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Review Article

The unmet need for better risk stratification of non-proliferative diabetic retinopathy

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Abstract

Diabetic retinopathy is a common microvascular complication of diabetes and remains one of the leading causes of preventable blindness in working-age people. Non-proliferative diabetic retinopathy is the earliest stage of diabetic retinopathy and is typically asymptomatic. Currently, the severity of diabetic retinopathy is assessed using semi-quantitative grading systems based on the presence or absence of retinal lesions. These methods are well validated, but do not predict those at high risk of rapid progression to sight-threatening diabetic retinopathy; therefore, new approaches for identifying these people are a current unmet need. We evaluated published data reporting the lesion characteristics associated with different progression profiles in people with non-proliferative diabetic retinopathy. Based on these findings, we propose that additional assessments of features of non-proliferative diabetic retinopathy lesions may help to stratify people based on the likelihood of rapid progression. In addition to the current classification, the following measurements should be considered: the shape and size of lesions; whether lesions are angiogenic in origin; the location of lesions, including predominantly peripheral lesions; and lesion turnover and dynamics. For lesions commonly seen in hypertensive retinopathy, a detailed assessment of potential concomitant diseases is also recommended. We believe that natural history studies of these changes will help characterize these non-proliferative diabetic retinopathy progression profiles and advance our understanding of the pathogenesis of diabetic retinopathy in order to individualize management of people with diabetic retinopathy.

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Introduction

Diabetes is now regarded as a global epidemic. In 2017, it was estimated that 425 million people worldwide (aged 20–79 years) were affected by diabetes, and this number is expected to rise to 629 million by 2045 [1]. Consequently, the occurrence of the microvascular ocular complication, diabetic retinopathy, is also escalating. It has been estimated that a third of people with diabetes have signs of diabetic retinopathy [1] and that 10% of those have signs of sight-threatening retinopathy, one of the leading causes of blindness in working-age people [1]. Suboptimal management of diabetes may be associated with the development and subsequent progression of diabetic retinopathy at a population level but not necessarily on an individual level. Independent risk factors for diabetic retinopathy development and progression include hyperglycaemia, hypertension and increasing duration of diabetes [2].

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Diabetic retinopathy is associated with hyperglycaemia-induced metabolic stress [3], which leads to vascular basement membrane thickening in the retina and damage to all major retinal cells, including endothelial cells and pericytes. Inflammatory and structural neurodegenerative changes are often present during the early stages of microvascular change attributable to diabetic retinopathy [4,5]. Early retinal non-perfusion in people with diabetes may cause ischaemia and impaired oxygenation of retinal neurons, and is likely to be associated with leukostasis, which has important implications for continuing capillary non-perfusion [6].

Non-proliferative retinopathy, the earliest stage of diabetic retinopathy, involves microvascular changes that are typically asymptomatic, even at advanced stages [7]. Non-proliferative retinopathy progresses from mild through to moderate to severe and, in some people, may progress to sight-threatening diabetic retinopathy, such as proliferative diabetic retinopathy or diabetic macular oedema [6]. Rates of non-proliferative retinopathy progression to sight-threatening diabetic retinopathy can vary: the accumulative occurrence rates of 5-year progression from mild non-proliferative retinopathy and moderate non-proliferative

What's new?

- Diabetic retinopathy, one of the leading causes of preventable blindness in working-age people, is assessed based on the presence or absence of retinal lesions in the fundus.
- Current classifications of non-proliferative diabetic retinopathy are not predictive of the risks of rapid progression to sight-threatening diabetic retinopathy.
- Non-proliferative retinopathy progression profiles may benefit from assessments of the following lesion characteristics: shape and size of lesion; angiogenic origin; location, including peripheral retina; turnover and dynamics; and concomitant hypertensive retinopathy.
- Natural history studies of these changes may improve our understanding of the pathogenesis, progression and management of diabetic retinopathy.

retinopathy to proliferative diabetic retinopathy in people with Type 2 diabetes was determined to be 14% and 58%, respectively [8]; however, predicting which people with non-proliferative retinopathy are at high risk of progressing to sight-threatening diabetic retinopathy remains a challenge.

