition, a review by Atchison et al. [52] summarized four theories that related to the myopia control of optical solutions: accommodation response and the consequent defocus with vision tasks, relative peripheral refraction as the cause of myopia development, mechanical tension of intraocular tissue (eye lens, ciliary body), and contrast signals related to photoreceptors.

The application of DIMS (Defocus Incorporated Multiple Segments, Hoya, Japan) leads the development of multi-segment lenses for myopia control in recent years [33]. These lenses maintain the same optical stimulus as concentric bifocal contact lenses (DISC) designed for myopia management (+2.5D defocus at the corneal plane) while offering enhanced treatment efficacy without the typical drawbacks associated with contact lens wear [53]. Long-term studies on DIMS lenses report no adverse effects or myopia rebound [54], and users maintain stable visual function throughout extended wear [55,56].

Following the success of DIMS, other multi-segment designs have emerged, such as Stellest (Essilor, France) [57] and MyoCare (ZEISS, Germany) [35].

- DIMS lenses feature a central clear zone (9 mm) surrounded by micro-lenslets (1.0 mm diameter, 0.5 mm spacing) arranged in nine hexagonal patterns with an additional +3.5D power.
- Stellest lenses incorporate similar micro-lenslets but add a highly aspheric design arranged in 11 concentric rings.
- MyoCare lenses employ concentric cylindrical refractive patterns in the periphery, providing approximately +4D of additional myopic defocus (equal to 8–9D cylindric power). These lenses are available in two configurations tailored to age groups: MyoCare for children under 10 years and MyoCare S for older children.

These designs claim significant myopia control efficacy compared to single-vision glasses. Published data suggests similar efficacy between DIMS and Stellest, both outperforming MyoCare. Specifically, myopia progression is reported to be reduced by approximately 50%, 74%, and 21%, and axial length control by 60%, 60%, and 23% for DIMS, Stellest, and MyoCare, compared to single-vision glasses, respectively [33,57,58]. However, as some researchers caution, using percentage reduction as a metric for myopia control can be misleading, as these values vary with factors such as age, baseline refractive error, ethnicity, and progression rates [59]. In addition, the aforementioned efficacies were observed in well-controlled randomized clinical trial, with definitive inclusion and exclusion criteria. But real-world studies reported much less effectiveness for these lenses [60,61].

5. The Characteristics of Peripheral Refraction in the Human Eye

5.1. Cross-Sectional Studies

Numerous studies have investigated the characteristics of peripheral refraction in the human eye (intrinsic peripheral refraction). This research is crucial for understanding how peripheral defocus impacts myopia development. For instance, the degree of intrinsic defocus in specific regions may influence the threshold at which defocus affects refractive development. Moreover, intrinsic peripheral refractive patterns might result from extrinsic peripheral refraction and could impact the efficacy of certain optical solutions, as suggested in recent hypotheses involving DIMS lens wearers [62].

Early clinical studies on peripheral refraction were typically limited to a few eccentricities. General trends observed include the following: hyperopes exhibit relatively peripheral myopic defocus, emmetropes show relatively flat or slightly myopic patterns, and myopes demonstrate relatively peripheral hyperopic defocus [63–71]. These findings are consistent with pilot studies dating back to 1971 [15,16]. Based on large-field refractive patterns, Mathur and Atchison proposed that refraction beyond 40 degrees likely has minimal influence on myopia development [64]. Asymmetric refractive patterns have been observed in both horizontal [72] and vertical meridians [69], with the latter often attributed to prolonged near-work activities [25]. This asymmetric pattern in vertical direction shows relative peripheral myopia for low myopes (although smaller than for emmetropes) [69], but it was observed again in other 2-D peripheral refraction studies [24,25].

However, discrepancies between studies remain, which may stem from factors such as ethnicity, accommodation, or differences in measurement instruments. For example, Lan et al. reported that Chinese children tend to have more relatively peripheral hyperopia compared to Caucasian children [24]. Kang et al. found that only moderate myopes exhibit increased relative peripheral hyperopia in East Asian populations [67]. Despite these variations, most studies support the association between peripheral hyperopia and myopia progression.

