Changes in fundus by optical coherence tomography in patients with chronic obstructive pulmonary disease: A systematic review

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) exerts a negative impact on various tissues and organs throughout the body due to chronic hypoxia. The retina and choroid are implicated in this process, and the application of optical coherence tomography (OCT) enables the detection of potential changes in the fundus. This study aims to explore and discuss OCT-assisted fundus alterations in individuals with COPD by undertaking a systematic review.

Materials and Methods: A systematic review of the literature was conducted in adherence to the PRISMA checklist. Exclusion criteria encompassed articles published in non–peer-reviewed journals or unpublished literature. Consistent criteria were applied during both the title-and-abstract screening and full-text screening phases. Inclusion criteria comprised research conducted in the English language and published after 1993. Selection criteria were articulated in accordance with PICOS. Articles falling within the purview of meta-analyses, systematic reviews, guidelines, case reports, pilot studies, and non-human studies (e.g., laboratory research) were excluded from consideration.

Results: A total of 68 articles were initially identified, 10 reports met inclusion criteria and were included in qualitative analysis. In Turkey were conducted 8 studies and 2 studies in Egypt. All the studies included are case-control designed. Above-mentioned changes in retina were studied in 10 cases and found in 8 of them. In the same time changes in choroid were studied in 9 cases and found in 6 of them.

Conclusions: The findings of this systematic review indicate that, as observed through OCT, chronic hypoxia and systemic inflammation resulting from COPD predominantly impact the retina and choroid.

KEYWORDS:
OCT, COPD, hypoxia, retina, choroid

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality today. COPD is projected to become the third leading cause of death worldwide by 2030.[1] This condition poses a substantial public health issue, significantly burdening healthcare systems worldwide.[2] COPD may affect up to 10% of the general population with some significant contrasting prevalence in men and women[3], where the former are most exposed due to high smoking prevalence, occupational exposures4 and late admission for care, especially in the developing countries. Some population-based studies estimate that only one in four COPD patients know of the condition and receive a timely diagnosis.[5] COPD is a progressive chronic condition and affects almost all organs, leading to dramatic decrease in health-related quality of life and colossal costs for healthcare. One of these target organs can be retina and other ocular structures.[6-13] The retina, a crucial part of the eye, shares its embryonic origins with the brain, forming from the diencephalon.[12] Eye, retinal, and choroidal cells exhibit structural and mechanistic similarities with central nervous system cells.[13]

Distinguishing features of retinal circulation include a greater difference in oxygen content between arteries and veins, lower arteriolar saturation, and almost double the oxygen extraction from arterial blood compared to most body tissues.[14-15] The retina receives blood from two sources: the inner six layers are nourished by branches of the central retinal artery (a branch of arteria ophthalmica), while the outer layers are supplied by the choriocapillary layer of the choroid. Branches of the central retinal artery and vein traverse the nerve fiber and ganglion cell layers, forming a capillary network, that is the most prominent in the posterior retina.[16-18] This network lies between the feeding artery and draining vein. Retinal capillaries arise from precapillaries in the nerve fiber layer, creating a network at the junction of the outer plexiform and inner nuclear layers. The walls of retinal capillaries, similar to those in the brain, consist of a basement membrane and a non-fenestrated epithelium.

Approximately 98% of eye's blood flow occurs in the choroid, with 85% in the choriocapillary layer, which supplies the retinal pigment epithelium and outer retina. Choroidal circulation is characterized by high velocity, low oxygen extraction, and low resistance, regulated by the sympathetic nervous system, making it more responsive to systemic vascular changes than retinal vessels. Hypoxia's negative impact can lead to damage in retinal and choroidal cells.[19-26] Given the retina's heightened sensitivity to chronic hypoxia, fundus examination proves relevant for diagnosing and

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tracking the progression of diseases like chronic obstructive pulmonary disease, diabetes, hypertensive retinopathy, among others.[27-36]