Progression of non-proliferative retinopathy to sight-threatening diabetic retinopathy and blindness is preventable, particularly when detected at an early stage [7], therefore, the prediction and prevention of progression are crucial. Currently, in the UK, the Royal College of Ophthalmologists guidelines recommend annual screening for all people with diabetes [9]; however, this may be too infrequent for people at high risk of rapid progression to sight-threatening diabetic retinopathy and too frequent for those at a low risk of progression to sight-threatening diabetic retinopathy [10], suggesting that a new method for identifying diabetic retinopathy in people with diabetes is needed. Identifying people with the greatest risk of progression and greatest potential to benefit from treatment is of the utmost importance; healthcare resources must be prioritized for those who need regular follow-up and timely treatment during this diabetes epidemic.

Treatment options are lacking in non-proliferative retinopathy; in those receiving treatment, therapy is largely limited to pan-retinal photocoagulation [11]. Pan-retinal photocoagulation reduces the risk of visual loss and blindness, in most cases preserving rather than improving visual acuity. Pan-retinal photocoagulation is also associated with some decline in visual function, which may affect the person's ability to drive as well as other aspects of day-to-day living [11,12]. Furthermore, active disease, such as vitreous haemorrhages, may still develop during or after pan-retinal photocoagulation treatment; therefore, treatment is usually deferred until non-proliferative retinopathy is severe [11,12]. As most studies report the use of pan-retinal photocoagulation for the treatment of proliferative diabetic retinopathy, there is a lack of data specifically reporting the efficacy of pan-retinal photocoagulation for non-proliferative retinopathy [11]. Recent trials show promise for intravitreal anti-vascular endothelial growth factor (VEGF) treatments in severe non-proliferative retinopathy and proliferative diabetic retinopathy (NCT00473382, NCT00473330 and NCT014899189), although these trials also include people with diabetic macular oedema. Despite the recent approval given to the VEGF inhibitor ranibizumab for diabetic retinopathy [13], it is not yet clear what role ranibizumab will play in non-proliferative retinopathy treatment. Another concern is that intravitreal injections are invasive and inconvenient, and usually require the person to travel to a hospital for treatment. Alternative treatments that are effective at all stages of diabetic retinopathy and may help to prevent progression to sight-threatening disease are therefore desirable, particularly treatments that can be administered outside of a clinical setting such as oral or topical formulations. In this paper, we review the current non-proliferative retinopathy classification systems and consider how these could be optimized with risk stratification strategies based on the current understanding of retinal lesions.

Classification

Optometrists, ophthalmologists and retinal specialists classify diabetic retinopathy and identify people at risk of developing sight-threatening diabetic retinopathy based on the lesions identified, including microaneurysms, haemorrhages (including pre-retinal and vitreous), hard exudates, cotton wool spots, intraretinal microvascular abnormalities and venous and arteriolar abnormalities. The severity of diabetic retinopathy is determined using semi-quantitative grading systems, whereby the morphological appearance of the fundus is matched with the retinopathy grade, as observed on a set of standard fundus photographs. Lesions may be graded differentially depending on whether they are detected in single or multiple fields [14].

It was widely recognized that a uniform qualitative and quantitative analysis approach is needed to critically evaluate diabetic retinopathy and, consequently, a reproducible grading system has evolved over the past 50 years [14] (Table 1 [14–19])

Airlie House classification

The conference held at Airlie House, Virginia, in 1968 evaluated the current knowledge of the natural history of diabetic retinopathy and, after consensus, the attendees devised a formal and comprehensive standard classification of diabetic retinopathy [14]. This classification used standard stereoscopic fundus photography in four or five predetermined fields for the grading of lesions, whereby changes considered less severe than the standard example were classified as grade 1, and changes that were equal or worse than the standard example were classified as grade 2. Written

Table 1 Evolution of the non-proliferative retinopathy classification systems by year of development.

