

Diabetic Papillopathy: Diagnose and Treatment of A Rare Diabetes Mellitus Ocular Complication (A Literature Review)

Maasa Sunreza Millenia^a, Lukisari Agustini^{b*}, Hermawan Susanto^c

email: lukisari.agustini@fk.unair.ac.id

^aMedical Program, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, Indonesia

^bDepartment of Ophthalmology, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Hospital, Surabaya, 60132, Indonesia

^cDepartment of Internal Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Hospital, Surabaya, 60132, Indonesia

Abstract

Diabetic papillopathy (DP) is a rare complication of DM that reduces the patient's visual function. Until now the lack number of studies, diagnosis, and treatment is still uncertain. Considering there still limitations of research on DP must continue to be explored as this literature is made. This study is a literature review that was carried out in 2022 to disclose more information on diabetic papillopathy. We searched for this topic using a systematic search of Google Scholar, PubMed, Scopus, Elsevier, and SAGE review databases. Some of the keywords we used for the literature search were "diabetes mellitus," "diabetic papillopathy," and "optic disc edema." To this end, this literature review aims to present, examine, diagnose, and treat diabetic papillopathy. DP has intravitreal clinical signs such as optic disc swelling or atrophy which have many differential diagnoses. To eliminate this differential diagnosis it is important for a doctor to understand the patient's history as DP is a manifestation of complications of metabolic disorders (hyperglycemia). Investigations include ophthalmological testing, MRI, neuroimaging, and clinical evaluation for infection signs will aid in determining the diagnosis of DP and discover optic nerve injury. It should be noted that, a better understanding of DP can determine an appropriate, effective, and plan B therapy modality.

Keywords: diabetic papillopathy; optic disc edema; papilledema; diabetes mellitus

1. Introduction

Diabetes mellitus (DM) is a long-term (chronic) condition of increasing blood sugar levels (hyperglycemia) caused by the body's inability to produce the hormone insulin or the use of the insulin hormone that is produced is not used effectively. According to estimates from the International Diabetes Federation (IDF) there will be at least 537 million people in the age range 20-79 years in the world in 2021 suffering from diabetes and it is estimated that in 2030 there will be 643 million and will increase to 783 million people in 2045. In 2021, Indonesia is ranked 5th out of 10 countries with DM sufferers, namely 19.5 million people (International Diabetes Federation 2021).

Chronic DM complications can affect several organs both vascular and non-vascular. Vascular disorders include microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (CHD, peripheral arterial disease [PAD], and cerebrovascular disease). Non-vascular disorders occur such as infections, skin changes, and hearing loss (J. Larry Jameson, MD et al. 2020). According to statistics, one-third of all people with diabetes mellitus around the world have diabetic retinopathy; with this group, one-third are likely to have diabetic retinopathy that threatens their vision (American Academy of Ophthalmology 2021). However, diabetic retinopathy is not the only ocular complication of DM. Diabetic papillopathy (DP) is swelling of the optic disc that can occur bilaterally and unilaterally which can be found with or without visual disturbances in

patients with type 1 DM (T1 DM) and type 2 DM (T2 DM) (American Academy of Ophthalmology 2021).

Lubow, & Makrley (1971) found the first case DP in patients with type 1 DM (T1 DM) (Lubow and Makrley 1971) then 24 years later it found with type 2 DM (T2 DM) either (Regillo et al., 1995). Compared with other manifestations of ocular complications, research on DP is still limited (Becker et al., 2021). This may be due to DP which are rare complications, have an acute onset and are self-limiting, also have a diverse differential diagnosis. In fact, according to Felldman & Dupas (2021), cases of DP were found in only 1% of the 3,235 DM patients studied (Feldman-billard and Dupas 2021). Although rare, cases of DP cannot be ruled out because in some cases it can cause visual impairment (Appen et al. 1980). Therefore, the goal of this literature review was to present, examination, diagnose, and treat diabetic papillopathy.

2. Overview

Patients with T1 DM or T2 DM mellitus may get DP, which is some authors believe it connected to NAION. Patients who are affected may not present any symptoms or may describe vague symptoms like blurry vision or "distortion" without pain. Visual acuity, visual field, and RAPD (Relative Afferent Pupillary Defect) testing do not often reveal any signs of optic nerve impairment. The absence of retinopathy does not rule out a diagnosis of DP because diabetic retinopathy is not universal among individuals with the illness (occurring in 63%-80% of patients with the condition) (American Academy of Ophthalmology, 2021).