Routine fundus examination methods encompass direct and indirect ophthalmoscopy. For a more detailed assessment, especially in diseases necessitating early detection, optical coherence tomography (OCT) serves as a valuable tool. Since its introduction in 1993, OCT employs non-invasive, intravital infrared radiation to provide a layer-by-layer assessment of eye structures. Its extensive research potential extends beyond ophthalmology into general medicine, facilitating early disease identification and prevention of irreversible tissue and organ changes.[19,37]

Numerous studies have explored the association between OCT-assisted fundus findings and somatic diseases.[19,38-42] Although, there is a noticeable lack of a comprehensive review specifically examining the relationship between OCT findings and chronic hypoxia in individuals with COPD. This study aims to address this gap by conducting a systematic narrative review of OCT-assisted fundus changes in patients with COPD.

MATERIALS AND METHODS

Literature search strategy

A systematic review of the literature was meticulously conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[43] checklist (Figure 1). Prior to initiating the review, the authors established internal protocols outlining the search strategy, selection criteria, and procedures for data extraction. Two authors independently conducted searches on Pubmed and MEDLINE. The search strategy incorporated specific terms of interest, with the search string adapted to include database-specific filters and relevant search terms. The search strings employed were: ((OCT) AND (retina)) AND (COPD), ((OCT) AND (retina)) AND (chronic obstructive pulmonary disease), ((optical coherence tomography) AND (retina)) AND (COPD), ((optical coherence tomography) AND (retina)) AND (chronic obstructive pulmonary disease), ((OCT) AND (choroid)) AND (COPD), ((OCT) AND (choroid)) AND (chronic obstructive pulmonary disease), ((optical coherence tomography) AND (choroid)) AND (COPD), ((optical coherence tomography) AND (choroid)) AND (chronic obstructive pulmonary disease). The search results were last updated on May 10, 2022. Any discrepancies between reviewers were resolved through discussion.

Inclusion and exclusion criteria

Articles published in non–peer-reviewed journals or unpublished literature were systematically excluded from this review. Consistent criteria were applied during both the title-and-abstract and full-text screening phases. Research conducted in the English language and published after the year 1993 was considered for inclusion. The selection criteria were defined in accordance with Population, Intervention, Comparison, Outcome, Study Design.[44] Exclusion criteria involved evidence from meta-analyses, systematic reviews, guidelines, case reports, pilot studies, and non-human studies (e.g., laboratory research). The exclusion of studies was executed following a thorough review of abstracts. Subsequently, articles were manually examined to eliminate those associated with other methods of ophthalmological assessment, oncology, pediatric cases, studies involving healthy subjects, separate diseases, lifestyle-related studies not directly related to disease, and studies lacking measurements of hypoxia signs in the retina or choroid. Both prospective and retrospective studies were considered in the review. Unspecified information in the abstract regarding any of the criteria did not automatically lead to exclusion during the title-and-abstract phase. In such cases, the full text was scrutinized before making a determination on inclusion or exclusion.

Data extraction

The process of data extraction and quality assessment was conducted independently by two reviewers. The information extracted from each study encompassed bibliographic details (authors and year of publication), the number of eyes included, patients' age, gender distribution, concomitant pathology, and pathological changes observed in the retina and/or choroid. Studies lacking any of the aforementioned information were excluded from consideration.

RESULTS

Initially, 68 articles were identified, and after eliminating 46 duplicates, 22 publications remained. Subsequently, 7 articles were excluded during the screening process for the following reasons: study type (n=2), non-English language (n=1), studies unrelated to COPD (n=4). This left 15 publications for full-text review, and 5 of them were excluded for the following reasons: utilization of another assessment method (n=3), studies involving children (n=1), and non-English language (n=1). Ultimately, 10 reports met the inclusion criteria and were included in the qualitative analysis (Fig. 1). Quality assessment utilized checklists with responses of 'yes,' 'no,' or 'unclear' to eight questions, each signifying whether the study met specific quality criteria. All 10 studies clearly articulated their objectives. Among these, 8 studies were conducted in Turkey, and 2 studies were conducted in Egypt, all following a case-control design. The age range of participants was 43-80 years, with children defined as individuals under the age of 18. Gender information was absent in only one study. Five studies categorized patients based on the severity of COPD, while the remaining five did not consider COPD severity. Changes in the thickness of any quadrant of the retina and/or choroid were considered indicative of the effects of COPD. The fundamental characteristics of the included studies are summarized in Table I, with more detailed information available in Table II.