Direct comparisons across studies are challenging due to variations in sampling discrete eccentricities. A more comprehensive approach involves the use of 2D refractive maps, which facilitate faster comparisons. For instance, Osuagwu et al. employed a close-view aberrometer with 38 targets covering a 42° × 32° field, revealing that refractive patterns in the human eye lack radial symmetry [71]. However, this method is not efficient for long-term clinical trials.

In 2019, a high-resolution 2D mapping technique covering 60° × 36° field was applied to investigate the characteristics of peripheral refraction in Chinese children [24]. Their study demonstrated homogeneous refractive patterns across the peripheral retina in emmetropes, serving as a baseline in a two-year longitudinal study involving over 200 subjects [25]. The detailed 2D defocus maps revealed consistent features: relatively flat refraction in the vertical meridian and more pronounced peripheral defocus in the horizontal meridian [69,71], which aligns with differences in eye shape growth rates in different directions [73]. Myopic children and adults displayed greater variability and asymmetry in their refractive patterns, highlighting the potential benefits of customized myopia corrections for both myopia management and peripheral vision quality [74]. Although VPR technology has significantly improved measurement efficiency, its speed limitations restricted its use during the COVID-19 pandemic, allowing measurements for only one eye during tightly scheduled follow-up visits. Nevertheless, the observed mirror symmetry in binocular refraction among individuals with equal refractive errors reduced the necessity of simultaneous binocular measurements [75].

Recognizing the importance of 2D refractive maps, researchers developed a new prototype: Ultra-wide-angle Peripheral Refraction (UPER). This device measures 2D peripheral refraction within a 50-degree central field across 88 anchor points in just 2 s using a two-axis scanning mirror and a customized eyepiece [21,22]. The field explored can expand to 100° by altering internal fixation points. Intriguingly, the developers noted that far peripheral refraction cannot be accurately predicted based on near-peripheral refraction alone.

We compiled and reprocessed data from our previous publications, comprising 433 children and 473 adults, to generate the Myopia Development Evolution Tree Based on Retinal Refraction Maps (Figure 3). The majority of the data were sourced from studies by Lan (2019 [24]), Lin (2020 [76], 2023 [25]), Wang (2020 [75]), Xue (2023 [77]), Xi (2023 [74]), and colleagues. This evolution tree provides a clear visualization of how peripheral refraction patterns change across different levels of central refractive error. The high variability observed in emmetropic children and those with low myopia underscores the critical role of peripheral refraction management in the early stages of myopia development.

The establishment of the Evolution Tree was based on the two steps:

First, perform cluster analysis to classify peripheral refraction maps: (1). Combined the date sets for children and adults separately. The numbers of subjects in each group were as follows: for children, 157 in EM (emmetropia, $-0.5\ \text{D} \leq \text{SER} \leq 0.5\ \text{D}$), 106 in LM (low myopia, $-2.0\ \text{D} < \text{SER} < -0.5\ \text{D}$), 88 in MM (moderate myopia, $-4.0\ \text{D} < \text{SER} \leq -2.0\ \text{D}$), 59 in HM1 (high myopia group 1, $-6.0\ \text{D} < \text{SER} \leq -4.0\ \text{D}$), and 23 in HM2 (high myopia group 2, $\text{SER} < -6.0\ \text{D}$); for adults, 26, 83, 81, 97, and 186 subjects in EM, LM, MM, HM1, and HM2 groups, respectively. (2) Peripheral refraction data were converted into relative peripheral refraction values and normalized. (3) Cluster analysis was performed for each refractive group, generating dendrograms to identify categories. (4) The four most representative categories for each refractive group were selected based on dendrogram distance metrics. (5) Refraction maps for all subjects within each category were visualized. Categories exhibiting excessive intra-group variation were excluded to ensure group homogeneity. This cluster analysis protocol followed the methodology described in our previous publication [24]. The average matrix of each group's refraction map was then used as a representative map for constructing the Evolution Tree.