Airlie House, 1968 [14] (level) Definition	ETDRS, 1991 [15] (level) Definition	International Clinical Diabetic Retinopathy Disease Severity Scale, 2003 [16] (level) Definition	National Screening Committee UK [17], 2003 (level) Definition	Scottish Diabetic Retinopathy Grading Scheme, 2003 [18] (level) Definition	DR Deep Learning Algorithm, 2016 [19] Definition
(0) None	(10) Diabetic retinopathy absent	No apparent retinopathy	(R0) None	(R0) None	NA
(1) Mild to moderate	(20) Microaneurysms only	Mild non-proliferative retinopathy	(R1) Background diabetic retinopathy	(R1) Mild background diabetic retinopathy	
	(35) Mild non-proliferative retinopathy	Moderate non-proliferative retinopathy	(R2) Pre-proliferative diabetic retinopathy		Moderate non-proliferative retinopathy
	(43) Moderate non-proliferative retinopathy			(R2) Moderate background diabetic retinopathy	
(2) Moderate to severe	(47) Moderately severe non-proliferative retinopathy				
	(53 A-D) Severe non-proliferative retinopathy	Severe non-proliferative retinopathy		(R3) Severe background diabetic retinopathy	Severe non-proliferative retinopathy
	(53E) Very severe non-proliferative retinopathy				

The approximately mapped Airlie House, International, UK and Scottish classification systems.
ETDRS, Early Treatment of Diabetic Retinopathy Study; NA, not applicable.

materials documenting the number/size and type of lesions were also used to evaluate findings, such as new vessels, fibrous proliferation, and retinal elevations [14].

Early Treatment for Diabetic Retinopathy Study and international diabetic retinopathy classifications

The subsequent Early Treatment for Diabetic Retinopathy Study (ETDRS) disease severity scale is based on a modified version of the Airlie House classification system (Table 1). The ETDRS used stereoscopic colour fundus photography in seven standard fields (30 degrees), and became the reference standard against which screening tests were judged [15]. Of these seven standard fields, field 1 is centred on the optic disk, field 2 is centred on the macula, field 3 is temporal to the macula and fields 4–7 surround fields 1–3 [15]. More recently, digital evaluations were found to be comparable to both the ETDRS severity levels and design outcomes from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, and have therefore largely replaced stereoscopic colour photographs [20]. The ETDRS classification system allowed therapeutic endpoints and techniques for measuring endpoints to be defined in clinical trials, and provided a reliable assessment of treatments, whereby the efficacy of a treatment could be assessed according to stepwise changes in diabetic retinopathy severity levels [15]. While the ETDRS classification is widely recognized as appropriate for publications, research, and communications between retinal specialists, it was considered overly complicated for everyday clinical practice so an alternative, simplified scale was developed: the International Clinical Diabetic Retinopathy Disease severity scale [16]. This simplified scale allows disease severity to be easily communicated to primary healthcare providers who may not be experts in the field to ensure appropriate clinical recommendations for follow-up or treatment.

UK-based classifications: England and Scotland

In the UK, the ETDRS classification has also been simplified in screening protocols and applied to one-field (Scotland) and two-field (England, Wales and Northern Ireland) fundus photography [17]. These simplified approaches are based on diabetic retinopathy features that a non-ophthalmologist/accredited photographic grader might see in a population of diabetic people, but still provide sufficient diabetic retinopathy detection levels to merit referral for expert opinion from an ophthalmologist and possible treatment [9].

Artificial intelligence and automated diabetic retinopathy detection

The most transformative advance in diabetic retinopathy screening of this century is automated diabetic retinopathy detection. Software for automated detection of diabetic retinopathy lesions from fundus photographs have been developed, with the potential to reduce the workload of retinal graders by providing an automated real-time evaluation that can expedite referral and diagnosis, thus improving efficiency and cost-effectiveness [21]. In addition, integrating digital diabetic retinopathy images with electronic medical records may improve the individual's prognosis and provide an opportunity for predictive modelling of medical risk factors based on broad population data. Telescreening and remote analysis have the potential to improve access to diabetic retinopathy screening by improving efficiency and reducing costs, and new techniques are currently being developed. For widespread adoption of these methods, there is an urgent need for large studies evaluating the best telescreening approach, the hardware, the number of fields used and when to use mydriasis. When fully implemented, this approach has the potential to substantially improve the way diabetes eye care is delivered [21].

