



Retinal Imaging Findings in Patients with Maturity-Onset Diabetes of the Young



Maturity-onset diabetes of the young (MODY), a group of monogenic disorders inherited in an autosomal dominant fashion, is a rare cause of diabetes mellitus.¹ It affects 1% to 2% of individuals with diabetes, usually of younger age, and is often misdiagnosed as type 1 diabetes (T1DM) or type 2 diabetes (T2DM).¹ Similar to these more common forms of diabetes, MODY can lead to cardiovascular, renal, and retinal complications, among others.

Unlike T1DM and T2DM, the effects of MODY on the retina have been poorly studied. The prevalence of retinopathy in MODY patients has been reported in a number of studies, including 21.5% of patients with HNF1A-MODY (formerly MODY3) and 5.4% of patients with GCK-MODY (formerly MODY2).^{2,3} However, literature detailing the specific retinal manifestations in these patients is currently limited to single case reports, such as Purtscher-like retinopathy in a 19-year-old patient and severe proliferative diabetic retinopathy (PDR) in a 32-year-old patient.^{4,5} There have been no prior case series focused on the retinal phenotypes of MODY. Therefore, this case series sought to characterize the retinal findings in patients with MODY using multimodal and ultrawidefield (UWF) retinal imaging.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Weill Cornell Medicine Institutional Review Board. Informed consent was waived because as a retrospective case series, the study posed minimal risk to the patients. In this retrospective case review series from 2008 to 2024, International Classification of Diseases, 10th Revision codes were used to identify all patients at New York Presbyterian/Weill Cornell with a MODY diagnosis and fundus photography. Charts were reviewed to confirm their MODY diagnosis, which was endorsed by either genetic testing revealing a MODY mutation or a consistent MODY diagnosis from an endocrinologist. Patient age, sex, body mass index, MODY subtype, duration of diagnosis, most recent glycated hemoglobin (HbA1c) and HbA1c range since diagnosis, diabetes treatment, and cardiovascular comorbidities were recorded, all in reference to the date of their most recent retinal imaging. Then, all available retinal imaging, including UWF fundus photography, autofluorescence, fluorescein angiography, and OCT, was analyzed by a retina specialist. All imaging was obtained as part of routine screening examinations for diabetic retinopathy with the retina service at our institution or as a part of routine telemedicine screening for retinopathy at endocrinology follow-ups. Any retinopathy findings were recorded. The presence of ischemic changes and macular edema was also noted.

Nine patients, 6 women and 3 men, were confirmed to have MODY and retinal imaging. Their ages ranged from 22 to 68 years at the time of their most recent imaging, and their body mass index ranged from 20.36 to 28.94 kg/m². Four patients had GCK-MODY, whereas 1 patient each had HNF4A-MODY, HNF1A-MODY, and HNF1B-MODY. Two patients had an unspecified

MODY subtype, as they were diagnosed at another institution with their genetic testing unavailable for review. Most recent HbA1c, which were all within 6 months prior to imaging, ranged from 6.0 to 13.2. Four patients were being treated with insulin. Additional demographic and endocrine information can be found in [Table 1](#).

All 9 patients had available UWF fundus photography and autofluorescence. Four patients also had OCT, and 3 patients had fluorescein angiography. Patient-specific imaging details are provided in [Table 1](#). In addition, 33.3% (3) of patients had normal retinal imaging findings, and 66.7% (6) of patients had signs of retinopathy. Among patients with diabetic retinopathy, 66.7% (4) of patients had mild nonproliferative diabetic retinopathy (NPDR) with predominantly peripheral lesions, including 1 patient who also had mild nonperfusion. One patient had severe NPDR and ischemic changes. The last patient had PDR, macular edema, and severe ischemic changes on angiography.

This case series, the first to focus on retinal findings in MODY patients, found that 6 of the 9 MODY patients had signs of retinopathy on advanced multimodal retinal imaging. The most common retinopathy was mild NPDR with PPL, which was present in 4 of 9 patients. A UWF color fundus photograph and fluorescein angiogram of this phenotype are shown in [Figures S1 and S2](#) (available at www.ophtalmologyscience.org). Predominantly peripheral lesion is also a common finding among T1DM and T2DM patients with NPDR and may indicate a greater risk of future disease progression; hence, retinopathy in MODY patients cannot yet be differentiated from retinopathy in T1DM and T2DM patients.⁶ However, the high prevalence of peripheral lesions in this case series indicates that UWF imaging may be a valuable tool for screening MODY patients before their retinopathy worsens.

Analyzing specific endocrine variables reveals additional trends. The 5 patients not being treated with insulin and whose most recent HbA1c was the lowest (<6.3) had either no signs of retinopathy or mild NPDR. On the other hand, the 4 patients on insulin and whose most recent HbA1c was >6.3 had mild NPDR, severe NPDR, or PDR. Specifically, the 2 patients with severe NPDR and PDR had an HbA1c >8. This association between a higher HbA1c, insulin treatment, and more severe retinopathy highlights the importance of glucose control in MODY patients. However, without more longitudinal HbA1c data or metrics like time in range, our understanding of patients' long-term glycemic control and its impact on retinopathy is limited. Furthermore, other systemic factors that can influence retinopathy, such as hypertension or lipid levels, were not analyzed or controlled for in this study.