Second, analyze the similarity between adjacent layers. Similarity was defined as the mean slope between two matrices (with slopes normalized between –1 and 1), divided by the mean root mean square (RMS) of their differences, treating each matrix as a vector. Based on the calculated similarities, black arrows were drawn to indicate the most probable developmental connections from the lower to the upper layers. Only the strongest connections were retained, meaning that if three groups existed in the upper layer, only three arrows were drawn to illustrate potential connections.

It is important to note that the Myopia Development Evolution Tree Based on Retinal Refraction Maps is a speculative model based solely on the morphological similarities of refraction maps from cross-sectional studies. Thus, the findings should be interpreted with caution. Since adults are unlikely to develop further myopia

(reflecting a more stable peripheral refraction profile), results from adult groups are recommended for consideration when evaluating the evolution of peripheral refraction trajectories. Details regarding the study population are summarized in Table 1 (children) and Table 2 (adults).

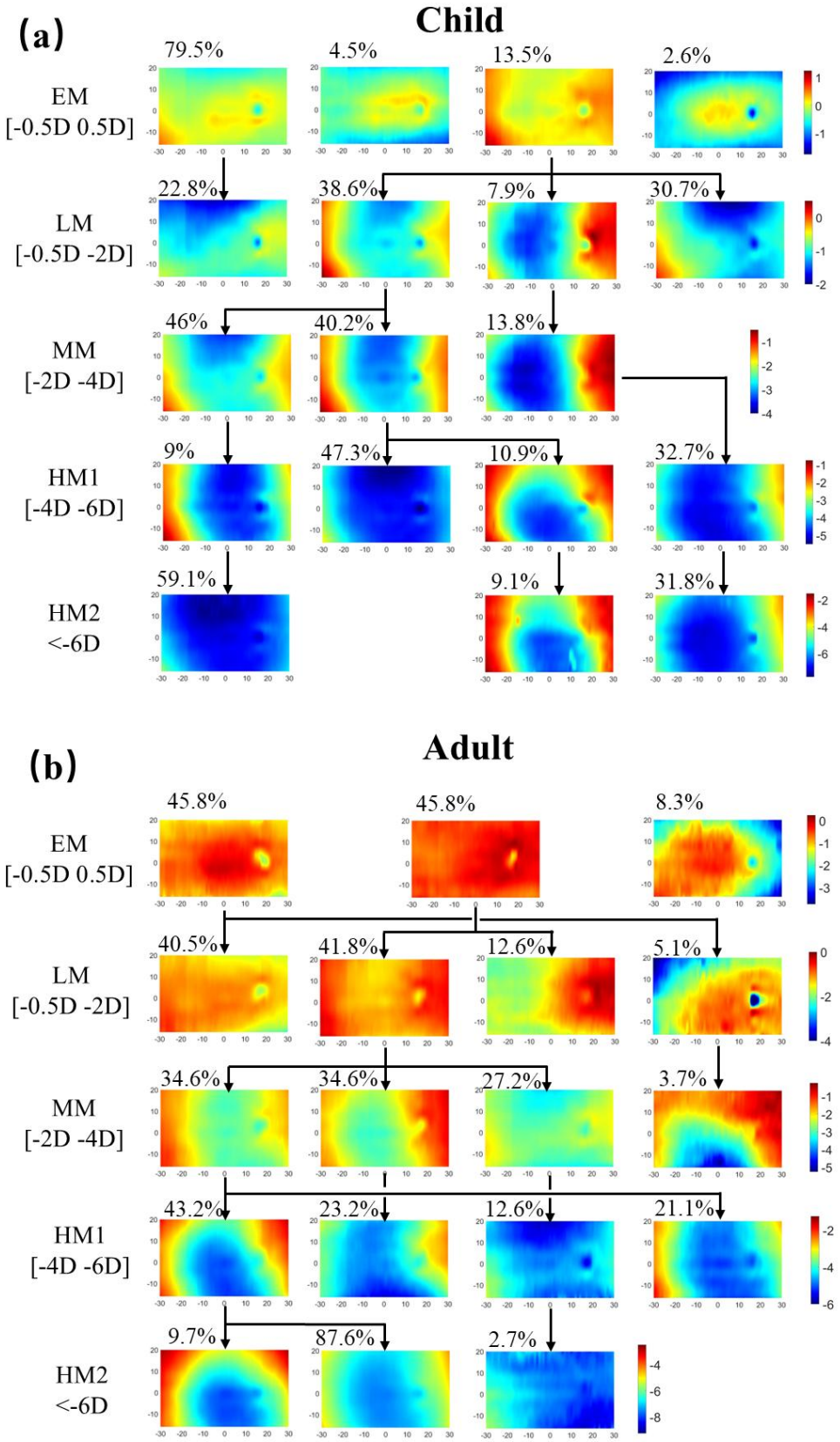

Figure 3. Myopia Development Evolution Tree based on retinal refraction maps. This figure illustrates the evolution tree of myopia development derived from retinal refraction maps from the right eyes of each participant.

Each map represents the average refraction data from a specific group of subjects. Each layer corresponds to a classified pattern determined through cluster analysis. The abbreviations EM, LM, MM, HM1, and HM2 denote emmetropia (−0.5D ≤ SER ≤ 0.5D), low myopia (0.5D < SER ≤ −2D), moderate myopia (−2D < SER ≤ −4 D), high myopia group 1 (−4D < SER ≤ −6 D), and high myopia group 2 (SER < −6 D), respectively. The maps in each layer represent the