2.1 Clinical Finding

Distended or edematous optic nerve heads can be seen using slit lamp biomicroscopy, direct or indirect ophthalmoscopy, and are common in DP individuals. With hyperemic edema of the optic nerve, 50% of patients have significant dilation of the ONH (Optic Nerve Head) surface microvasculature, which resembles NVD (See Figure 1) (American Academy of Ophthalmology 2021). In DP, swelling is assumed to be self-limited in the absence of optic atrophy or material adjustments to visual function (visual fields and visual acuity). While various causes of pseudo-papilloedema, such as inflammation, infection, elevated intracranial pressure, neuro-vascularization of the disc, traction, drusen of the optic disc, and other conditions are taken into consideration, the diagnosis of DP may be made as an exclusion (Huemer et al. 2021).

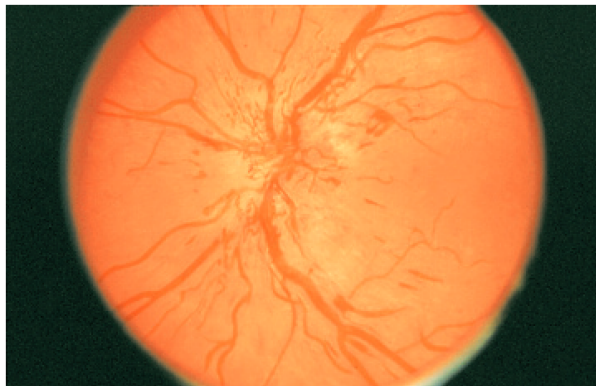


Figure 1. Edema with significant surface telangiectasia is visible in the fundus photo graph of an ONH in diabetic papillopathy (American Academy of Ophthalmology 2021).

- Retinal Vascularization Anatomy

The retina is a neurosensory network composed of 9 layers including rod cells and cone cells, as well as the retinal pigment epithelium. The ophthalmic artery has a major branch, the central ophthalmic artery, which supplies the innermost layer of the retina. The ophthalmic artery has another branch, namely the ciliary artery, which supplies the outer layer of the neurosensory retina via the choriocapillaris artery (See Figure 2)(Giuliari et al. 2011).

The optic disc is vascularized differently from the retina in that it has two layers of a capillary vascular complex (superficial and inner capillary network), which are surrounded by the superficial capillary network of the optic nerve head and extending along part of its canal. The radial peripapillary vascular network is a sensitive area for hypertension and hyperglycemia because these capillaries originate from arteries with large diameters and empty into large veins with limited anastomoses (Giuliari et al. 2011).

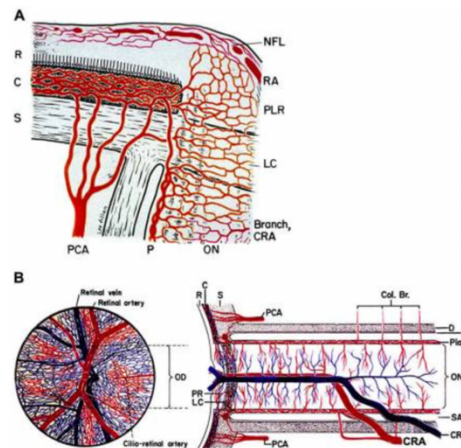


Figure 2. Optic nerve vascularization scheme (McCallister 2013)

- Pathophysiology

In 1971, DP were found in patients with T1 DM. Along with the development of research, it also occur in T2 DM so that the occurrence of chronic conditions of hyperglycemia affects vascular damage, especially in the arteries in the retina. Chronic hyperglycemia is a significant factor in a number of DM complications, however it is unclear exactly how different cells and organs are involved in these issues. Several hypotheses explain that chronic hyperglycemia increases the production of AGEs (advanced glycosylation end products) such as pentosidine, glucosepane, and carboxymethyl which cause cross-linking between proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and changes in matrix composition. Several other theories are (1) increasing glucose metabolism through the sorbitol pathway which is related to the aldose reductase enzyme (polyol pathway); (2) increases the formation of diacylglycerols, which causes activation of protein kinase C, which alters gene transcription for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons; and (3) increasing flux through the hexosamine pathway, which produces fructose-6-phosphate, a substrate for O-linked glycosylation and production of proteoglycans, which causes functional alteration by glycosylation of proteins such as endothelial nitric oxide synthase (J. Larry Jameson, MD et al. 2020). In DP vascular abnormalities caused by persistent hyperglycemia, it is thought

that edema can have an ischemic, compressive, or toxic effect on ONH due to inadequate perfusion caused by disruption of capillary membranes and interstitial fluid dynamics. Similar to NAION, both illnesses similarly include anterior optic nerve ischemia by ischemia pathophysiology (Hayreh and Zimmerman 2008). However, the resulting optic nerve ischemia can be distinguished by variations in perfusion insufficiency (Slagle, Musick, and Eckermann 2009)