Overall, most included studies concluded that COPD patients exhibited changes in both retina and choroid compared to healthy controls, but these differences did not reach statistical significance in all studies. Thus, retinal changes were found in eight out of ten studies. In those eight studies, where statistically significant differences in COPD patients compared to controls were identified, seven studies consistently showed retina thinning, whereas the remaining study showed the opposite effect, with retinal thickening in COPD patients. The country of origin did not affect such

Table I: Characteristics of the included studies

Author	Country	Sample size	Age range	Gender (m/w)	Division to groups according to the severity of COPD**	Effects of COPD	
						Retina	Choroid
M. Ozcimen et al. (2015)[49]	Turkey	73 (50)*	57-73	45/28	No	Was indicated significant changes	Studied, without
E. Ugurlu et al. (2016)[50]	Turkey	43 (31)*	53-73	43/0	No	Was indicated significant changes	Studied, without
M. Gok et al. (2017)[7]	Turkey	79 (71)*	51-73	59/20	Yes	Was indicated	Studied, without significant changes
O. Kocamıs and D. Zorlu (2018)[52]	Turkey	60 (23)*	56-72	N/A	Yes	Studied, without significant changes	Was indicated
M. Gunduz et al. (2019)[51]	Turkey	30 (29)*	50-70	26/4	No	Was indicated	Not studied
Mai G. Abd El-Naser et al. (2019)[45]	Egypt	40 (20)*	52-62	33/7	Yes	Was indicated	Was indicated
N. Ogan et al. (2019)[46]	Turkey	48 (40)*	50-80	38/10	Yes	Was indicated	Was indicated
S. Alim et al. (2019)[53]	Turkey	26 (26)*	50-68	26/0	No	Studied, without significant changes	Was indicated
P. Ozer and N. Ogan (2020)[47]	Turkey	55 (48)*	56-78	39/16	No	Was indicated	Was indicated
Noha Othman Ahmed et al. (2021)[48]	Egypt	50 (50)*	43-60	42/8	Yes	Was indicated	Was indicated