corresponding populations. Black arrows indicate the highest similarity between maps in adjacent layers, with each map in the lower layer connected to its most similar counterpart in the upper layer. Consequently, if the lower layer contains three maps, only three lines will connect to the upper layer. The proportion of the study population for each category is noted in the upper-left corner of the respective maps. For children, the color bar ranges are set as follows: EM [−1.75, +1.25] D, LM [−2.0, +0.5] D, MM [−4.0, –0.5] D, HM1 [−5.5, −0.75] D, and HM2 [−7.75, −1.5] D. For adults, the color bar ranges are set as: EM [−3.75, +0.25] D, LM [−4.0, 0] D, MM [−5.25, −0.25] D, HM1 [−6.0, –1.25] D, and HM2 [−9.25, −2.5] D.

Table 1. The demographics of the data set of Myopia Development Evolution Tree (children).

Group	Category 1			Category 2			Category 3			Category 4		
	N	SER (D)	Per	N	SER (D)	Per	N	SER (D)	Per	N	SER (D)	Per
EM (156)	124	0.0 ± 0.3	79.5%	7	−0.1 ± 0.2	4.5%	21	−0.1 ± 0.2	13.5%	4	0.1 ± 0.3	2.6%
LM (101)	23	−1.1 ± 0.4	22.8%	39	−1.2 ± 0.5	38.6%	8	−1.4 ± 0.3	7.9%	31	−1.1 ± 0.5	30.7%
MM (87)	40	−2.7 ± 0.6	46%	35	−3.2 ± 0.5	40.2%	12	−3.4 ± 0.4	13.8%	Not applicable		
HM1 (55)	5	−4.9 ± 0.7	9%	26	−4.9 ± 0.6	47.3%	6	−4.6 ± 0.4	10.9%	18	−4.9 ± 0.5	32.7%
HM2 (22)	13	−7.3 ± 1.3	59.1%	2	−6.6 ± 0.6	9.1%	7	−7.1 ± 1.3	31.8%	Not applicable		

Per: Percentage; N: The number of subjects; EM: emmetropia, −0.5D ≤ SER ≤ 0.5D; LM: low myopia, 0.5D < SER ≤ −2D; MM: moderate myopia, −2D < SER ≤ -4 D; HM1: high myopia group 1, −4D < SER ≤ −6 D; HM2: high myopia group 2, SER < −6D. The number in the parentheses means the total number of subjects in the corresponding group. This number is equal to or less than the original number as some of the refraction maps were excluded due to high individual variation. The sum of the percentage values in the corresponding refraction group should be added to 100%.