Using retinal images from the EyePACS database and other sources, Google Research, Inc. has developed and tested an automated deep learning system for the detection of diabetic retinopathy. This system has demonstrated consistent interpretation, high sensitivity and specificity, and rapid reporting of results [19]. Detection accuracy can be further improved by using an adjudicated tuning dataset and higher resolution images [22]. Other algorithms for automated grading of retinal images, capable of recognizing microaneurysms and other diabetic retinopathy lesions, have been developed, including the US Food and Drug Administration-approved IDx-DR system [23]. This is the first autonomous artificial intelligence diagnostic device approved for the detection of diabetic retinopathy in primary care, and is viewed as a promising system for modernizing healthcare delivery. In terms of real-world application, automated diabetic retinopathy detection is already implemented in Scotland using a two-tier strategy, replacing initial manual grading to assess image quality and to detect the presence of any retinopathy [24].

Risk factors and diabetic retinopathy

In clinical practice, risk factors such as diabetes duration, HbA_{1c} levels, hypertension, and hyperlipidaemia are often considered alongside the classification when diagnosing or grading diabetic retinopathy. In some countries, such as Iceland and Sweden, these risk factors are used to determine screening frequency [10], and this approach has also been successfully piloted in the Netherlands, Spain, and Denmark [25–27]. These risk factors may be relevant for determining the risk of initial diabetic retinopathy development, but they do not explain the highly variable progression of non-proliferative retinopathy; however, baseline severity of diabetic retinopathy continues to predict clinical outcomes: Sato *et al.* [8] reported that 35% of people with moderate non-proliferative retinopathy developed proliferative diabetic retinopathy within 2 years, whereas people with mild non-proliferative retinopathy did not. Furthermore, using baseline diabetic retinopathy as a risk factor for determining the rescreen interval led to demonstrable cost savings, highlighting the importance of accurate initial grading [18].

The concept of stratification based on the risk of progression, although not widely implemented, is gaining popularity: Cunha-Vaz *et al.* [28] illustrated that distinct patterns of diabetic retinopathy evolution were associated with different prior manifestations of diabetic retinopathy; by categorizing people into phenotypes dependent on retinal features, differential patterns of progression were identified (ischaemia, leakage, and inflammation). Other studies have shown that profiling of lipoprotein sub-types was associated with diabetic retinopathy severity levels, but this is yet to be validated in large-scale studies before inclusion in routine screening [29].

Approaches investigating the influence of various factors on the progression of non-proliferative retinopathy and the responses to diabetic retinopathy therapy remain an unmet need, and further investigation may improve the current understanding of the pathogenesis of diabetic retinopathy and the potential benefits of accurate classification and early intervention.

Non-proliferative retinopathy lesions

Moderately severe and severe non-proliferative retinopathy are diagnosed during systematic screening by identifying the different features and lesions in the retina. Currently, the severity of non-proliferative retinopathy is determined using the '4-2-1' rule of the ETDRS [15,30]: haemorrhages and microaneurysms in four quadrants, with venous beading in at least two quadrants and intraretinal microvascular abnormalities in at least one quadrant. Using this classification system, which grades diabetic retinopathy on the presence or absence of lesions and quadrants of involvement, can result in non-specific classifications of non-proliferative retinopathy. With the available classification systems it can be difficult to accurately determine the severity of non-proliferative retinopathy, particularly in those with moderately severe to severe non-proliferative retinopathy, and to predict the risk of developing sight-threatening diabetic retinopathy.