*Control group
** COPD - Chronic obstructive pulmonary disease

Table II: COPD*-associated changes by OCT

Author	COPD-associated retinal changes	COPD-associated choroidal changes
M. Ozcimen et al. (2015)[49]	Average RNFL** thickness was significantly lower in COPD patients (p=0.044).	SFCT*** measurements of the COPD group were lower than the control group; but did not show any statistical significance (p = 0.111).
E. Ugurlu et al. (2016)[50]	Changes in all parts of the retina, but statistically significant changes only in the inferior quadrant (p=0.003). The inferior quadrant RNFL was significantly thinner in the COPD group.	The mean SFCT was found to be similar in both groups, COPD and control.
M. Gok et al. (2017)[7]	Statistically significant changes in the mean value of all RNFL quadrants (p = 0.023) and the nasal segment of RNFL (p = 0.027); separately, other RNFL quadrants did not show statistically significant results in comparison with the control group. RNFL thickness was lower in COPD group.	The macular choroidal thickness at all locations were somewhat lower in both patient subgroups compared with the control group, but statistical significance was not attained (p=0.536).
O. Kocamıs and D. Zorlu (2018)[52]	No statistically significant difference was present between the mean RNFL of the COPD patients and the control group.	SFCT of the COPD patients in both the exacerbation and stable groups was found to be statistically significantly thinner than the control group (p = 0.047 and p = 0.046, respectively).
M. Gunduz et al. (2019)[51]	The average and superior quadrant RNFL thickness parameters were found to be significantly thicker in COPD subjects compared to the control subjects (p<0.05).	Not studied.
Mai G. Abd El-Naser et al. (2019)[45]	RNFL was significantly thinner in the COPD groups than the control group in all quadrants (except the superior one) and in the average values (p<0.001). When comparing group 1a (mild to moderate COPD group) and group 1b (severe to very severe COPD group), was found a statistically significant thinning in the RNFL in inferior and temporal quadrants in group 1b (severe to very severe COPD group).	SFCT was significantly thinner in the COPD groups compared to the control group. The thinnest SFCT was observed in group 1b (severe to very severe COPD group) compared to control group and group 1a (mild to moderate COPD group). These differences were statistically highly significant (p<0.001).
N. Ogan et al. (2019)[46]	Statistically significant thinning of RNFL in the inferior (p<0.001) and temporal (p=0.009) quadrants.	Significant thinning in the thickness of the choroid (p < 0.001) in severe COPD patients compared with mild COPD and the control group.
S. Alim et al. (2019)[53]	There was no statistically significant difference between patients and control group regarding mean, superior, nasal, inferior, and temporal RNFL thicknesses.	SFCT measurements revealed a statistically significant lower results in COPD patients versus the control group (p<0.05).
P. Ozer and N. Ogan (2020)[47]	Inferior RNFL was lower than control during the initial and sixth month examination (p=0.002, p<0.001, respectively). Average RNFL was lower in COPD patients in sixth month examination (p=0.020).	Average SFCT was lower in COPD patients at the sixth month examination (p = 0.015).
Noha Othman Ahmed et al. (2021)[48]	The thickness of the superior, inferior, and temporal RNFL thickness was statistically decreased significantly in the patients with higher GOLD classification (p-value 0.001).	SFCT thinning showed a highly statistically significant thinning with the higher GOLD classification (p-value of 0.001)

* COPD - Chronic obstructive pulmonary disease
** RNFL – Retinal nerve fiber layer
*** SFCT - Subfoveal choroidal thickness