The most common MODY subtype in this study was GCK-MODY. As expected, these 4 patients had excellent glycemic control on only oral medications. Surprisingly, however, 2 of the 4 GCK-MODY subjects did have evidence of early retinopathy. GCK-MODY patients have fewer and less severe microvascular complications compared with other MODY subtypes, with a study of 74 patients with GCK-MODY finding only 1 patient with

Table 1. Demographic, Endocrine, and Retinal Imaging Details

Age (yrs)	Sex	BMI (kg/m ²)	Duration of MODY Diagnosis (yrs)	MODY Gene	Most Recent HbA1c (Range Since Diagnosis)	Diabetes Medications	Cardiovascular Comorbidities	Imaging Modalities Available	Retinal Findings
45	F	20.36	12	GCK	6.1 (5.9–6.5)	Sitagliptin	None	Fundus, autofluorescence	Mild NPDR, PPL
53	M	21.25	5	GCK	6.2 (6.2–6.8)	Sitagliptin, metformin	None	Fundus, autofluorescence, OCT, FA	Mild NPDR, PPL
48	F	26.63	16	GCK	6.0 (5.7–6.6)	None	HLD	Fundus, autofluorescence	Normal
68	F	25.53	1	Not specified	6.9 (6.9–7.3)	Insulin, sitagliptin, semaglutide	HTN	Fundus, autofluorescence	Mild NPDR, PPL
20	F	22.30	3	<i>HNF1A</i>	6.1 (6.1–6.4)	Metformin	None	Fundus, autofluorescence, OCT	Normal
36	M	28.43	3	GCK	6.0 (6.0–6.3)	Metformin	HLD	Fundus, autofluorescence	Normal
28	F	28.94	2	<i>HNF1B</i>	6.4 (6.3–13.5)	Insulin, semaglutide	None	Fundus, autofluorescence	Mild NPDR, PPL, peripheral nonperfusion
66	F	24.49	5	<i>HNF4A</i>	8.5 (8.2–11.3)	Insulin	HTN	Fundus, autofluorescence, OCT, FA	PDR, marked nonperfusion, macular edema
22	M	26.71	1	Not specified	13.2 (12.7–13.2)	Insulin, sitagliptin, metformin	None	Fundus, autofluorescence, OCT, FA	Severe NPDR, marked nonperfusion

BMI = body mass index; F = female; FA = fluorescein angiography; HbA1c = glycated hemoglobin; HLD = hyperlipidemia; HTN = hypertension; M = male; MODY = maturity-onset diabetes of the young; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PPL = predominantly peripheral lesions.

retinopathy (mild NPDR).^{1,3,7} Our observations differ from these findings and suggest the need for retinal screening in all subtypes of MODY patients.

Nonetheless, the small sample size and nature of a retrospective case series are inherent limitations of this study. Conclusions about the prevalence and phenotypes of retinopathy in MODY patients, as well as the role of MODY subtype, glucose levels, diabetic treatments, and other factors, cannot be statistically estimated from this case series. Moreover, the lack of a control group of patients with T1DM or T2DM limits the ability to identify unique retinal features in MODY patients. Thus, although these results suggest that NPDR with predominantly peripheral lesion is common in MODY patients, additional research is needed to further elucidate their retinal findings. Future studies should ensure consistent and comprehensive imaging, as this study potentially missed findings because some patients did not undergo fluorescein angiography or OCT. Other advanced imaging modalities, such as adaptive optics and OCT angiography, could help develop a greater understanding of disease pathogenesis in MODY and differentiate the phenotypic variants across subtypes. Larger longitudinal cohort studies, tracking the progression of retinal imaging findings in MODY patients, will help inform targeted screening and intervention strategies.

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Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

This work was supported in part by a grant from the New York Eye and Ear Foundation.

HUMAN SUBJECTS: Human subjects were included in this study. The Weill Cornell Medicine Institutional Review Board approved the study. All research adhered to the tenets of the Declaration of Helsinki. Informed consent was waived because as a retrospective case series, the study posed minimal risk to the patients.

No animal subjects were used in this study.

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Abbreviations and Acronyms:

MODY = maturity-onset diabetes of the young; **NPDR** = non-proliferative diabetic retinopathy; **OCT** = optical coherence tomography; **PDR** = proliferative diabetic retinopathy; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **UWF** = ultra-widefield.

Keywords:

Retinal imaging, Diabetic retinopathy, Maturity-onset diabetes of the young, Predominantly peripheral lesions.

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References

1. Anik A, Çatlı G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab.* 2015;28:251–263.
2. Zhao Q, Ding L, Yang Y, et al. Clinical characteristics of patients with HNF1-alpha MODY: a literature review and retrospective chart review. *Front Endocrinol (Lausanne).* 2022;13:900489.
3. Sagen JV, Bjørkhaug L, Molnes J, et al. Diagnostic screening of MODY2/GCK mutations in the Norwegian MODY Registry. *Pediatr Diabetes.* 2008;9:442–449.
4. Oh AJ, Javaheri M, Hosseini H, Prasad PS. Purtscher-like retinopathy in a 19-year-old with maturity-onset diabetes of the young: a case report. *J Med Case Rep.* 2023;17:255.
5. Tymms DJ, Reckless JP. Proliferative diabetic retinopathy in a patient with maturity-onset diabetes of the young (MODY). *Diabet Med.* 1989;6:451–453.
6. Marcus DM, Silva PS, Liu D, et al. Association of predominantly peripheral lesions on ultra-widefield imaging and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol.* 2022;140:946–954.
7. Szopa M, Wolkow J, Matejko B, et al. Prevalence of retinopathy in adult patients with GCK-MODY and HNF1A-MODY. *Exp Clin Endocrinol Diabetes.* 2015;123:524–528.