We propose that a more detailed characterization of the morphological measurements of diabetic retinopathy lesions may help optimize and individualize the screening interval and improve the prediction of visual prognosis (i.e. the likelihood of non-proliferative retinopathy progression to sight-threatening disease). Using published findings, we propose that a detailed assessment of non-proliferative retinopathy features may assist with stratifying people into those most likely and least likely to progress; in turn, this

may help to inform treatment decisions or rescreen intervals. The distinct lesion types and their relevance to future development and progression of sight-threatening diabetic retinopathy are summarized in Table 2.

Lesion types

Microaneurysms and haemorrhages

Published studies have reported that the presence, size, and shape of microaneurysms may be critical in determining the development of diabetic retinopathy. High numbers of microaneurysms (up to seven in people with diabetic retinopathy in both eyes) in people with non-proliferative retinopathy was found to increase the risk of long-term development of sight-threatening diabetic retinopathy (both in people with proliferative diabetic retinopathy and diabetic macular oedema) without predicting the stepwise progression of diabetic retinopathy [31]. The size of microaneurysms may be important as smaller microaneurysms, compared to larger microaneurysms, may be more prone to leakage and rupture on account of a greater microaneurysm radius-to-vessel diameter ratio [32]. It would be advantageous to know which microaneurysm confers higher risk given the option of

Table 2 Types of lesions detected in non-proliferative retinopathy and potential relevance in non-proliferative retinopathy diagnosis and characterization

Lesion type	Description	Relevance in non-proliferative retinopathy diagnosis and characterization
Microaneurysms and haemorrhages	• Occur secondary to capillary wall outpouching as a result of pericyte loss • Earliest clinical sign of diabetic retinopathy • Rupture of microaneurysms results in haemorrhages	• Number, size, distribution, and turnover of microaneurysms and haemorrhages are important for diagnosis and may help to determine progression rates to sight-threatening diabetic retinopathy
Intraretinal microvascular abnormalities	• Characterize remodelling of pre-existing vessels or growth of new vessels • Intraretinal microvascular abnormalities are distinctive from the neovascularization observed in proliferative diabetic retinopathy in their larger size and broader arrangement • Found adjacent to or surrounding areas of occluded capillaries • Visible as telangiectatic, dilated capillaries within the retina	• Presence of intraretinal microvascular abnormalities is necessary for the diagnosis of moderate-to-severe non-proliferative retinopathy • Unclear whether the distribution of intraretinal microvascular abnormalities is important in assessing severity • Intraretinal microvascular abnormalities originating via angiogenesis may be important for the development of proliferative diabetic retinopathy
Venous beading/ loops/ reduplications	• Venous beading is produced by irregular constriction and dilation of venules in the retina • Venous loops and reduplications are rarer than venous beading and might result from accentuation of a bead, traction from vitreoretinal adhesions or may be shunt vessels	• Evidence linking venous beading to proliferative diabetic retinopathy development is unequivocal • Venous loops/reduplications do not appear to lead to sight-threatening changes in the diseased retina
Cotton wool spots	• Areas of nerve fibre ischaemia or infarction and axonal swelling induced by areas of retinal capillary closure • Signs of poor retinal perfusion and are easily visualized • Associated with systemic hypertension diabetes and are common in diabetic retinopathy and hypertensive retinopathy	• The early appearance of cotton wool spots helps in the early diagnosis of non-proliferative retinopathy but may lack predictive value for determining retinopathy progression
Hard exudates	• Lipid and lipoprotein deposits, usually found in the outer layers of the retina • Hard exudates have a 'waxy' appearance, with sharply defined borders, and result from leakage from abnormally permeable microaneurysms or capillaries in the retina	• The presence of hard exudates plays a vital role in grading diabetic retinopathy into different stages, but their appearance was not found to be associated with diabetic retinopathy progression

laser-targeted treatment for preventing microaneurysm rupture. Leaking microaneurysms have been correlated with retinal thickening in diabetic retinopathy [33], so identification of morphological differences between lesions is of prognostic importance.