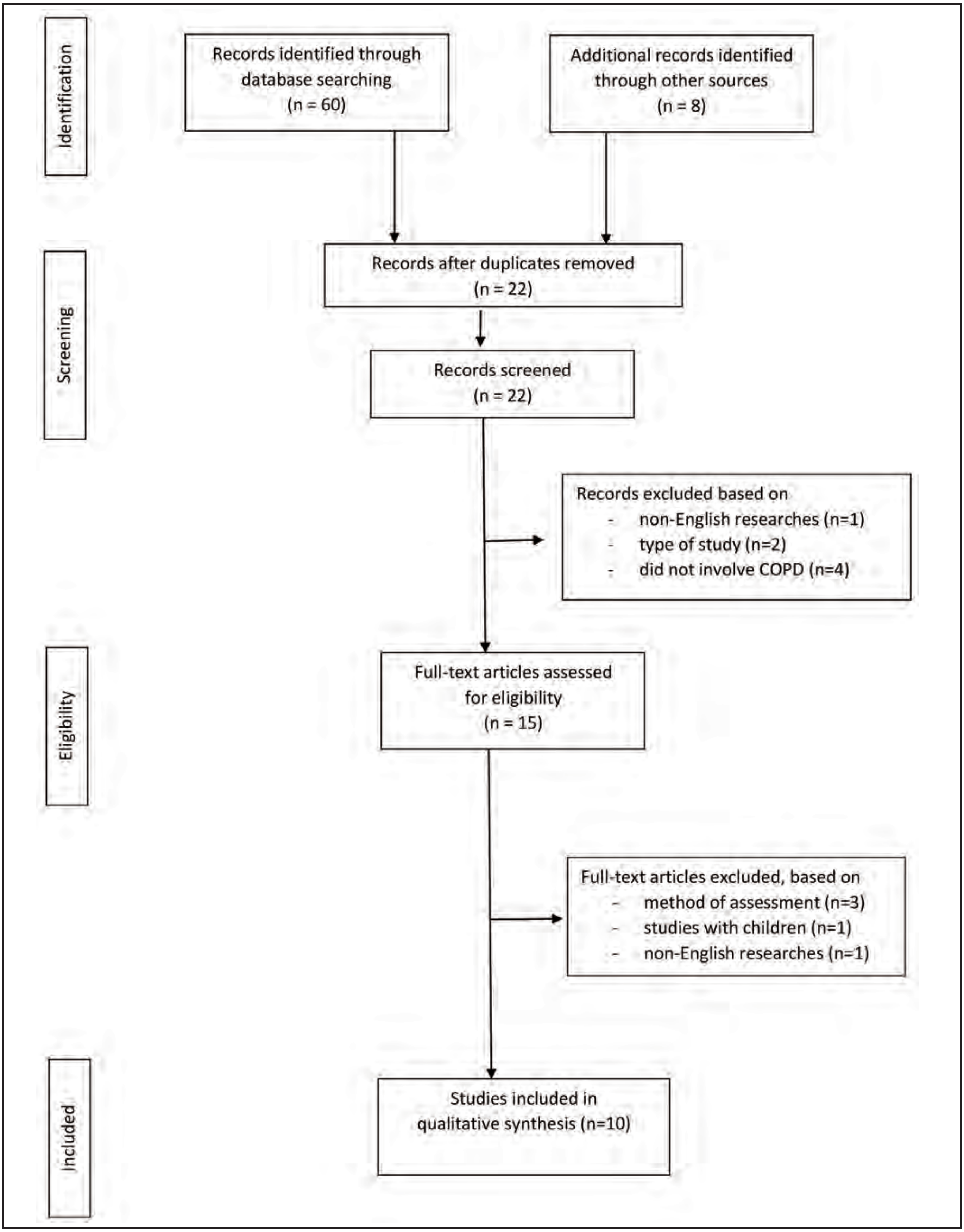

Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the process of study selection. Retrieved from Moher et al. (2009).

finding, because reports with consistently thinner retina in COPD patients were not only from Turkey, but from Egypt as well. Furthermore, location of such retina thinning could differ between studies. Finally, we found no differences in sample size, sex distribution or other attributes between studies showing thinner retina in COPD patients compared to those with thicker retina or no effect. We, therefore, conclude that some association between COPD and retina thinning is present.

With regard to choroid, all studies demonstrated either thinner choroid or no effect with no reports confirming the opposite effect. Thus, six studies out of nine with some choroid thickness data (66%), demonstrated thinner choroid in COPD patients, and in some studies the effect was also associated with COPD severity. Moreover, when studies showing a correlation between COPD and choroidal thickness were compared to those showing no correlation, we did not confirm differences in either sample size of the distribution. We thus conclude that some association between COPD and choroid thickness is likely.

DISCUSSION

The aim of this review was to elucidate the role of OCT in detecting changes in the retina and choroid attributed to COPD. To the best of our knowledge, this study represents the first systematic review on the application of OCT in assessing the fundus of patients with COPD. The qualitative analysis encompassed 10 studies, which utilized OCT to identify changes in the retina, choroid, or both. Four publications[45-48] reported statistically significant COPD-induced changes in both the retina and choroid. Changes in the retina alone were significant in four studies[7,49-51], while alterations in the choroid alone were observed in two manuscripts.[52-53]

The first metric we tested in our paper was retinal thickness. Retinal thickening was observed in one study[49], thinning in seven studies[7,45-50], and no changes in two studies.[52,53] The study by Gunduz et al. (2019)[51] attributed thickening to hypoxia/ischemia-induced retinal and optic disc edema, potentially masking peripapillary Retinal Nerve Fiber Layer (RNFL) loss associated with retinal ganglion cell death. Conversely, studies by Ozkan Kocamıs and Duygu Zorlu (2018)[52] and S. Alim et al. (2019)[53] showed no changes in RNFL thickness, with sample sizes of 60 and 26 patients, respectively. The study by S. Alim et al. (2019)[53] did not include group divisions among COPD patients. In the other seven studies[7,45-50], thinning of RNFL in COPD patients was attributed to systemic inflammation and chronic hypoxia, with larger sample sizes (40 patients and above) and variations in the severity of COPD.