Table 2. The demographics of the data set of Myopia Development Evolution Tree (adult).

Group	Category 1			Category 2			Category 3			Category 4		
	N	SER (D)	Per	N	SER (D)	Per	N	SER (D)	Per	N	SER (D)	Per
EM (24)	11	−0.1 ± 0.2	45.8%	11	−0.3 ± 0.1	45.8%	2	−0.4 ± 0.0	8.3%	Not applicable		
LM (79)	32	−1.1 ± 0.4	40.5%	33	−1.4 ± 0.4	41.8%	10	−1.3 ± 0.6	12.6%	4	−1.0 ± 0.4	5.1%
MM (81)	28	−3.0 ± 0.5	34.6%	28	−3.1 ± 0.6	34.6%	22	−2.8 ± 0.6	27.2%	3	−2.9 ± 1.0	3.7%
HM1 (95)	41	−5.1 ± 0.6	43.2%	22	−4.8 ± 0.5	23.2%	12	−4.9 ± 0.7	12.6%	20	−5.2 ± 0.6	21.1%
HM2 (185)	18	−8.0 ± 1.2	9.7%	162	−7.6 ± 1.0	87.6%	5	−7.4 ± 1.3	2.7%	Not applicable		

Per: Percentage; N: The number of subjects; EM: emmetropia, −0.5D ≤ SER ≤ 0.5D; LM: low myopia, 0.5D < SER ≤ −2D; MM: moderate myopia, −2D < SER ≤ −4D; HM1: high myopia group 1, −4D < SER ≤ −6D; HM2: high myopia group 2, SER < −6 D. The number in the parentheses means the total number of subjects in the corresponding group. This number is equal to or less than the original number as some of the refraction maps were excluded due to high individual variation. The sum of the percentage values in the corresponding refraction group should be added to 100%.

5.2. Longitudinal Studies

A longstanding debate surrounding peripheral defocus theory is whether relatively peripheral hyperopia is a cause or a consequence of refractive development. Before addressing this question, it is important to distinguish between intrinsic peripheral defocus (IPD) and extrinsic peripheral defocus (EPD), as these two types of peripheral refraction may have differing impacts on myopia progression.

Animal studies and clinical trials involving optical interventions overwhelmingly support the idea that EPD can influence myopia progression. Peripheral myopic defocus appears to slow myopia progression, while peripheral hyperopic defocus promotes it. Methods for modifying EPD in animal studies include altering the visual environment (EPD-E) [78], using defocus lenses (EPD-EG) [79–82], and employing lenses with apertures (EPD-EG) [12]. In clinical settings, testing peripheral defocus theory involves the use of spectacles (EPD-EG) [48,57,58,83] and soft contact lenses (IPD-AG) [53,84]. This body of evidence underscores the significance of EPD in shaping refractive development, providing strong support for its role in both mitigating and exacerbating myopia progression. Orthokeratology (Ortho-K) has also been shown to influence peripheral refraction. Lin et al. [76] and Xue et al. [77] found that Ortho-K can introduce asymmetric 2-D peripheral refractive pattern in the

wearers, with decentered lenses shows more myopic defocus on one side of retina. This finding is consistent with the optical simulations conducted in Zemax. Li et al. [85] validated those decentered lenses was associated with the control of axial elongation and more oblate retinal shape. However, some studies indicate that the decentration of Ortho-K is irrelevant to the myopia treatment efficacy, which suggests that the myopia treatment effectiveness of Ortho-K might be independent of the peripheral refraction modification [86,87].