The shape of a haemorrhage is also important; using fluorescein angiography, Dubow *et al.* [32] were able to classify microaneurysms into six morphological groups: focal bulge, saccular, fusiform, mixed, pedunculated, and irregular. Moreover, the findings of the study also indicated that the complex dynamics of microaneurysms may offer insight into disease progression [32]. Microaneurysm shape is also indicative of its location, reflecting the architecture of the retinal layer in which they occur. Haemorrhages in the nerve fibre cause blood to dissect among the axons in the superficial retina, resulting in flame-shaped haemorrhages; these are indistinguishable from those observed in hypertensive retinopathy and may indicate the co-existence of systemic hypertension [34]. Dot- or blot-shaped haemorrhages, which emanate from the deep capillary plexus, are more common in diabetic retinopathy. The authors of the large, multicentre ETDRS reported that in severe non-proliferative retinopathy, dot- or blot-shaped haemorrhages in four quadrants were indicative of future development of vitreous haemorrhage secondary to proliferative diabetic retinopathy [35].

Intraretinal microvascular abnormalities

Intraretinal microvascular abnormalities typically develop next to areas of non-perfused capillaries or cotton wool spots [30] and are either vascular shunt vessels or the early growth of neovascular vessels. It is thought that intraretinal microvascular abnormalities that originate via angiogenesis may be precursors to the earliest stages of neovascular growth in the retina [36]. Indeed, in a large UK longitudinal case evaluation, intraretinal microvascular abnormalities were found to be predictive of future development of proliferative diabetic retinopathy [35]; therefore, distinguishing between the types of intraretinal microvascular abnormalities may help to predict people at risk of developing proliferative diabetic retinopathy.

According to the 4:2:1 rule of the ETDRS, severe non-proliferative retinopathy is diagnosed with ≥1 prominent intraretinal microvascular abnormailty in ≥1 quadrant by comparing fundus findings with ETDRS standard photograph 8A [15]. Therefore, although a person with prominent intraretinal microvascular abnormalities in one quadrant is likely to have a lower risk of non-proliferative retinopathy progression, compared with a person with prominent intraretinal microvascular abnormalities in four quadrants, the ETDRS weighting is the same and the two people are deemed to have the same risk of developing sight-threatening diabetic retinopathy (20.7%) [35]. It is unclear why the presence of intraretinal microvascular abnormalities is normally reported in such broad terms, when intraretinal microvascular abnormalities pose a significant risk for the development of sight-threatening diabetic retinopathy. A more detailed assessment of detected intraretinal microvascular abnormalities including the type, number, and which particular quadrant is affected, may be more predictive of progression.

Venous beading, loops and reduplications

Changes in vessel calibre are caused by regulatory responses of the vascular, smooth muscle adjacent to areas of non-perfusion because of the lack of sympathetic vasomotor innervation in retinal vessels, reflecting increased retinal ischaemia. Venous beading in diabetic retinopathy has traditionally been known to indicate future progression of non-proliferative retinopathy to proliferative diabetic retinopathy [37], whereas the presence of loops and reduplications indicates established proliferative diabetic retinopathy [38]. A recent study questioned the relevance of changes in vessel calibre in non-proliferative retinopathy grading, and determined that the presence of other types of diabetic retinopathy lesions, such as intraretinal microvascular abnormalities, were significantly more predictive of progression, questioning whether venous beading should remain a criterion for severe non-proliferative retinopathy [39]. Further insight into the pathogenesis of retinal venous loops and reduplications is needed to establish the relative weighting of this criterion in diagnosing moderately severe non-proliferative retinopathy.

Cotton wool spots

Cotton wool spots are focal nerve fibre layer infarcts and appear as pale yellow to white, superficial inner retinal lesions with ill-defined feathery margins, resulting in coagulative necrosis of isolated retinal foci [40]. Cotton wool spots are detected where the retinal capillary bed already showed marked abnormalities. While cotton wool spots may be a hallmark of early diabetic retinopathy, wide areas of subclinical retinal microvascular disease are likely to predate their onset/detection, and as a result, the role of cotton wool spots as predictors of future progression to sight-threatening diabetic retinopathy is not clear [40,41].