Choroidal thickness, the second metric under study in our analysis, was examined in six studies[45-48,52,53], and no changes were identified in three studies.[7,49,50] Thinning in six studies was explained by impaired choroidal vascular autoregulatory mechanisms or chronic hypoxia-induced increase in vascular resistance in COPD patients. The absence of changes in choroidal thickness in three studies might be attributed to small sample sizes and heterogeneity of COPD stages. Such findings need a deeper insight into the potential mechanism of the association, and the latter can be explained with the changes in blood flow, which develop gradually in COPD patients.

All included studies were published from only two countries, Turkey and Egypt, neglecting some potential association of COPD with eye pathology in other countries. The findings of our analysis should be interpreted with caution given that patients included did not have concomitant decompensated somatic pathologies, ophthalmological pathologies (a history of prior laser and intraocular surgeries, glaucoma, optic neuropathy, amblyopia, advanced cataracts, spherical equivalent refractive errors (RE) greater than ± 3.0 diopters, axial length (AL) over 25 mm, choroidal neovascularization or myopic degeneration, clinically significant opacities in the ocular media, and poor-quality images due to unstable fixation). Therefore, these findings cannot be generalized to the entire cohort of the world COPD population, which usually exhibits high heterogeneity in terms of comorbidities, COPD severity and compensation, as well as some interaction with other medications taken for the concomitant conditions. In addition, other confounders may affect the overall effect, including cigarette smoking, electronic cigarette use, secondhand smoke, leisure physical activity, occupational exposures, air pollution, and all these confounders may be hard to control and classify. Together with some unmeasured confounding usually present in epidemiological studies, these attributes may seriously bias the association, and we consider this a limitation of our analysis.

Cigarette smoking and electronic cigarette use deserves special attention in COPD patients and the associated changes in the eye fundus. From the current data, it is unclear whether the changes reflect the general smoking-related vascular pathology or, alternatively, COPD as a chronic condition. Smoking itself is a strong predictor of retinal vascular changes[54-55]; therefore, future studies should stratify all COPD patients based on their smoking status, and retinal abnormalities must be assessed separately in those who have never smoked and current daily smokers, including those amongst COPD patients.

Another limitation of our study is the overall small sample size. COPD is a prevalent disease, and millions of people in the world should be diagnosed with the condition; nevertheless, only very few COPD patients are included in the studies involving OCT, because eye involvement traditionally gets little attention in these patients. None of included studies enrolled more than 100 COPD patients, and this indeed necessitates larger studies with greater samples for greater statistical power. One more limitation in this analysis is heterogeneity between studies with regard to COPD severity and clinical attributes. COPD is a disease with contrasting clinical severity between patients, which may differ in the number of hospitalizations, severity of daily symptoms, use of medications, physical exercise tolerance, health-related quality of life, and even need for oxygen. Clear stratification into groups with varying clinical severity and even spirometry in these studies was challenging.

Future studies are needed to establish stronger, more consistent evidence in more homogenous groups of COPD patients. Longitudinal studies with larger cohorts, standardized protocols for OCT imaging, and control for confounding variables (e.g., comorbidities, smoking status, medications use, etc.) will be critical to determine whether OCT can serve as a reliable marker of COPD severity. The future trajectory of OCT devices, including advancements like OCT angiography (OCTA) and Doppler OCT (FD OCT), holds promising potential for diverse clinical applications, transcending the realm of ophthalmology. This evolution is likely to open new frontiers in understanding and managing COPD and various diseases across medical disciplines.

CONCLUSION

This systematic review underscores that chronic hypoxia and systemic inflammation resulting from COPD likely impact the retina and choroid, with more pronounced changes observed in advanced stages of the disease. The widespread adoption of OCT devices extends beyond ophthalmology, enabling not only ophthalmologists but also specialists from diverse fields such as physicians, cardiologists, endocrinologists, and pulmonologists to confirm or monitor changes in the underlying disease.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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