Conflicts exist within IPD (Intrinsic Peripheral Defocus) studies. Researchers aiming to verify the correlation between baseline intrinsic peripheral refraction and myopia progression have reported mixed results. Some studies indicate that peripheral refraction is not related to myopia progression [88–90], while others support the theory [25,91]. These discrepancies may be attributed to the retinal locations investigated. Studies showing non-significant results often examine peripheral refraction only in the horizontal direction and at a few eccentricities. In contrast, 2D peripheral refraction studies have found that the entire central vertical region of the retina, especially the superior retina, is associated with myopia progression. Therefore, it is plausible that studies unable to conduct a comprehensive exploration of pan-retinal refraction might arrive at incorrect conclusions. Comparisons of peripheral refraction in emmetropic children prior to the onset of myopia suggest that 2D intrinsic peripheral defocus is more likely a consequence of early-onset myopia due to near-work activities such as reading [25]. In fact, the refractive pattern resembles long-term exposure to extrinsic peripheral defocus from the inferior visual field [13].

A three-year clinical study compared peripheral eye elongation across four quadrants (nasal, temporal, superior, and inferior, up to 30°) between single-vision and +2.5 D addition contact lenses [92]. The authors hypothesized that myopia control would be more effective in the central vertical meridian than in the horizontal peripheral meridian, as relatively more peripheral hyperopia is typically observed in the nasal and temporal regions of the general population. However, the study found that the inhibition of peripheral eye elongation was relatively symmetric across the two perpendicular meridians. This finding suggests that the optical effects of the addition lenses may work through extensive spatial integration or mechanisms beyond localized defocus.

Nevertheless, the study may have overlooked key factors, including differences in retinal response mechanisms between emmetropic and myopic eyes [93,94], potential variability in the defocus response threshold across different eccentricities, and most importantly, the distinctions between the roles of intrinsic peripheral defocus (IPD, ocular refraction) and extrinsic peripheral defocus (EPD, contact lens refraction) in refractive development. For example, intrinsic relative peripheral refraction has been shown to have no correlation with relative peripheral multifocal electroretinogram (mfERG) amplitudes [95] but is significantly associated with additional absolute defocus [96,97].

6. Possible Mechanisms of Peripheral Defocus in Myopia Control

6.1. Optical Sign Recognition

A key premise of the peripheral defocus theory is that the retina can recognize the sign of defocus. While the underlying biomechanisms remain unclear, several hypotheses have been proposed from an optical perspective. For instance, Zheleznyak et al. simulated the through-focus images of point spread functions by using the wavefront data from periphery (nasal visual field), and they proposed that retina can identify the sign of defocus by recognize the orientation of retinal blur through the interaction of chromatic aberrations, primarily due to oblique astigmatism [98,99]. Thus, the notable astigmatism in periphery is the foundation to support the recognition mechanism [24,76,100], as well as the varied spectral sensitivity in different photoreceptors [101–104]. This mechanism has also been linked to the activation of accommodation to near objects. For example, a near object can produce a vertically elongated blur image in emmetropic eyes before accommodation occurs. In response, the eye adjusts to correct the orientation of the blur. Kendrick et al. conducted a similar study, providing further support for this theory [105].

Animal studies have also validated the theory of defocus recognition by demonstrating refractive changes and axial elongation in response to defocus. Rosen et al. found myopic eyes showed more sensitive visual perception to positive defocus (myopic defocus) than negative defocus (hyperopic defocus) [94]. Swiatczak and Schaeffel later confirmed that emmetropic eyes could distinguish between myopic and hyperopic defocus, but this ability was absent in myopic eyes [93,106]. Further evidence comes from Pusti et al., who found that changes in peripheral choroidal thickness in response to myopic and hyperopic defocus occurred only when native peripheral aberrations were preserved [107]. This finding also supports the possibility of a local defocus threshold in the periphery that influences myopia development.