There is significant overlap between diabetic retinopathy and hypertensive retinopathy, whereby severely elevated blood pressure may cause similar pathology to diabetic retinopathy, including cotton wool spots, flame-shaped haemorrhages, arteriovenous nicking and optic disc oedema [34]. Indeed, some lesion patterns have characteristics of both diabetic retinopathy and hypertensive retinopathy, and could be interpreted as either diabetic retinopathy worsened by hypertension or hypertensive retinopathy developing in people with diabetes [42]. Matthews *et al.* [43] showed that the level of hypertension in people with diabetes was related to the presence and number of cotton wool spots. The pathogenesis

and overlap of cotton wool spots in these conditions are not fully understood, but impaired retinal blood flow autoregulation in people with diabetes may be involved [44] in addition to the well-documented disturbed microcirculation.

Hard exudates

Hard exudates, found principally in the posterior pole of the macular region, are one of the hallmarks of diabetic retinopathy and can severely compromise sight [34]. Hard exudates are composed largely of extracellular lipid that has leaked from abnormal retinal capillaries and may present as exudates forming a ring pattern around the leaking vessels [40]. Quantitative measurement of hard exudates in people with diabetes is associated with triglyceride and lipid levels, and a higher risk of central involvement [45]. While this information may be useful for monitoring the progression of hard exudates or treatment response in persons with diabetic macular oedema, it is not understood if the early presence of hard exudates would identify those at risk of developing sight-threatening diabetic retinopathy.

Lesion distribution

The ETDRS photography protocol covers the central posterior 90 degrees of the retinal area, which is ~30% of the retinal surface, so lesions in the retinal periphery are not typically assessed [46]. Different patterns of diabetic retinopathy lesions are observed in the clinic [42], but the importance of regional distribution is not widely understood and, according to the current classification systems, the diagnostic value in regional distribution is largely unknown.

Using ultra-wide imaging, Silva *et al.* [46] showed that, in addition to those lesions detectable in the standard ETDRS fields, peripheral lesions were also present, suggesting that diabetic retinopathy severity may be underestimated in some people. Moreover, these findings also showed that people with predominantly peripheral lesions (mostly microaneurysms and haemorrhages, but also intraretinal microvascular abnormalities) had a greater than fourfold increased risk for progression to proliferative diabetic retinopathy compared with people with diabetic retinopathy lesions within the seven standard ETDRS fields [46].

The importance of lesion distribution in progression to sight-threatening diabetic retinopathy was also highlighted by Bek and Helgesen [42], describing the association of progression of diabetic retinopathy to sight-threatening diabetic macular oedema with the early progression of lesions that were distant from the vascular arcades in a similar manner to hypertensive retinopathy. It is thought that the localized distribution of lesions may correlate with known risk factors and background factors for the development of diabetic retinopathy in advanced (but not early) disease, further highlighting the need to accurately stage people with diabetic retinopathy [47].

Lesion dynamics

The '4-2-1' rule of diabetic retinopathy is generally unidirectional, based on the number, location, and type of discrete microvascular lesions at screening, meaning that the chronological appearance and disappearance of fundus lesions are not considered; however, lesions in non-proliferative retinopathy, such as cotton wool spots and microaneurysms, do not simply accumulate to reveal disease progression as previously thought. Instead, the regenerative activity of the retina results in the gradual reabsorption of some lesions, meaning that they can disappear from fundus photographs [48]. Alternatively, microaneurysms may rupture, forming haemorrhages, which are significantly associated with the development of vitreous haemorrhages and diabetic macular oedema in later life [49].

Microaneurysm turnover is a composite of microaneurysm formation and disappearance rate. Microaneurysm formation rate represents microvascular disease activity and may serve as an important biomarker; microaneurysm disappearance rate is considered to be a sign of capillary closure (non-perfusion). RetmarkerDR analysis (using Optomap ultra-wide field imaging) showed that high turnover (with a net increase in new microaneurysms) was associated with the development of proliferative diabetic retinopathy [48] and clinically significant macular oedema [28], and that high turnover (with a net decrease in new microaneurysms) was positively correlated with a reduction in central retinal thickness after anti-VEGF therapy [48]. This finding might serve as a quantification of response to treatment in the future [48].