2.2 Clinical Evaluation

- Visual Acuity

Visual acuity is an assessment of a person's ability to distinguish between fine details in strong contrast. Each eye should be checked independently for best corrected vision, with the other eye being occluded by a hand, tissue, or other object. Pinhole testing should be performed on patients who still have subnormal visual acuity despite receiving the best refracted correction since it may help to correct some refractive issues (such as irregular astigmatism) and media opacities (cataract). Nonrefractive causes of vision loss should be taken into account when acuity cannot be improved by a pinhole (Grant T., Nicholas J, and Steven L. 2018). The visual acuity test is a quick, low-cost assessment that uses a notation like 20/40 to describe visual function. The Snellen chart can be used to assess optic nerve function. This evaluation is crucial because patients with DP often suffer subjective vision blurriness; nevertheless, in certain cases, normal visual acuity is discovered together with impaired visual acuity (Becker and Nichols 2021).

- Pupillary Testing

Pupillary dysfunction lesions often reflect lesions in the visual afferent and efferent pathways. Examination can include pupillary size and light reactivity (Grant T., Nicholas J, and Steven L. 2018). In normal pupils when given a response to light that leads both pupils to shrink equally. If there is dysfunction of the afferent pathway of one optic nerve it will produce a weaker parasympathetic signal for pupil contraction. Pupillary testing is helpful in examining patients with suspected DP (Becker and Nichols 2021). Findings of relative afferent pupillary defect conditions (RAPD) indicate the degree of optic disc nevus disturbance, but are not found in all cases. Signs of significant short-term optic nerve dysfunction such as RAPD, central or altitudinal field changes and dyschromatopia serve to differentiate DP from optic neuritis (ON) (Regillo et al. 1995).

- Visual Field Evaluation

Visual field evaluation was performed to evaluate changes and progression of visual fields. Impaired visual field confrontation indicates significant optic nerve disturbance, although this is rare in DP. The tools commonly used in DP cases are Humphrey Visual Field and Goldmann kinetic perimetry (Becker and Nichols 2021). Implementation of computerized thresholds is more sensitive in the examination of papilledema and ON than other visual field testing. On visual field tests, an extended blind spot is frequently seen in DP. Confrontation, however, is inappropriate since it runs the risk of missing more subtle problems. The blind spot, which is represented as a blind spot because there are no photoreceptors overlaying the optic nerve, is around 15 degrees temporal to and slightly below fixation. Following the patient's care, the ophthalmologist should decide how frequently to monitor the patient's visual field function (Grant T., Nicholas J, and Steven L. 2018).

- Optic Coherence Tomography (OCT)

OCT is an imaging modality that produces micro meter resolution images of soft tissues in a non-

invasive and non-contact. On OCT will describe the thickness of the tissue that can be measured approximately as thick as the retinal fiber layer (American Academy of Ophthalmology 2020). In cases of optic disc atrophy, for example ON, the use of OCT is used as a quantitative assessment of the thickness of the peripapillary retinal nerve layer (pRNFL) and the macular ganglion cell layer (mGCL). In cases of DP and diabetes NAION atrophy or thinning occurs in pRNFL and mGCL. However, the OCT examination is not sufficient to differentiate DP and diabetic NAION, so additional investigations are needed, such as past medical history and laboratory tests (Huemer et al. 2021).

- Fundus Photography

In order to track the development of a disease or its cure, fundus photography is frequently obtained. Fundus photography shows optic nerve oedema, intravitreal coexisting conditions, and measure size of cup-to-disc ratio. Based on research by Ostri et al (2010) cup-to-disc ratio size of 0.18 or less has significance with the incidence of DP (Ostri et al. 2010).