6.2. Lag of Accommodation

Theoretically, accommodative lag can create relative hyperopic defocus in the periphery, thereby promoting myopia development through optical recognition mechanisms. Early studies observed greater accommodative lag in myopes compared to hyperopes [108,109], suggesting that increased lag could act as a contributing factor in myopia progression. In orthokeratology wearers, a shift toward peripheral myopic defocus has been noted [76,77], and improved accommodative accuracy following lens fitting has been proposed as a mechanism for the treatment's efficacy [110]. Similarly, studies on multifocal soft contact lenses indicate that greater accommodative lag is associated with faster myopia progression compared to single-vision contact lenses [111].

However, longitudinal studies in natural populations have presented a different perspective. Mutt et al. found that accommodative lag may be more of a consequence than a cause of myopia development, as lag increased after the transition from emmetropia to myopia [112]. Weizhong et al. also investigated the relationship between accommodative lag and myopia progression in mild and moderate myopes over a one-year period and found no significant correlation [113]. More recently, Lin et al. demonstrated that the myopia control effects of defocus-incorporated spectacles (e.g., DIMS, Stellest, MyoCare) are unlikely to result from improved accommodative abilities [114]. Overall, while accommodation plays a role in the process of myopia development, evidence suggests that it does not directly influence progression [115]. Instead, it appears to be a consequence of peripheral image modifications that drive refractive development.

6.3. Biological Mechanisms

Myopia progression may result from the cumulative stimulation of defocus-related signals, ultimately altering the endpoint of ocular development. In clinical settings, directly investigating the cellular and molecular mechanisms of peripheral defocus is challenging, as such studies require invasive methods to record transient changes in neuronal electrical activity and the release of neurotransmitters or growth-promoting factors across different layers of eye tissue. The biochemical pathways and regulatory mechanisms involved in this process are comprehensively documented by Troilo et al. [116]. First, the eye is believed to distinguish defocus signals through retinal photoreceptors, likely involving ganglion cells, by recognizing the orientation of the blurred image [98,105]. This hypothesis is supported by the discovery of melanopsin [117,118] and neuropsin [119] within retinal cells, which are sensitive to optical cues. Additionally, the bidirectional response to defocus has been validated through multifocal electroretinogram (mfERG) studies [96,97,120].

Second, photoreceptors activate a signaling cascade from the retina to the retinal pigment epithelium (RPE) by mediating the release of growth modulators, such as dopamine (DA), vasoactive intestinal peptide (VIP), nitric oxide (NO), gamma-aminobutyric acid (GABA), glucagon, and insulin. The RPE then promotes or inhibits the synthesis and release of various growth factors, including IGF-1, TGF-β, FGF, VEGF, and BMP, as well as cytokines. These factors regulate choroidal thickness, which in turn modulates the synthesis and secretion of specific growth mediators, most notably all-trans-retinoic acid (RA) and its synthesizing enzyme, to control scleral remodeling. Finally, the scleral remodeling process increases the extensibility of the vitreous chamber under intraocular pressure, resulting in myopia.

7. Challenges and Future Directions

7.1. Identifying the Type of Peripheral Defocus

The causal relationship between peripheral defocus and myopia development remains a key debate in the field. A major issue is the frequent conflation of intrinsic peripheral defocus (IPD) and extrinsic peripheral defocus (EPD). As Pusti et al. demonstrated, peripheral choroidal responses to localized defocus occur only when native peripheral refraction is preserved. This suggests that intrinsic peripheral refraction serves as a baseline, akin to a "growth factor" in the body, with its levels needing to remain within a specific range to prevent excessive or insufficient ocular growth. Moreover, this "baseline" may vary with central refractive error. To fully understand the role of peripheral defocus in refractive development, it is essential to isolate the distinct effects of IPD and EPD and study their physiological impacts on myopia progression.