The disappearance of non-proliferative retinopathy lesions could indicate vascular closure and damage; therefore, to fully assess non-proliferative retinopathy progression, lesion counting should be considered with every newly developed microaneurysm that is identified in a new location. Thus, to establish progression, it is crucial to be able to compare examinations performed at regular intervals. Detailed investigation of evolving microaneurysm features may be advantageous in predicting people with non-proliferative retinopathy who are likely to progress rapidly to sight-threatening diabetic retinopathy, facilitating earlier and targeted intervention.

Recommendations for future studies

The studies presented in this review suggest that specific non-proliferative retinopathy lesion patterns may be weighted to individual risks of developing sight-threatening diabetic retinopathy. To implement additional lesion measurements into current classification systems, robust natural history studies of lesion types are needed to fully characterize these non-proliferative retinopathy progression profiles. Future studies investigating the systematic progression and regression and local distribution of different lesion types should be performed to identify markers of the risk of rapid progression

Table 3 Suggested supplementary measurements for non-proliferative retinopathy lesion assessment

	Measurement	Rationale
1	Shape and size of lesions	○ Small or large microaneurysms: small microaneurysms may be an indication for laser treatment of individual lesions
		○ Leaky microaneurysms: may be at risk of leakage, rupture, or capillary dropout
		○ Flame-shaped haemorrhage: may be indicative of hypertensive retinopathy
2	Type of intraretinal microvascular abnormality	○ Angiogenesis-based intraretinal microvascular abnormalities: may be a precursor to proliferative diabetic retinopathy
3	Concomitant hypertensive retinopathy	○ Presence of cotton wool spots and flame-shaped haemorrhages
		○ Microaneurysm distance from venous arcades
4	Peripheral location of microaneurysms and intraretinal microvascular abnormalities	○ High levels of peripheral lesions may be more predicative of progression to sight-threatening diabetic retinopathy
5	Turnover of lesions (microaneurysms and cotton wool spots)	○ May predict treatment responses as well risk of progression

to sight-threatening diabetic retinopathy so that appropriate actions can be taken to prevent sight loss.

In addition to the standard stepwise changes on the diabetic retinopathy severity scale and best-corrected visual acuity, valuable information on the progression of non-proliferative retinopathy could be acquired in future clinical trials specifically to investigate treatment effects on early and reversible lesion changes. Suggested supplementary measurements are listed in Table 3.

A detailed assessment of concomitant hypertension would be helpful, particularly in determining whether hypertensive retinopathy affects non-proliferative retinopathy disease progression and whether specifically targeting hypertension would be more effective in the non-proliferative retinopathy population.

Advances in adaptive optics can already reveal the microscopic changes that could help elucidate underlying pathology imaging such as vessel occlusion and the presence of leukostasis [50]; therefore, future developments in imaging could involve high-resolution visualization of retinal circulation. Further research is required to determine new blood biomarkers, retinal imaging markers, and genetic determinants of diabetic retinopathy. These findings will enable us to further our understanding of the pathogenesis, risk prediction, prevention, and treatment of diabetic retinopathy.

Current non-proliferative retinopathy classifications are limited owing to their broad description of moderately severe and severe non-proliferative retinopathy categories, which presents a challenge when predicting people with a high risk of progressing to sight-threatening diabetic retinopathy, even if stratified by 'traditional' risk factors (such as diabetes duration, haemoglobin levels, hypertension, and hyperlipidaemia). Furthermore, standard imaging techniques may not capture predominantly peripheral lesions. There is a clear unmet need for improved and earlier detection of moderate-to-severe non-proliferative retinopathy to improve outcomes. It is hoped that combining a robust qualitative classification with quantitative metrics may allow us to better stratify people with non-proliferative retinopathy. Clinical applications of this approach may prove useful in better understanding microvascular disease progression and may help point the way to more successful treatment regimens.

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