2.3 Diagnosis

The diagnosis formed depending on DP symptoms may also apply to other ophthalmologic disorders, particularly if the visual acuity and visual field tests for DP are both normal. Optic disc oedema disorders both unilateral and bilateral have several differential diagnoses (See Table 2 & Table 3). As a diagnosis of exclusion, to distinguish DP from other disorders in this situation, it is crucial to obtain a thorough history of any prior medical conditions, perform a physical check for infection, and run OCT, neuroimaging, MRI, and laboratory tests (See Table 1). On the other hand, Ostri et al. (2010) found that a significant drop in HbA1c levels would have an impact on the occurrence of DP. Fundus examination may be used to detect people with cup-to-disc diameter ratios of 0.18 or below so that chronic hyperglycemia occurrences, such as those in T1 DM and T2 DM, which are chronic, are important before a planned intensification of insulin treatment (Ostri et al. 2010). One in 30 people have compared to T2 DM, however this does not rule out the possibility that T1 DM patients have a risk of developing DP (Bayraktar and Alacali 2002).

Table 1. Systemic investigation to exclude differential diagnosis of DP (Becker and Nichols 2021)

Systemic Investigation of DP
MRI or CT scan
Complete blood count with differential and platelets
Erythrocyte sedimentation rate
Angiotensin converting enzyme and lysozyme
Syphilis serology
Tuberculosis testing
Lyme disease titer as indicated
Vitamin B1, B12, copper, and folate
MOG and NMO antibody testing

Table 2. Differential diagnosis of unilateral optic disc swelling (Becker and Nichols 2021)

Differential diagnosis of unilateral disc optic swelling	
Non-arteritic anterior ischemic optic neuropathy	Optic perineuritis
Arteritic anterior ischemic optic neuropathy (temporal arteritis, giant cell arteritis)	Thyroid eye disease
Infiltrative optic neuropathy: Lymphoma, leukemia, syphilis, sarcoidosis, tuberculosis, and other infections or neoplastic diseases	Hereditary optic neuropathies
Optic neuritis, chronic relapsing inflammatory optic neuropathy	Optic disc drusen
Neuromyelitis optica (Devic disease)	Traumatic optic neuropathy
Myelin Oligodendrocyte Glycoprotein (MOG) Optic Neuritis	Radiation
Neuroretinitis	Diabetic papillitis

Table 3. Differential diagnosis of bilateral optic disc swelling (Becker and Nichols 2021)

Causes of bilateral optic disc swelling		
Papilledema	Increased intracranial pressure	Toxic optic neuropathy
	Intracranial mass	Nutritional optic neuropathy
	Idiopathic intracranial hypertension	Any of the diseases in Table 2 may infrequently present with bilateral disease

2.4 Treatment

As DP has a diverse variety of differential diagnoses, the first approach a physician should take is to rule out other potential causes of optic disc swelling that might suggest other systemic disorders. In some cases, DP is associated with decreased visual acuity, but is generally found without decreased visual acuity. Optic disc swelling in DP can also spontaneously disappear within 3-4 months (Savino et al. 2002). Several case reports describe the use of intravitreal corticosteroids or anti vascular endothelial growth factor. Previous case studies have shown improvement in optic disc oedema and improvement in visual acuity using intravitreal injections such as intravitreal injections of triamcinolone acetate, intravitreal injections of bevacizumab (Avastin) or ranizumab, and periocular corticosteroids (Al-hinai, Al-abri, and Al-hajri 2011) (Yildirim et al. 2017). The most significant determinant is efforts to control either the patient's metabolic condition or prevent further DM and vascular complications, such as glycemic control (assessed by HbA1c level), hypertension, and other risk factors for atherosclerosis (Becker and Nichols 2021). According to Marfici et al (2020) the addition of insulin to the oral hypoglycemic medication caused the acute papillary injury rather than hyperglycemia due to a rapid change in the general metabolic and glycemic balance, causing cellular stress. Therefore, research into the use of oral hypoglycemic therapy to combine oral and insulin therapy with a side effect on the visual nerve is still required in the future (Mafrici, Toscani, and Lorenzi 2020).

3. Conclusions

Diabetic papillopathy is an exclusion diagnosis of optic disc swelling or atrophy on these days. Another key fact to remember, doctors do as the first step are look for the health history, physical examination and signs of infection. Other important examinations are performed such as visual acuity, visual field evaluation, and optic nerve head imaging to know the progressivity of optic nerve disfunction. This suggest that, a better understanding of DP can determine an appropriate, effective, and plan B therapy modality.