7.2. Development of Instruments for IPD Measurement

A significant barrier to large-scale clinical studies is the lack of devices capable of accurately measuring Two-dimensional IPD maps. While some research prototypes exist, they are not widely available for clinical use. Current commercial devices, such as the Grand-Seiko WAM5500, are often used but lack the efficiency and

precision required for high-resolution peripheral refraction mapping. An ideal instrument for IPD measurement would be open-view, allowing for the consideration of accommodation responses under various visual scenarios, enabling a more comprehensive understanding of peripheral refraction.

7.3. Development of Instruments for EPD Measurement

As proposed in the "retinocentric view", a thorough understanding of peripheral refraction must account for both ocular refraction and the optical properties of the external environment. While some studies have investigated environmental diopter properties, the current approaches face limitations for large-scale application. For instance, Choi et al.'s method required access to children's homes [29,30], and helmet-based devices, though effective, are bulky and can alter the wearer's visual behavior [31]. A wearable, unobtrusive eye tracker resembling regular glasses would be ideal for EPD studies. Such a device should prioritize the comfort and mental well-being of the wearer while accurately tracking visual fixation, accommodation, and the spatial and temporal integration of total refraction across the retina.

7.4. Access to Peripheral Modification Approaches

Numerous optical solutions incorporating peripheral defocus have been developed for clinical myopia control. However, these products are not typically customized to the individual wearer due to high costs and incomplete understanding of peripheral refraction. Researchers must explore how different peripheral modifications affect the eye and refine these interventions. The current lack of methods for clinicians to design personalized peripheral modification approaches (e.g., customized glasses) restricts experimentation to a few specialized institutions, slowing the advancement of peripheral defocus theory. A promising future solution is 3D printing technology, which could reduce costs and enable the creation of complex, tailored optical structures for individualized myopia control.

7.5. Interdisciplinary Cooperation

Total peripheral defocus encompasses both ocular refraction (IPD: peripheral defocus + accommodation + contact lenses) and external optical cues (EPD: dioptric environment + fixation + glasses). Understanding the mechanisms underlying peripheral defocus and its effects on myopia development requires a comprehensive analysis of these factors. Given the complexity of these interactions, interdisciplinary collaboration is crucial. Experts from diverse fields, including ophthalmology, optometry, statistics, optical engineering, software development, and basic medical sciences, must work together. Mathematical models can be developed to explain the global impact of total peripheral defocus on myopia progression. An optimized solution for myopia control in children should integrate optical and pharmacological interventions with strategies for managing visual behavior, improving indoor environments, and implementing school policies to reduce near-work durations.

8. Conclusions

Peripheral defocus has emerged as a critical concept in understanding and managing myopia progression. This review provides a comprehensive overview of its definition, measurement methods, and the mechanisms through which peripheral defocus influences refractive development. Advances in optical technologies, such as multi-segment spectacle lenses and orthokeratology, have leveraged peripheral defocus theory to slow myopia progression, offering significant promise for clinical applications. Despite these advancements, multiple challenges remain to solve, including the need for precise measurement tools for intrinsic and extrinsic peripheral defocus, a deeper understanding of their distinct roles, and cost-effective customization of optical solutions.

The evidence supports that both intrinsic and extrinsic peripheral defocus contribute to myopia development, with their effects mediated through optical, accommodative, and biological pathways. However, discrepancies in study results underline the importance of standardizing methodologies and conducting comprehensive 2D refractive mapping. Furthermore, interdisciplinary collaboration is essential to unravel the complex interactions between ocular and environmental factors and to optimize myopia control strategies.

Future research should focus on refining measurement technologies, exploring personalized optical interventions, and integrating behavioral and environmental adjustments into myopia management protocols. By addressing these challenges, we can advance the understanding of peripheral defocus and develop more effective strategies to combat the growing global myopia epidemic.

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We thank Karger Publishers for granting permission to reproduce [Figure 1A] from reference [15] (License number: 6025951337366).

Conflicts of Interest

The authors declare that they have a patent application (US Patent App. 17/920,791) related to the measurement of peripheral retinal refraction, which is relevant to the topic discussed in this paper.

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