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References

- Al-hinai, Ahmed S, Mohammed S Al-abri, and Rayah H Al-hajri. 2011. "Diabetic Papillopathy with Macular Edema Treated with Intravitreal Bevacizumab." *Oman Journal of Ophtalmology* 4(3): 135–39.
- American Academy of Ophthalmology. 2020. *American Academy of Ophthalmology Basic and Clinical Science Course, Section 12 : Retina and Vitreous*. San Francisco: American Academy of Ophthalmology.
- . 2021. *American Academy of Ophthalmology Basic and Clinical Science Course, Section 5: Neuro-Ophtalmology*. San Francisco: American Academy of Ophthalmology.
- Appen, R., S. R. Chandra, R. Klein, and F. L. Myers. 1980. "Diabetic Papillopathy." *American Journal of Ophthalmology* 90(2): 203–9.
- Bayraktar, Zerrin, and Nilay Alacali. 2002. "DIABETIC PAPILLOPATHY IN TYPE II DIABETIC PATIENTS." *The Journal of Retinal and Vitreous Diseases* 22(6): 752–58.
- Becker, Karl N., and Jeffrey Nichols. 2021. "Review of Diabetic Papillitis." *Disease-a-Month* 67(5): 101141. <https://doi.org/10.1016/j.disamonth.2021.101141>.
- Feldman-billard, Sylvie, and Benedicte Dupas. 2021. "Eye Disorders Other than Diabetic Retinopathy in Patients with Diabetes." *Diabetes & Metabolism* 47: 1–6.
- Giuliari, Gian P, Ama Sadaka, Peter Y Chang, and Rafael T Cortez. 2011. "Diabetic Papillopathy: Current and New Treatment Options." *Current Diabetes Reviews* 7: 171–75.
- Grant T., Liu, Volpe Nicholas J, and Galetta Steven L. 2018. "Neuro-Ophthalmology Diagnosis and Management 3rd Ed."
- Hayreh, Sohan Singh, and M Bridget Zimmerman. 2008. "Neuropathy : Clinical Characteristics in Diabetic Patients Versus Nondiabetic." *American Academy of Ophthalmology* 115(10): 1818–25.
- Huemer, Josef et al. 2021. "Re-Evaluating Diabetic Papillopathy Using Optical Coherence Tomography and Inner Retinal Sublayer Analysis." *Eye (Basingstoke)* 36(7): 1–10. <http://dx.doi.org/10.1038/s41433-021-01664-1>.
- International Diabetes Federation. 2021. *IDF Diabetes Atlas 10th Edn*. Brussels, Belgium. <https://www.diabetesatlas.org>.
- J. Larry Jameson, MD, PhD et al. 2020. *Harrison's Manual Of Medicine*. 20th ed. San Francisco: McGraw-Hill Education.
- Lubow, Martin, and A Makley. 1971. "Pseudopapilledema of Juvenile Diabetes Mellitus." *Arch Ophthalmology* 85: 417–22.
- Mafrici, Marco, Laura Toscani, and Umberto Lorenzi. 2020. "Bilateral Diabetic Papillopathy Developed after Starting Insulin Treatment. Potential Toxic Effect of Insulin? A Case Report." *European Journal of Ophthalmology*: 1–5.
- Mcallister, Andrew S. 2013. "A Review of the Vascular Anatomy of the Optic Nerve Head and Its Clinical Implications." *Cureus* 5(2): 6–10.
- Ostri, Christoffer et al. 2010. "Bilateral Diabetic Papillopathy and Metabolic Control." *Ophthalmology* 117(11): 2214–17. <http://dx.doi.org/10.1016/j.ophtha.2010.03.006>.
- Regillo, Carl D et al. 1995. "Diabetic Papillopathy Patient Characteristics and Fundus Findings." *Arch Ophthalmol* 113: 889–95.

- Savino, Peter J et al. 2002. "CLINICAL CHALLENGES The Disk Edema Dilemma." *Survey of Ophthalmology* 47(2).
- Slagle, William Scott, Angela N Musick, and Daniel R Eckermann. 2009. "Diabetic Papillopathy and Its Relation to Optic Nerve Ischemia." *Optometry and Vision Science* 86(4): 395–403.
- Yildirim, Mine, Deniz Kilic, Mehmet Emin Dursun, and Birgul Dursun. 2017. "Diabetic Papillopathy Treated with Intravitreal Ranibizumab." *International Medical Case Reports Journal* 10: 99–103.